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Academy of Pulmonary & Critical Care Medicine

# Pulmon

The Journal of Respiratory Sciences

Editorial

# Adherence to inhaled medications: Why does it matter?

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Medications in the inhaled form has revolutionised the management and outcome of obstructive airway disorders. Though an age-old concept, patients opting inhalers as the preferred modality of treatment seems to be low. The patient's ability to use inhaled devices appropriately and the adherence to the treatment protocol are likely to be influenced by their beliefs, attitudes and concerns about the use of inhalers.

Adherence is defined as the degree to which the person's behaviour corresponds with the agreed recommendations from a health care provider.[1] Non-adherence may be divided into three distinct time related phases: failure to initiate treatment, failure to implement treatment as per schedule, and non-persistence with treatment. Initiation is a two-point event, with patients either starting to take their medication or not. The second step – implementation – can be defined as the extent to which a patient's actual dosing corresponds with their prescribed dosing regimen over time, from initiation until the last dose is taken. This involves taking the medication as per the direction of the competent person(s), which includes inhaler technique in obstructive airway disorders. Persistence – the final step – refers to the time that elapses between initiation and eventual treatment discontinuation.[2] After this time point, a period of nonpersistence may follow until the end of the intended prescribing period.

Non adherence is a major issue especially among adolescents, who have age specific barriers for following a regular therapeutic schedule, which can have a detrimental effect on asthma control and subsequent outcomes.[3,4,5] It is a common problem that may be deliberate or accidental. Deliberate or intentional non adherence refers to patients missing or altering doses according to their convenience, and includes reluctance to take medication as per prescription owing to beliefs or cultural preferences. Accidental or unintentional non adherence includes unknowingly using the inhalation device incorrectly or forgetting to take medication as directed or due to logistic issues like non affordability and non availability. There can be pseudo adherence too which also cause poor control of the condition. Beyond the labelled number of actuations, propellant can release an aerosol plume that contains little or no drug and patients believe that they are taking the drugs as per schedule. The dose of delivered drug per actuation may be highly inconsistent and unpredictable after the labelled number of actuations and this is called as tail off effect.[6]

**Non adherence – contributing factors**

Regimens for obstructive airway disorders often require intake of appropriate medications at regular intervals of time. Inadequate instructions or a complex regimen which is time-consuming are important issues that affect adherence. The hectic schedules of patients and family members with insufficient communication and coordination between them, can all affect adherence.[4,5] Lack of education and negative perceptions about treatment also frequently influence adherence.

Patient's beliefs, cultural preferences, attitude towards disease and their health seeking behaviour are significant issues in realizing and responding to various heath conditions including asthma and COPD. Misconceptions about the use of inhalers may constitute a major obstacle in the

proper management, which result in adverse treatment outcomes and poor disease control. Concerns for patients include worries about addictive nature of inhaled medications, the misconception that they are stronger than medications in the tablet or parenteral form, fear of side effects and the belief that once started it can't be stopped for life time. Moreover, patients may also be less inclined to take medication to prevent or reduce risks rather than taking medication for immediate symptoms.[4]

Many patients are not aware that various drugs are available in the inhaled form and they do not know the difference between a reliever and a controller. This ignorance on controller medications is of great concern with regard to disease control. Studies shows that 64% of asthmatics in India believed that regular controller medications are not really needed and about half of the asthmatics had fears on the use of inhaled steroids.[7] This observation emphasizes the fact that all asthmatics need to be educated on the importance of using optimal doses of inhaled steroids for the adequate control of their condition. Many studies have shown that females were more reluctant in using inhalers owing to the social reasons and majority preferred to keep inhaler use a secret to avoid social stigma and prefer oral medications over inhalers if possible.[8]

Most of the patients do not know how to take an inhaler medication properly. The major factor leading to these errors is the lack of formal training on the proper usage of inhaled devices by trained personnel. A few believe that the particles in the dry powder inhaler can block the already narrowed air passages and cause lung damage.[9] Studies have shown that asthma education programmes focusing self management and behavioural modification improves inhaler device usage, adherence to proper treatment and thereby control.[10] These issues are compounded by physician related issues, such as poor rapport with patients. Most doctors/nurses/trainers themselves do not know how to demonstrate and educate patients in the proper use of their inhaler devices.[11] Studies have shown that depression and anxiety disorders, associated with airway disorders will have adverse impact on adherence.[12] In terms of symptom perception, many accept mild exacerbations as normal, or attribute them to other causes[13] and these events are associated with emergency visits and hospitalizations.

As children with asthma become adolescents, the barriers impeding good adherence begin to change. While younger children rely largely on parents for the administration of medication,[7] adolescence is the age during which children begin to claim more independence and responsibility, which may in turn affect adherence.[14] Their individual opinions and beliefs about their health, and self-regulatory behaviour can significantly affect adherence. In contrast, some adolescents still largely rely on their parents for management,[15] and so parental motivation may still remain important for adherence.

The intentional nonadherence is associated with other factors, such as not being bothered, being too time-consuming or conflicting with other activities, as well as a lack of perceived effect of medications.[16] Stigma around using inhalers can affect adherence at the levels of initiation, implementation or persistence.[4] For adolescents embarrassment in front of friends is a predominant reason for non-adherence, including a desire to hide their condition and treatment from their peers.[3] Addictive behaviours such as smoking and drinking alcohol can also have a significant negative impact on adherence.

**Problems of non adherence**

The major issues of non adherence to medications include decrease in disease control, poor symptom control, higher rates of exacerbations and reduced quality of life.[5,11] Studies have shown that significant number of hospitalization due to asthma and about one fourth of exacerbations are attributed to poor adherence to inhalers.[17] Non adherence to inhalers is a known risk factor of

asthma related mortality.[18] J Vestbo et al in their paper 'adherence to inhaled therapy, mortality and hospital admission in COPD' reported a strong association between adherence and mortality as well as risk of hospital admission due to an exacerbation in a three year long trial of inhaled medications in patients with moderate to severe COPD.[19] If non adherence remains undetected, the dose of medication may be increased or extra treatment may be prescribed unnecessarily in order to try to achieve disease control, thus further increasing the cost and complexity of the regimen.[20] Other consequences may include sleep disruption and a limited ability to do sports or recreational activities.[21]

**Addressing non adherence**

**Reassess the Inhaler Technique**

Poor inhaler instruction and technique represent a primary cause of medication nonadherence resulting in ineffective/ insufficient drug delivery to the airways and decreased medication efficacy. Improving understanding of the need for inhaled therapy and advice on optimal technique for using the inhaler device should increase patient adherence.[11] The ease of use and acceptance of the inhaler device is of paramount importance in achieving and maintaining adherence. If a patient does not like the inhaler device or is unable to use it correctly, no doubt it is useless. A preferred device that is taken by the patient and is effective represents a better device. Almost all inhaler devices like pMDI, DPI, breath actuated inhalers (BAI) can effectively be used by most patients and it is better to consider patient preferences while choosing the inhaler device unless there is solid reasons to pick the physicians choice. Inhaler technique, should be assessed at every visit and retraining and/or alternative treatment options to be considered where appropriate.[11,22] Some studies suggest that specific inhaler types may be associated with better adherence, although further investigation is needed to confirm this.[23] Many factors, including age, dexterity, inspiratory capacity, cognitive ability, health literacy and ethnicity, affect the ability and motivation of patients to use their inhaler devices, and it is most important that the inhaler device which is most appropriate to the patient is chosen to achieve good adherence. Adherence can also be affected by the choice of medications as well.

**Communication and Patient education**

The communication between patients, care takers and physicians to ensure understanding of the disease and its treatment will likely to enhance adherence. Clear and open patient physician communication that builds empathy and incorporates motivational interviewing techniques and shared decision making/treatment goals is vital.[24] This approach can address patient specific concerns, evaluate their beliefs, engage patients in the management of their disease, and ensure family members are able to support the patient. It is also important to ensure that regular follow-up appointments are arranged with the treating physician, with reminders and other organizational factors to help improve adherence.[24] Studies on Inhaler technique knowledge and skills before and after an educational program in obstructive airway disease patients showed that education may improve adherence irrespective of the type of device used, gender, age and low educational level of patients. [25]

**Other measures to enhance adherence**

Many methods of adherence monitoring are available, which include subjective monitoring tools such as physician assessment of adherence, or questionnaires like test of adherence to inhalers' (TAI). Objective monitoring strategies include analysis of prescriptions, weighing inhaler canisters, dose counters, directly observed therapy and nurse home visits.[26] Other approaches that may help to influence adherence among adolescents include peer support, medication reminders via smart phone applications and user-friendly online support systems with messaging

facilities.[27] These measures may help to identify patients with poor control despite good adherence who may be considered for escalation of inhaled medications or newer therapies.[28]

Considering the influence of socio demographic and cultural differences in the adherence of inhaled medications, studies in this regard in different populations and settings are very important. Unfortunately studies from India addressing this issue are very few. In this context the study from a tertiary care centre from Kerala by Sonia Santhakumar and Afsana Ibrahim Kamarunniza, which is published in this issue of Pulmon is laudable. In their cross-sectional observational study involving one hundred and eleven asthmatics aged between 10 to 50 years, they reported age below forty, female gender, poor education and poor economy were important factors influencing non adherence to inhalers. This is in comparable with many of the similar studies. The study will hopefully serve as a stimulus for young pulmonologists and researchers to initiate multicentre studies to address this vexing issue.

Medication adherence faces many challenges especially in chronic medical conditions. This is true for obstructive airway diseases too where inhaled medications, which are supposed to take regularly for longer periods are the preferred modality of treatment. Identifying the reasons for non adherence is essential to help improve disease control, outcome and patient quality of life.

**References**


1. World Health Organization. (2003). Adherence to long-term therapies : evidence for action / [edited by Eduardo Sabateì].World Health Organization.https://apps.who.int/iris/handle/10665/42682.
2. Vrijens B, Dima AL, Van Ganse E, et al. What we mean when we talk about adherence in respiratorymedicine. J Allergy Clin Immunol. 2016;4:802–812.

   doi:10.1016/j.jaip.2016.05.019
3. De Simoni A, Horne R, Fleming L, et al. What do adolescents with asthma really think about adherence to inhalers? Insights from a qualitative analysis of a UK online forum. BMJ Open. 2017;7: e015245. doi:10.1136/bmjopen-2016-015245
4. Naimi DR, Freedman TG, Ginsburg KR, et al. Adolescents and asthma: why bother with our meds? J Allergy Clin Immunol. 2009; 123:1335–1341. doi:10.1016/j.jaci.2009.02.022
5. Desai M, Oppenheimer JJ. Medication adherence in the asthmatic child and adolescent. Curr Allergy Asthma Rep. 2011;11:454–464. doi:10.1007/s11882-011-0227-2
6. Conner JB, Buck PO. Improving asthma management: The case for mandatory inclusion of dose counters on all rescue bronchodilators. J Asthma. 2013;50:658–663. doi:10.3109/02770903.2013.789056.
7. Salvi SS, Apte KK, Dhar R, et al. Asthma insights and management in India: lessons learnt from the Asia pacific - asthma insights and management (AP-AIM) study. Journal of the Association of Physician of India 2015; 63:36-41.
8. Gupta VK, Bahia JS, Maheshwari A, et al. To study the attitudes, beliefs and perceptions regard ing the Use of inhalers among patients of obstructive pulmonary diseases and in the general population in Punjab. Journal Of Clinical And Diagnostic Research 2011; 5(3):434-439.
9. Sulaiman SP, Panicker V. Attitudes of patients with asthma on inhaler use. A cross sectional study from south Kerala. J. Evid. Based Med. Healthc. 2017; 4(19), 0000 0000. DOI: 10.18410/jebmh/2017/1.
10. Takemura M, Kobayashi M, Kimura K, et al. Repeated instruction on inhalation technique improves adherence to the therapeutic regimen in asthma. J Asthma 2010; 47(2):202-208.

11. Braido F, Chrystyn H, Baiardini I, et al. "Trying, but failing" – the role of inhaler technique and mode of delivery in respiratory medication adherence. J Allergy Clin Immunol. 2016;4:823–832. doi:10.1016/j.jaip.2016.03.002

12. McCauley E, KatonW, Russo J, et al. Impact of anxiety and depression on functional impairment in adolescents with asthma.Gen Hosp Psychiatry. 2007;29:214–222. doi:10.1016/j.genhosppsych.2007.02.003

13. Yawn BP. The role of the primary care physician in helping adolescent and adult patients improve asthma control. Mayo Clin Proc. 2011;86:894–902. doi:10.4065/mcp.2011.0035

14. Costello RW, Foster JM, Grigg J, et al. The seven stages of man: the role of developmental stage on medication adherence in respiratory diseases. J Allergy Clin Immunol. 2016;4:813–820. doi:10.1016/j. jaip.2016.04.002

15. Blaakman SW, Cohen A, Fagnano M, et al. Asthma medication adherence among urban teens: a qualitative analysis of barriers, facilitators and experiences with school-based care. J Asthma. 2014;51:522–529. doi:10.3109/02770903.2014.885041

16. Edgecombe K, Latter S, Peters S, et al. Health experiences of adolescents with uncontrolled severe asthma. Arch Dis Child. 2010;95:985–991. doi:10.1136/adc.2009.171579

17. Barnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives.Respir Care 2015;60:455-68. https://doi.org/ 10.4187/respcare.03200

18. HDhruve . Management of asthma: Adherence, inhaler technique and self-management .Prac tice Nursing 2018, Vol 29, No 10.https://doi.org/10.12968/pnur.2018.29.10.465

19. J Vestbo, J A Anderson, P M A Calverley, et al. Adherence to inhaled therapy, mortality and hospital admission in .Thorax 2009;64:939–943. doi:10.1136/thx.2009.113662

20. Burgess S, Sly P, Devadason S. Adherence with preventive medication in childhood asthma. Pulm Med. 2011;2011:973849.doi:10.1155/2011/973849

21. Ahmad A, Sorensen K. Enabling and hindering factors influencing adherence to asthma treat ment among adolescents: a systematic literature review. J Asthma. 2016;53:862–878. doi:10.3109/02770903.2016.1155217

22. Kaplan A, Price D. Matching inhaler devices with patients: the role of the primary care physi cian. Can Respir J. 2018;2018:9473051. doi:10.1155/2018/9473051

23. Laube BL, Janssens HM, de Jongh FH, et al. What the pulmonary specialist should know about the new inhalation therapies. Eur Respir J. 2011;37:1308–1331. doi:10.1183/09031936.00166410

24. Plaza V, Fernández-Rodríguez C, Melero C, et al. Validation of the 'Test of the Adherence to Inhalers' (TAI) for asthma and COPD patients. J Aerosol Med Pulm Drug Deliv. 2016; 29:142–152. doi:10.1089/jamp.2015.1212

25. Vitacca M, et al. Inhaler technique knowledge and skills before and after an educational pro gram in obstructive respiratory disease patients: A real-life pilot study. Pulmonol. 2020. https://doi.org/10.1016/j.pulmoe.2020.04.0

26.. Pearce CJ, Fleming L. Adherence to medication in children and adolescents with asthma: meth ods for monitoring and intervention. Expert Rev Clin Immunol. 2018; 14:1–9. doi:10.1080/1744666X.2018.1532290

27. Koster ES, Philbert D, de Vries TW, et al. "I just forget to take it": asthma self-management needs and preferences in adolescents. J Asthma. 2015;52:831–837. doi:10.3109/02770903.2015.1020388

28. Panzera AD, Schneider TK, Martinasek MP, et al. Adolescent asthma self-management: patient and parent-caregiver perspectives on using social media to improve care. J School Health. 2013;83:921–930. doi:10.1111/josh.12111

# Manuscript writing standards and principles

**Kumari Indira KS**

Research and publication is a key factor for innovations and progress of science. The scope of medical research is huge. Health research has high values in improving the quality of patient care and improving health of society as a whole. Twenty first century has experienced tremendous advancement in medical care leading to improved longevity and quality of life through innovative methods in medical diagnostics and treatment. Advancements in the field of biotechnology and bioengineering has facilitated the introduction of faster and cheaper tools for diagnosis and treatment even for deadly diseases once considered to be incurable.

Publication is essentially meant for disseminating new information or new discoveries to the scientific world and society. Technological advancement has revolutionised the dissemination of medical information facilitating wide spread practice of evidence based medicine. With the introduction of electronic and open access publishing, the turnaround time for publication has considerably reduced and the opportunities for publication have gone very high.

Research and publication outputs from any Institution or individual are important indicators of performance quality and standards. Publications have direct and indirect impact in career development of medical professionals and in rating of Universities and Institutions. Globally, United States holds the highest position in number of annual scientific publications. Recently, China has made a giant leap superseding other nations to occupy the second position in the rating.[1] Given the abundance and diversity in health resources and clinical materials, India has a huge potential for research and publication. Moreover, the apex body for medical education in India mandates publications for career promotions and advancement. Citable publications from India has considerably increased over the past two decades and the country ranks ninth position in the quantum of publications. However the citation index of publications from India is far below the average.[1] Surge in publication can thus be attributed to compulsions for publication at the expense of quality. Reasons are highly may be varied. Majority of Universities and Institutions do not provide adequate funding and support (adequate facilities and infrastructure) for research or publication. Other commonly quoted barriers are lack of expertise and mentorship in research, lack of language proficiency and time constraints are the commonly quoted hindrances for publishing.[2] Introduction of open access system has enhanced the opportunity for publication; but one has to be extremely cautious before getting articles published in these journals. Most of the open access journal publishers charge authors for publishing the articles to compensate for providing free access without subscription. Pay and publish concept is good as long as review process is rigorous. However a good majority of these open access journals do not follow standard procedures of review process resulting in publication of irrelevant and poor quality articles.[3]

Inexperienced authors can get easily exploited by these predatory journals and one has to be wary when submitting papers in open access journals. This article is intended for guiding the budding authors on how to write an article in an attractive way and to overcome the hassles of publication.

**Why publish?**

Medical research is essentially meant for making a change existing practice thereby improving health of mankind. The message should be disseminated without delay to the public and scientific community through publication. The implied message is that all research should be original, innovative and relevant. Thus every research should be published be it yields positive or negative results or else the research is considered waste of resources.

In countries like India, most doctors are not motivated to take up the challenge of publication for various reasons discussed. Moreover they are generally overbur-

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dened and work in a highly stressful environment. Change in Institutional policy prioritising research and providing technical and financial support can bring about an attitudinal change among doctors.

Getting articles accepted and published requires lot of hard work and perseverance. The chances of rejection in first attempt are very high with indexed journals. However, if the authors make appropriate revisions or changes suggested by the reviewers, the article will get accepted during resubmission.

Even in settings where research is not mandatory, there are several special benefits through research and publication. It improves their acumen in clinical decision making and practice of ethical and evidence based medical practice, a key factor for career advancement and reputation of the individual. So once the initial inhibition is overcome, many doctors take it with great passion the process of publication.

**Qualities required for writing an article**

The most important attribute favoring article writing is a positive attitude. All barriers can be overcome by an attitudinal change enabling favorable team work and milieu. Apart from subject knowledge, researchers should have good awareness on methodological and ethical aspects of research and publication.

**Get started**

Writing an article requires lot of thinking and planning. An article that is swiftly written upon available data is very likely to be rejected. Planning is required for two aspects. First is on the structure and contents of the article, second on the selection of suitable journal. Both are interrelated. Most authors start thinking about article writing after research is over. However the best time to plan writing is initially when we plan the study. No research is complete without publication and the message has to be new, relevant and factual. Otherwise, the article is likely to be rated low and rejected. So start thinking at the outset, how the given research objectives and methodology can be transformed to one befitting for publication within the scope. Preparing a structure of the manuscript from the very outset will enable one to consider revising the theme and methodology in such a way that the study suits with the expectation of the editors and reviewers. Even a minor change can potentially bring a major twist in the significance and acceptance of the study. Such a change can never be made after the study is completed.

Second is to choose a befitting journal, once the theme is finalised. It has to be a peer-reviewed indexed one, the scope of the journal matching with the subject of the study. It is possible to get the credentials of the journal from the web sites of the journal ranking platforms like SCImago Journal Rank (SJR) , Eigenfactor, JRank etc. One has to bear in mind that the rejection will be very high for highly rated journals and the authors should select the journal(s) in a balanced way.

Articles are scrutinized at two levels. At the editors' desk the article will be screened for general features like if it fits within the scope of the journal and abides with the author guidelines, plagiarism, novelty and relevance, length, language etc... If these general features are not satisfactory, the article will be rejected at this level itself without peer review. If the editor accepts the article, it will be sent for peer review. Reviewers will critically assess the entire content of the article right from title through references in an objective manner and submit the decision whether to accept, revise or reject. Other than methodology and other specific subject matters, poor writing style, too lengthy and disorganised text are some common reasons for non-acceptance of the article. Along with the recommendation, the reviewers provide a list of constructive suggestions to authors. If the authors make appropriate changes and revisions as advised and resubmit the article, the chance of acceptance is very high.

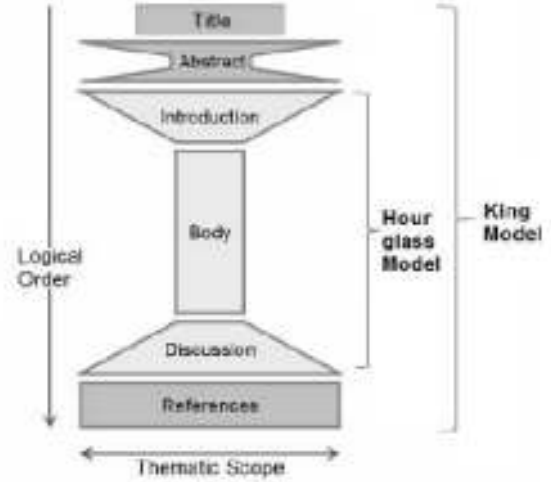
**Important Considerations for writing a manuscript**.[4]

1. Plan writing as you conceptualise and plan the study
2. Conceptualize a scientific work that is relevant and likely to get published
3. Choose the journal (and an alternative) from the very beginning
4. Familiarize with instructions to authors.
5. Coordinate task delegation among team members with time frame
6. Involve a biostatistician from the beginning of the study.
7. Prepare a skeletal framework of the manuscript (with dummy tables and pictures)
8. Delegate time for thinking and writing at regular intervals.
9. Circulate among co-authors and peers for advice editing and revisions

The structure of a manuscript depends on the type of study and should be prepared in accordance with the "guidelines for authors". The article should be presented in a clear, readable and logical order. Brevity adds to the beauty of the article. Most journals follow the simple format of IMRaD (Introduction, Methods, Results and Discussion) for scientific papers. This can aptly be described as an hour glass model in which the top (introduction) and bottom (discussion) sessions have broader base and tapers from either side to the body or methods and results section (fig: 1).[5]

The width of this structure indicates the sheer size of the concept and not per se the volume of the write up. Accordingly in the introduction, start describing the broader concepts of the topic and then narrow down gradually to state the specific research question after addressing the gaps in knowledge. The body of the article is the methodology, detailing how exactly the study was executed as it is without any extrapolations. Results of the study are to be described in the last part of the body. The discussion should start with the observed results of the study (narrow), which is gradually expanded out to describe the topic in a wider perspective and how the observations of the study can be translated to real world scenario (broad base). Discussion part ends with a message(s) derived from the study observations. Extended hour-glass model (King model) is more befitting as it also includes title, abstract and references (fig: 1).[5] Content writing under each subtitle will be briefly described below.

**Fig: 1 Structure of Scientific Paper**




The model depicts the logical order and thematic scope of a Manuscript. Light grey area representing Hour glass Model, while the modified 'King model' includes title, abstract and references.[5]

**Title**

Title should be attractive such that the readers should be prompted to read the rest of the manuscript. It should be brief and clear indicating the objectives and should include key words enabling search engines to identify the article. It can be aptly stated that title is a short sentence that adequately describes the content of the paper with fewest possible words.[5] Abbreviations should be avoided in the title excepting the ones that are universally accepted.

**Authorship**

Authorship adds to academic and professional credentials of an individual and has social and financial implications. As per International committee of Medical Journal Editors (CMJE) authors should have contributed substantially to the conception and design of the study, in acquisition of data and interpretation of the results. They should have actively contributed for drafting and editing the article and should have approved the version submitted for publication. In effect, all the authors are accountable for all the merits and demerits of the published work. The practice of including colleagues, seniors or reputed personalities as authors (honorary authorship) should be avoided if they have not contributed in the above mentioned processes. Their contributions are to be acknowledged in the article and not to be included as authors. Name of an author should not be purposely excluded (ghost author) for avoiding visibility in conflict of interest.[6]

**Abstract**

Abstract is the summary of the entire work either written as free text or in a structured format, the total word count is usually limited to 300.[7] Abstract is perhaps the most important section of the article. Title and abstract are the most read section of the article and should be prepared with extreme precautions. Title attracts one to read the abstract. Readers (editors, reviewers and subscribers) make a decision whether to proceed further based on the virtues of the matter provided in the abstract. Abstract should provide clear and specific message on why this study was done (Introduction), how it was done (methods), what was the observation (results) and its relevance (conclusion). Abstract should contain information on all important outcomes be it positive or negative and should not include anything that is not there in the text. There should be no citations in the abstract. Abstract is the last part in the writing sequence of the manuscript.

**Introduction**

Generally introduction should be less than 10–15% of the entire text.[8] The purpose of introduction is to provide basic information about the topic and to justify the conduct of the study. The information should be self sufficient such that readers need not have to refer to other publications for comprehending the problem. The section should start with a wider perspective describing the importance of the problem with respect to its clinical and epidemiological impact. This should lead on to describing the current area of interest, what is already known and summarising previous publications. Information thus presented should be supported with appropriate citations. The study should be justified by presenting the gaps and uncertainties about the topic and the implications on how the newly acquired information would benefit in tackling the problem more effectively. The last paragraph should briefly state the research question outlining how the study is appropriately planned.

**Materials and methods**

This session should contain a detailed description on how exactly the study was conducted. The description should be explicit such that there should be no ambiguity at any level and another researcher should be able to replicate the study, exactly the same way it was conducted by the present team. This section should contain detailing on the objectives, study design, subject recruitment (sample size, inclusion and exclusion criteria and sampling), variables, intervention, measurements (how, when and where), data entry and data analysis. There should be details on what steps were undertaken for ensuring unbiased recruitment process and accuracy (controlling bias and confounding) and reliability of measurements and analysis. All the steps undertaken should be indicative of its accuracy, reliability and appropriateness to the context. Newly applied tools (including questionnaires adopted from other sources) and equipments should be justified with validity and reliability testing. For specialised investigations like spirometry and lung diffusion studies etc. the specifications and brand of the machine and procedure followed should be briefly described. There should be details on how ethical issues were appropriately managed in the study, substantiated with documents. There should be disclosures on external funding and technical support received for the project.

**Results**

Data provided in the methods and results section should be presented in past tense. Results section should reflect materials and methods section. It should start with a brief description of subjects recruited (with numbers and details of included and excluded subjects). Inclusion of flow charts of subject recruitment (in standard reporting format) will add to the transparency and credibility of the study. Examples are the Consolidated Standards of Reporting Trials (CONSORT) for randomized controlled trials, Strengthening the Reporting of Observational studies in Epidemiology (STROBE) for observational studies, and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for systematic reviews.

All the variables mentioned in methods section should be described in the results section, preferably in the same order it is mentioned there. First provide details of samples recruited with details of exclusion, followed by descriptive data of baseline and study variables and finally the analytical data. If there are more than one group, data on comparison between the groups should be presented, followed by simple and complex analysis in the same order. Description of results should be organized to convey central features first (like hypotheses and primary objective) followed by secondary, post hoc or less important aspects.

Results are to be summarised as text, tables and figures and there should not be any replication of data in the text except highlighting important points. The general mandate is to use the best form that is likely to be self explanatory, stand alone and occupying least space. Follow the format authorised by the journal or follow APA style providing appropriate legends and captions in tables and figures. Numerical values are to be presented with a maximum of one decimal place. Data presented as percentage should be accompanied by the actual value (e.g. 25%, n=200). For continuous data measures of variance like SD should follow the mean (e.g. FEV1 1.2 L, SD=230mL). Statistical inference tests should be provided with test values and confidence intervals apart from P values.

**Discussion**

It is the counterpart of introduction and the relevant matters stated there should be addressed in discussion. It is the bottom part of the hour glass. It starts with the narrow part recapitulating the study objectives and

brief summary of the results and ends in discussion and conclusions (wider perspective and extrapolations). Results should not be replicated as such, but important test values can be highlighted. This is to be followed by interpretation of results with reference to clinical context and statistical significance. Further discussion should start with statements of support or non-support for the original hypothesis of the study in light of the findings. This is followed by comments and explanations for deviations from expected results or earlier reports.

Describe the strengths and weakness of the study honestly highlighting the methodological limitations that could have compromised the precision of measurements and accuracy of the study results. All possible sources of bias or confounding (in sample size, subject recruitment, follow up, measurements and analysis) that affect the internal validly of the study should be listed and explained. There should be frank discussion about the limitations on the validity and generalisability of the study. There can be suggestions on proposed follow up of the study and outlook on further work. The conclusions on the study should be presented in a sentence or two based on the observations of the study and there should be no extrapolation based on assumptions or previous reports. Implications for policy decisions and scope of future research also have to be addressed.

**Rules of acronyms use**

Before adopting use of acronyms, one has to consider if it s really required. Acronyms can be used it is already an accepted standard (e.g. FEV1). It can be used if the term has to be used in the article repeatedly at least on three occasions and the term is too lengthy or difficult to spell. When using first time in the text, use the full version followed by the acronym in parenthesis. It is better to avoid acronyms in the title and abstract unless it is a standard one and unlikely to have a different meaning in other disciplines. Acronyms can be used in tables and figures, but they are to be defined in the table note or figure caption even if it is provided in the text.[9]

**References**

Any supportive information written in the article with a primary source elsewhere should be quoted with proper referencing. The references are to be listed at the end of the manuscript in the same order as it appears in the text and the index number should be provided at the end of sentence where the information is provided. Most journals would have an advisory on citation and the same format is to be followed. The common styles used are Vancouver, Harvard, APA, etc. and the details for referencing of different types of references are available in the respective web sites. Referencing is important to avoid plagiarism and allows one to acknowledge authors of their original idea or research work. A referencing tool such as EndNote™ may be used to store and organize the references.

**Acknowledgements:** People who have helped in various stages of the study should be acknowledged at the end of the article.

**Conflicts of Interest (COI):** In the event that the Institution, researchers or authors have conflicting links (likely to influence the outcome of the study) in the form of personal, commercial, political, academic or financial relationships can be considered as conflict of interest and should be notified.[4]

**General rules to be considered while writing.**

- Write for a specific journal
- Write while work is progress
- Text should follow an aesthetical and logical order
- Use short and clear sentences
- Be focused and concise
- Use past tense in materials and methods and results sections
- Avoid slangs and local nomenclatures
- Avoid using first person like 'I' and 'we'

**Summary**

Publication has a key role in improving clinical acumen and career advancement in all fields of medical profession. It requires lot of dedication and hard work for writing and getting articles published. Cumbersome writing process and fear of article rejection are the main factors why doctors keep aloof from publication. But if one follows strictly the author guidelines, the etiquette of publication, the important considerations (ten points provided in the beginning of the article) and the general rules for writing, the chances of rejection can be brought down to minimum. Comments given by the editors for making corrections or revision should be taken positively as the chance of accepting resubmitted articles is very high if the

modifications are made strictly in abidance to the given directions. With an attitude change, manuscript writing would definitely become a pleasant and gratifying job.

**References**


1. Scimago Institutions Rankings (SIR), SIR World orld Report 2012. [accessed on January 13, 2013]. Avail ablefrom:www.scimagoir.com/pdf/ sir_2012_world_report.pdf
2. Pujar, Shamprasad M *Predatory Open Access Journals Publishing: What, Why and How?*, 2017 . In National Conference on the Role of LIS Professionals in the Changing Academic Paradigm, Bangalore (India), 17-18 February 2018. [Conference paper]. http:// eprints.rclis.org/32032/ Accessed on October 22, 2020.
3. Padma R. Jirge. Preparing and Publishing a Scien tific Manuscript. J Hum Reprod Sci. 2017 Jan-Mar; 10(1): 3–9. doi: 10.4103/jhrs.JHRS_36_17: 10.4103/ jhrs.JHRS_36_17.
4. Michael Derntl. Basics of research paper writing and publishing. Int. J. Technology Enhanced Learning, Vol. 6, No. 2, 2014; 105-23.
5. Michael Derntl. Basics of research paper writing and publishing. Int. J. Technology Enhanced Learning, Vol. 6, No. 2, 2014; 105-23.
6. International Committee of Medical Journal Editors (ICMJE). Defining the Role of Authors and Contribu tors. http://www.icmje.org/recommendations/ browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html (Accessed No vember 4, 2020).
7. Tullu M. S. (2019). Writing the title and abstract for a research paper: Being concise, precise, and meticu lous is the key. *Saudi journal of anaesthesia*, *13*(Suppl 1), S12–S17. https://doi.org/10.4103/sja.SJA_685_18.
8. Cals JW, Kotz D. Effective writing and publishing scientific papers, part III: Introduction. J Clin Epidemiol 2013;66:702.
9. APA style. Definition of abbreviations. https:// apastyle.apa.org/style-grammar-guidelines/abbre viations/definition. Accessed on Nov 12, 2020.
10. Padma R. Jirge. Preparing and Publishing a Scien tific Manuscript. J Hum Reprod Sci. 2017 Jan-Mar; 10(1): 3–9. doi: 10.4103/jhrs.JHRS_36_17: 10.4103/

# Hypersensitivity pneumonitis (HP)- Global and Indian scenario

**Padma Sundaram**

**Abstract**

Pulmonologists face a challenge in the diagnosis of HP which has multiple clinical phenotypes. In all newly diagnosed interstitial lung disease, HP should always be considered. The current guidelines classify HP into two main criteria based on clinical, radiological and pathological subtypes. They are acute/inflammatory HP and chronic/fibrotic HP. Patients who have a positive exposure history with a typical/classical pattern on HRCT and with BAL lymphocytosis, a diagnosis with high confidence can be made. Additional histopathological sampling should be done after multidisciplinary discussion in patients when an alternative diagnosis cannot be established.

All efforts must be undertaken in patients of HP to identify the environmental inducers and eliminate the source to prevent and minimize exposure to the same and prevent the progression of the disease. Systemic corticosteroids still continue to remain the mainstay of treatment. Randomized clinical trials with existing and/new antifibrotic agents are required for effective management of patients with chronic HP. Lung transplantation offers some hope for patients with chronic progressive HP and patients should be evaluated early for the same

**Introduction**

HP is an inflammatory and/or fibrotic response occurring in the lung parenchyma and small airways. This disease occurs due to an immune-mediated reaction incited by an overt or occult inhaled antigen in prone individuals.[1] HP must always be considered in the differential diagnosis of all newly recognised interstitial lung disease (ILD) patients. It was first described as an occupational disease by Ramazzini. Many causative factors are being identified and the pathogenesis is better understood now. Currently, greater than 300 antigens are known to be involved. They are mostly proteins or glycoprotein's derived from fungal, bacterial or animal proteins but can also besmall molecular weight chemical compounds.

**Incidence and Prevalence**

The incidence and prevalence vary worldwide as there is a lack of internationally accepted uniform diagnostic criteria and due to different seasonal, geographical conditions and host factors. The incidence ranges from 0.3-0.9 per 100,000 individuals in western countries. HP accounts for 4-15 % of all ILD in EUROPEAN countries. The studies in high-risk occupations reported that the HP occurs 19 % in farmers on exposure to mouldy hay and 6-20% of individuals who are exposed to bird droppings. In India, different studies showed that it accounts for 2.4 to 10.7% of all ILD patients.[2]

The latest Indian ILD registry reported that HP was the common cause in new-onset ILD in 47% cases, the majority of these patients were diagnosed as HP with a high level of confidence. The causative factors were either to birds, cooling devices or visible moulds. The high incidence of HP in India as compared to other countries may in part be due to the use of prompted questionnaires focused on exposure history to offending environmental agents. This study raises a concern about a variety of environmental exposures particularly avian antigens and moulds from cooling devices that could induce HP.[3] Older studies from India have been single-centre and small, with HP making up only 6%–11% of ILD cases with the most common ILDs being idiopathic pulmonary fibrosis (IPF) or connective tissue interstitial lung disease (CTD-ILD).[4] A recent retrospective study from a single Indian centre diagnosed 10.7% of ILD patients with HP and 42% with sarcoidosis.[5] The recent Indian registry for ILD showed HP as the second most common ILD in India (24% of total ILD).[6] Majority of the patients were female (73.3%) and nonsmokers (90%) and were homemakers (56.7%) stressing the importance of indoor antigens also. In 88.3% of cases of HP, exposure to the offending agent could be identified and the majority of them were pigeon or avian drop-

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pings. Of these 8.3% of patients were misdiagnosed as pulmonary tuberculosis on the clinico-radiological basis.[7]

Even though the prevalence of HP is highest among older individuals it has also been reported in children and often misdiagnosed as Asthma. A recent series showed around 8 children misdiagnosed as asthma. The diagnosis was established by clinical criteria, skin testing chest radiology, precipitins in serum, pulmonary function studies and open lung biopsy.[8,9] Chronic HP due to Pigeon Breeders' Disease has been also described in a 12-year-old girl. Children are more likely to be affected when they share the same space with backyard poultry or pigeon breeding.[9]

**Aetiology**

Recurrent exposure to occult or overt environmental antigens which are called HP inducers can cause immune-mediated reactions in the genetically predisposed. Exposure could occur at the home, working environment or due to hobbies undertaken by an individual. As many as 300 antigens have been known to cause HP, an inducing agent may be unidentifiable and the search for the occult inducer may not be fruitful in 60% of cases.[10,11] Patients with well-defined HP without an identifiable HP inducer usually tend to have a chronic course and appear clinically similar to patients with IPF. Because the HP inducer(s) remains occult, the term "cryptogenic HP" is used for such patients.[12] Some known inducers include hay, cotton fibre, cheese processing, sugarcane factory dust. When genetically susceptible individuals ("first hit") are exposed to an inciting antigen ("second hit") they develop HP. Air pollution, viral infections and pesticide exposure are considered as HP inducers. [13]

**Clinical Presentation**

Cough, dyspnea are the most common presenting features while constitutional symptoms such as weight loss, flu-like symptoms and chest tightness with wheezing are less common. Physical examination reveals cyanosis, rales and mid inspiratory squeaks. [1]

**Classification**

HP or extrinsic allergic alveolitis (EAA) was classified as an acute, sub-acute or chronic disease based on exposure to antigens and host response. The acute form occurs after high levels of exposure and the symptoms develop within 4 to 8 hours in the form of high-grade fever, chills, muscle pains, fatigue and a dry cough. The sub-acute form is due to a relatively lower level of exposure and the symptoms are more insidious. Chronic HP results from prolonged low-level exposure to the antigens which lead to irreversible lung damage. Further, this is categorized as either chronic insidious or chronic recurrent HP. Chronic HP presentation is with cough, weight loss malaise, progressive dyspnea while fever is absent. Acute and sub-acute forms of the disease generally resolve, with further avoidance of exposure. Chronic HP is a potentially severe disease which can progress and cause irreversible fibrotic lung disease which tends to be debilitating.[14]

This classification is now outdated and Vasakova et al. recently proposed a classification for HP based on clinical and radiographic manifestations. [11] Two main categories are based on clinico radiologic and pathologic manifestation, (acute/inflammatory HP and chronic/fibrotic HP). Acute/inflammatory HP has a symptom duration usually less than 6-months, is often reversible and is characterized by classical radiologic and histopathologic patterns. The presence of fibrotic changes in high-resolution computed tomography (HRCT) images or lung tissue (biopsy) defines chronic fibrotic HP and reflects a prolonged or recurrent course of acute HP over several months, usually beyond 6 months. The cut-off period of 6 months is arbitrary which reflects that beyond this period, the disease evolves to become chronic in nature due to ongoing exposure and persistence of radiologic changes with or without treatment. Proposed clinical criteria stratifies patients into four diagnostic categories if no lung biopsy is available (1) confident clinical diagnosis of HP; (2) probable HP; (3) possible HP; and (4) HP unlikely.[11]

The majority of patients with HP in the ILD-India registry had symptoms for a few years before diagnosis, suggesting that many had low-level chronic antigen exposure which may have been not been identified.[3]

**Diagnosis**

A positive history to antigen exposure, temporal association of symptoms, high resolution computed tomography (HRCT) pattern of ground glass with mosaic attenuation and non-necrotizing granulomas on histopathology were the factors associated with HP. [15]

The 2020 guideline on HP for diagnosis emphasizes three primary domains

1. Identification of antigen exposure (i.e clinical history with or without a questionnaire, serum IgG

testing against potential antigens causing HP, and/or specific inhalation challenge )

2. Imaging pattern on HRCT
3. Bronchoalveolar lavage (BAL) finding of lymphocytosis / histopathological findings.[1]

Serum IgG testing for identifying potential antigens causing HP distinguished it from other ILDs with a sensitivity and specificity of 83% and 68%. A positive serum IgG result only indicates that the patient has likely been exposed to a potential cause of HP at some point and particularly when other diagnostic findings of HP are less certain.[1]

**Radiology**

The most common finding on HRCT chest is ground glass haziness (90%), mosaic attenuation (65%) and centrilobular nodules (55%). The recent guideline classifies HRCT patterns for HP as (typical, compatible, and indeterminate) as it used in the idiopathic pulmonary fibrosis (IPF) guidelines.

**The acute or non-fibrotic**

Typical HP pattern is characterized by centrilobular nodules, mosaic attenuation on an inspiratory scan and air trapping on an expiratory scan.

Compatible-with-HP pattern is demonstrated by uniform and subtle ground-glass opacity and cysts.

**The chronic fibrotic**

Typical HP pattern consists of coarse reticulation and minimal honeycombing in a random axial distribution, no zonal predominance along with small airway disease.

Compatible-with-HP pattern varies in the patterns and/or distribution of lung fibrosis (e.g., basal, subpleural predominance,upper lung zone predominance, central [or peribronchovascular] predominance, or fibrotic ground-glass attenuation with Or without small airway disease).

Indeterminate-for-HP pattern includes the usual interstitial pneumonia pattern, nonspecific interstitial pneumonia pattern, organizing pneumonia-like pattern.[1]

The presence of HRCT findings indicative of small airways disease is (at least one of the following: ill-defined centrilobular nodules, mosaic attenuation, air trapping) also called as the three-density pattern is compatible with HP while the absence of small airways disease, irrespective of the morphological pattern of radiological fibrosis, HRCT is indeterminate for fibrotic hypersensitivity pneumonitis.[16]

HRCT-based diagnosis of HP has a (88–92% accuracy and 44–61% sensitivity), the radiologic findings are often not specific, and other granulomatous and fibrosing ILDs with a predominantly upper lobe distribution need to be considered also. Traditionally, the overwhelming burden of tuberculosis during the last century has tended to dominate the respiratory landscape. The fact that tuberculosis can cause fibrosis that mimics some of the ILDs, especially sarcoidosis and HP, has also undoubtedly contributed to delayed and inaccurate diagnoses the other primary reason for the under-recognition of ILDs in India and the absence of good-quality HRCT scanning machines. The current number of CT scanners across the country stands at no more than 5,000, which, in a country the size of India, translates into around 4 CT scanners per million population. We still rely mainly on the major cities and tertiary level hospitals to diagnose conditions such as HP, ILD etc.

There is often substantial uncertainty in confirming diagnosis most between fibrotic HP and IPF.[17] As per the 2011 criteria for the diagnosis of idiopathic pulmonary fibrosis (IPF), patients with usual interstitial pneumonia (UIP) pattern on HRCT but a history of exposure to an antigen associated with HP were to be diagnosed with HP rather than IPF.[18] This is also demonstrated in a recent study, that 20/46 of patients diagnosed with IPF as per the 2011 guidelines were reclassified as HP after reevaluation was done with detailed exposure histories and review of available histopathology in a centre managing patients with HP.[18]

**Bronchoalveolar Lavage**

The proportion of lymphocytes in BAL fluid among patients with HP when compared with patients with IPF or sarcoidosis led to the conclusion that BAL fluid lymphocyte analysis can play an important role in distinguishing fibrotic HP from IPF and sarcoidosis and in distinguishing non-fibrotic HP from sarcoidosis.[1]

Although there can be confidence in the diagnosis of HP based on the clinical features, imaging and BAL data the definite HP diagnosis requires histopathologicconfirmation.[17] Typical histopathological diagnosis of non-fibrotic HP requires the presence of typical features which include

1) Cellular interstitial pneumonia accentuated around small airways ("bronchiolocentric") along with

2)A cellular chronic bronchiolitis

3) A distinctive pattern of granulomatous inflammation

4) No pathological features to suggest an alternative diagnosis.

Typical histopathological features of fibrotic HP include

1) Subpleural and centriacinar fibrosis, with or without bridging fibrosis that extends from subpleural to centriacinar regions, or with centriacinar fibrotic lesions.

2) May include features that overlap with a UIP pattern, including patchy collagen fibrosis, fibroblast foci, and associated subpleural-dominant honeycombing.

A comprehensive multidisciplinary diagnosis is important in diagnosing HP, particularly fibrotic HP; however, there remains substantial diagnostic disagreement across MDD teams due to the absence of standardized diagnostic criteria. [11]

For the patient who is unable or unwilling to be subjected to lung biopsy a diagnosis of "probable or possible HP" is made if strong clinical and radiologic evidence is available. The low rate of surgical lung biopsy is multifactorial and includes reluctant patients or physicians, patient comorbidities with high risk for complications and mortality. Moreover, surgical biopsies are not sought due to lack of availability of dedicated lung pathologists as well as the cost involved which hampers accurate subtyping of ILD.

HP is diagnosed with high confidence in patients in whom an exposure history is identified, who have a typical HP pattern on HRCT and have BAL lymphocytosis; such patients do not require additional testing. Patients with absent exposure history, atypical HRCT pattern Or no classical BAL results should undergo a multidisciplinary discussion (MDD) that includes an ILD expert, a chest radiologist, and if lung biopsies were performed at the time of BAL, a pathologist familiar with histopathological features of interstitial pneumonia and HP.

Additional histopathological sampling should be considered after the MDD in some patients with a high-confidence diagnosis, moderate-confidence diagnosis, or low-confidence diagnosis or in patients for whom an alternative diagnosis has not been established.

**Treatment**

Early diagnosis of HP is important as it may reverse the disease or if delayed can lead to irreversible lung damage, respiratory failure and even death. Overall, outcomes of patients with HP even those with chronic HP have better survival than in patients with IPF. In the chronic progressive group, the median survival is only 7 years (range, 4.4–14.5 years).

**Exposure Avoidance [11]**

The first intervention is immediate and complete avoidance of further exposure to the inducer, by eradicating it from the patient's environment, with the help of environmental/industrial hygienists. Patients must also be explained the importance of a domestic clean air environment.

**Pharmacological Treatment**

**Corticosteroids**

Currently, systemic corticosteroids are the mainstay of pharmacological treatment. Prednisolone starting at 0.5 mg/kg (ideal body weight) for a few days and slow tapering to the lowest possible dose over several months to a year or longer, have been used.

**Immune-modulating agents[20]**

In a retrospective study by Morisset and colleagues treatment with azathioprine and mycophenolate mofetil was associated with an improvement of gas transfer with reduction of prednisone dose and improving the treatment of chronic progressive HP.

**Antifibrotic treatment**

For patients with progressive fibrotic HP, especially with a UIP-like pattern, randomized, controlled trials with either nintedanib or pirfenidone are underway the results are awaited.

**Lung Transplantation [21]**

Patients with progressive disease who are oxygen-dependent should be considered and evaluated early for lung transplantation. They have excellent post-transplant medium-term survival and relative to IPF, a reduced risk for death.

**Future research**

BAL and peripheral blood biomarkers offer hope for future minimally invasive diagnosis and prediction of prognosis of HP. Molecular genetic analysis of BAL and lung tissue may reveal distinct patterns of expression profiles helping to distinguish HP, IPF and other

entities. Genetic risks need to be identified which will be helpful for diagnosis, counselling in career choices and lifestyle of family members of patients with HP. With the advent of precision medicine and genetic testing, HP can be potentially prevented by pre-emptive avoidance of exposures to known HP inducers especially in susceptible people who would otherwise manifest HP. Existing antifibrotic treatments for IPF and novel anti-inflammatory/fibrotic agents currently being tested in IPF need to be used also in randomized clinical trials for patients with CHP.

**References**


1 Ganesh Raghu, Martine Remy-Jardin, Christopher J. Ryerson et al Diagnosis of Hypersensitivity Pneu monitis in Adults. An Official ATS/JRS/ALAT Clini cal Practice Guideline. American Journal of Respira tory and Critical Care Medicine Volume 202 Num ber 3 | August 1 2020

https://www.atsjournals.org/ https://doi.org/ 10.1164/rccm.202005-2032ST

2 Kumar R. Spalgais, S, & Ranga, V. (2020). Hypersen sitivity pneumonitis: clinical, radiological and pathol ogical profile of 103 patients from North India. Monaldi Archives for Chest Disease, 90(3). https:// doi.org/10.4081/monaldi.2020.1307.

3 Singh Sheetu, Collins Bridget F, Sharma Bharat B et al Hypersensitivity pneumonitis: Clinical manifes tations – Prospective data from the interstitial lung disease-India registry. Lung India Year: 2019 | Vol ume: 36 | Issue Number: 6 | Page: 476-482

4 Sen T, Udwadia ZF. Retrospective study of intersti tial lung disease in a tertiary care centre in India. Indian J Chest Dis Allied Sci 2010; 52:207-11.

5 Kundu S, Mitra S, Ganguly J, Mukherjee S, Ray S, Mitra R. Spectrum of diffuse parenchymal lung dis eases with special reference to idiopathic pulmonary fibrosis and connective tissue disease: An Eastern India experience. Lung India 2014; 31:354-60.

6 Dhooria .S , Agarwal R, Sehgal IS, Prasad KT, Garg M, Bal A, et al. Spectrum of interstitial lung diseases at a tertiary center in a developing country: A study of 803 subjects. PLoS One 2018; 13:e0191938.

7 Sinha AK Hypersensitivity Pneumonitis in the North Indian population. European Respiratory Journal 2019 54: PA4737. https://doi.org/10.1183/13993003.congress-2019.PA4737

8 Chetty, A, Malviya, A.N. Hypersensitivity pneu monitis due to cotton dust in Indian children. Indian J Pediatr 51, 341–344 (1984). https://doi.org/10.1007/BF0275468mm

9 Wonashi R Tsanglao, Devki Nandan, Sudha Chandelia and Minakshi Bhardwaj. Chronic Hyper sensitivity Pneumonia due to Pigeon Breeders' Dis ease. Indian Pediatr 2017; 54:55-57

10 V.P. Kurup, M.C. Zacharisen, J.N. Fink Hypersensi tivity pneumonitis Indian J. Chest Dis. Allied Sci., 48 (2000), pp. 115-128

11 Vasakova M, Morell F, Walsh S, Leslie K, Raghu G. Hypersensitivity pneumonitis: Perspectives in diag nosis and management. Am J Respir Crit Care Med 2017; 196:680-9.

12 Hanak V, Golbin JM, Hartman TE Ryu Jh . Causes and presenting features in 85 consecutive patients with hypersensitivity pneumonitis. Mayo Clin Proc 2007 ;82:812-6.

13 Singh, Sheetu et al. "Hypersensitivity pneumonitis and its correlation with ambient air pollution in ur ban India." The European respiratory journal vol. 53, 2 1801563. 31 Jan. 2019, doi:10.1183/ 13993003.01563-2018

14 Chopra V, Joshi JL, Mrigpuri P - Pigeon fancier's lung – An under-diagnosed cause of severely debili tating and chronic breathlessness. Egyptian Journal of Chest Diseases and Tuberculosis, Volume 66, Is sue 3, July 2017, Pages 557-559 https://doi.org/ 10.1016/j.ejcdt.2016.08.002

15 Morisset J, Johannson KA, Jones KD, Wolters PJ, Col lard HR, Walsh SLF, et al. Identification of diagnos tic criteria for chronic hypersensitivity pneumoni tis: An international modified Delphi survey. Am J Respir Crit Care Med 2018;197:1036-44.

16 Vasilios Tzilas, Argyris Tzouvelekis. Demosthenes Bouros Hypersensitivity pneumonitis: the first di agnostic guidelines. https://www.thelancet.com/ journals/lanres/issue/vol8no10/PIIS2213-2600(20)X0010-5Published:August 11, 2020 DOI:https://doi.org/10.1016/S2213-2600(20)30359-3

17 Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM,

Flaherty KR, Martinez FJ, Nathan SD, Wells AU, Collard HR, et al.; ARTEMIS-IPF Investigators. Treat ment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann In tern Med 2013; 158: 641–649.

18 Morel F, Villar A, Montero MÁ, Muñoz X, Colby TV, Pipavath S, et al. Chronic hypersensitivity pneu monitis in patients diagnosed with idiopathic pul monary fibrosis: A prospective case-cohort study. Lancet Respir Med 2013; 1:685-94.

19 Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: Idiopathic pulmonary fibrosis: Evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011; 183:788-824

20. Morisset J, Johannson KA, Vittinghoff E, Aravena C, Elicker BM, Jones KD, Fell CD, Manganas H, Dubé BP, Wolters PJ, et al. Use of mycophenolate mofetil or azathioprine for the management of chronic hy persensitivity pneumonitis. Chest 2017;151:619–625.

21 Kern RM, Singer JP, Koth L, Mooney J, Golden J, Hays S, Greenland J, Wolters P, Ghio E, Jones KD, et al. Lung transplantation for hypersensitivity pneu monitis. Chest 2015;147:1558–1565.

Original article

# Utility of needle core specimen in improving the diagnostic yield of EBUS TBNA

**Sujith Varghese Abraham[1], Ameer K.A[2], P. Arjun[3], Vinod Kumar Kesavan[4]**

ABSTRACT

OBJECTIVES

EBUS-TBNA has become a highly sensitive, minimally invasive, outpatient procedure for the assessment of mediastinal adenopathy. The standard cytological analysis is the preferred modality for diagnosis from EBUS-TBNA and diagnostic value of needle core specimen is less studied. The current study fills the gap by comparing utility of EBUS needle-core specimen histology to EBUS FNA cytology.

METHODS

196 patients who underwent EBUS-TBNA between January 2017 and March 2020 in a single centre were included in the study. Diagnostic yields of two specimen-processing techniques, fixed slides (cytology) and needle core samples (histology) were compared.

RESULTS

The composite diagnostic index had found disease etiology in 176 of the 196 patients. EBUS cytology specimens were diagnostic in 125 cases (63.77%) and needle core specimen histology in 154 cases (78.57%). Combining both increased the yield to 166 (84.69%). Out of the total 186 in which both samples were available, the additional yield of histology samples over cytology samples was 19.351% whereas, that of cytology over histology was only 5.37%. Evaluation of needle core specimen histology is statistically significant over smear cytology in terms of sensitivity, specificity and diagnostic accuracy ($p<0.05$). Also, combined evaluation of cytology and histology improved the negative predictive value of the test than both considered separate ($p<0.05$).

CONCLUSION

Procuring needle core specimens for histological analysis improves the overall diagnostic yield of EBUS-TBNA than cytology alone. EBUS TBNA technique has yielded tissue samples adequate enough to perform molecular profiling for targeted therapies in lung cancer and microbiological investigations related to tuberculosis.

Keywords: Endobronchial ultrasound, Mediastinal adenopathy, EBUS needle core biopsy, Cytology

## INTRODUCTION

Bronchoscopic blind transbronchial needle aspiration (TBNA), mediastinoscopy, and open thoracotomy were the conventional methods to obtain tissue for diagnosis of mediastinal adenopathy. Mediastinoscopy was the preferred technique for invasive mediastinal staging, providing definite tissue diagnosis with 100% specificity and almost 80% sensitivity [1]. However, it is limited by invasiveness of the procedure, requirement of general anaesthesia, and comparatively higher cost. Convex endobronchial ultrasound (EBUS) was introduced in 2003 and had rapidly emerged as a gold standard for mediastinal staging[2]. EBUS provides a sonographic view aiding in real-

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time visualization during TBNA of mediastinal and hilar lymph nodes and masses adjacent to the airways[3]. The utility of EBUS-TBNA has been extended to the diagnosis of sarcoidosis[4], tuberculosis [5], lymphoma [6] and metastasis from other solid tumors [7]. It helps in early and accurate diagnosis, and also reduces the cost burden on patients as it can be performed as an outpatient procedure under conscious sedation.

Specimen processing of EBUS-TBNA has multiple techniques[8]. Most centres rely upon the cytology from smear slides fixed in 95% alcohol and cell blocks prepared from paraffin-embedded haematoxylin and eosin-stained slides (often made from the centrifuged needle rinses) for diagnosis. EBUS-TBNA was introduced into clinical practice with the dedicated 22-gauge (G) fine needle for aspiration. Majority of the initial trials focussed only on the diagnostic yield of cytological specimens from smears [9]. Cytology material obtained by EBUS TBNA has been adequate to cell type both smallcell and non-small cell lung cancer [10]. Procuring specimens inside the EBUS-TBNA needle is not a routine practice in all centres. In the modern era of the individualized and targeted therapy, procuring adequate specimens for precise histological subtyping and for advanced analysis like detecting molecular alterations has become essential[11]. In addition, in benign lesions, substantial sample needs to be collected for molecular and microbiological studies. Finally, histologic core biopsies preserved in formalin can provide superior information to that obtained from cell blocks because they are often larger samples and architectural detail is maintained[8]. New advancements in EBUS-TBNA needles including procore needles and EBUS guided intra-nodal forceps biopsy (EBUS-IFB) have been introduced to procure core-biopsy for histologic evaluation and advanced studies[12,13]. However, the cost-effectiveness of such techniques in a resource-limited country like India is questionable.

The additional value of obtaining a core specimen (histology) in addition to a cytology specimen in the same setting with the EBUSTBNA 21/22gauge needle is not well studied. This study was intended to fill the lacuna by comparing the utility of linear EBUS needle core specimen analysis (histology) to cytology. This study aims at comparing various statistical parameters like sensitivity, specificity, positive and negative predictive values and diagnostic accuracy of cytological and histological specimens of linear probe EBUS-TBNA in overall diagnosis and among malignant versus non-malignant conditions.

## MATERIALS AND METHODS

Patients diagnosed with mediastinal or hilar lymphadenopathy who underwent EBUS-TBNA between January 2017 and March 2020, were included in this retrospective study. Computed tomography of the chest with contrast enhancement was routinely done initially in all patients. Those with enlarged hilar or mediastinal lymph nodes (nodes with a short-axis diameter greater than 10 mm) were selected for EBUS-TBNA procedure.

EBUS-TBNA procedure was performed using a linear curved-array ultrasonic bronchoscope BF TYPE UC180F (Olympus, Tokyo, Japan) and image processor EU ME2 processor (Olympus, Tokyo, Japan). The TBNA was performed by passing a 22- or 21-guage needle (ViziShot, Olympus, Tokyo, Japan). The needle with central stylet was passed through the working channel of the EBUS bronchoscope and then advanced through the airway wall, and into the lymph nodes under real-time ultrasound control. An integrated color–power Doppler ultrasound (Olympus, Tokyo, Japan) aids in preventing puncture of major vessels near to the lymph nodes. Minimum of three needle passes per lymph node was performed. The aspirate from lymph nodes were smeared onto glass slides for cytological examination. Dry smear was preserved for acid-fast bacilli microscopy. The stylet was used to expel the needle core sample into formalin for histological examination or into saline for AFB culture/ molecular studies like cartridge based nucleic acid amplification test (CBNAAT). No rapid onsite cytology was performed. The results were considered diagnostic if there was demonstration of malignancy, a defined benign entity (granulomas), or reactive/normal lymph nodes. Inadequate tissue sampling, pauci-cellular smears and inconclusive results after histological/cytological analysis were considered non-diagnostic.

### Statistical analysis

The final diagnosis obtained through a composite diagnostic index was considered the gold standard, to which each tissue processing method was compared. The composite diagnosis is obtained by clinical assessment, tissue analysis, other supportive investigations like mycobacterial culture, Immunohistochemistry and molecular tests, alternative investigations like mediastinoscopy/ Video assisted thoracoscopic surgery (VATS) in relevant cases and also considered response to treatment in certain conditions. And, if a new diagnosis is obtained during follow-up of inconclusive cases, those cases were cat-

egorized as false negatives. Diagnostic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated using standard definitions after data entry in MS Excel. Data were analyzed using the SPSS 16.0 (version for Windows) (IBM Corporation, New York, NY, USA) statistical software package. Categorical data were analyzed using the chi-square test. The continuous variable was compared with the t-test or ANOVA. Values of $p < 0.05$ were considered to indicate statistical significance.

**RESULTS**

One hundred and ninety-six patients were included in the study, in which 122(62.24%) were males and 74 (37.75%) were females. The mean age of the patients was 53.29± 14.40 years. Out of the total 336 lymph nodes that were sampled, the subcarinal (station 7) was most commonly involved as well as the one frequently subjected to aspiration, followed by right paratracheal (station 4R). The indications for performing EBUS-TBNA were suspected lung cancer (58%), where primary diagnosis was needed (some together with staging), suspected sarcoidosis/tuberculosis (30%) and mediastinal lymphadenopathy of unknown origin (12%).

The composite diagnostic index had found disease etiology in 176 of the 196 patients. EBUS cytology specimens had a diagnostic yield in 125 cases (63.77%) and needle core specimen histology was diagnostic in 154 cases (78.57%). The EBUS TBNA was diagnostic in 166 (84.69%) cases when both smear cytology and needle core specimen histology was combined. Various conditions diagnosed by combined evaluation of histological and cytological specimens from EBUS- TBNA is shown in table 1.

EBUS TBNA yielded inadequate needle core specimens for tissue analysis in 4 cases (2.04%) and cytology smears were pauci-cellular in 6 cases (3.10%). Both cytology and histology specimens were available adequately in 186 cases. Combined evaluation was diagnostic in 158 of the 186 cases (84.94%). Of the 186 cases, histology was diagnostic in 149 cases. In the 149 patients, cytology was positive in 113 cases. Therefore, out of the total 186, additional yield of histology samples over cytology samples was 36 (19.351%). Similarly, cytology was diagnostic in 124 of 186 patients, and of these, histology was diagnostic in 114 patients. Therefore, out of the 186, additional yield of cytology over histology was 10 (5.37%). Both cytology and histology were non-diagnostic in 27 of the 186 (14.51%) patients. The overall diagnostic yield of EBUS needle core histology over smear cytology was statistically significant ($p<0.05$). Considering that composite diagnosis is gold standard, the statistical parameters of cytology, histology and combined evaluation of EBUS-TBNA was calculated as shown in Table 2.

Table 1

| | Number | Percentage |
|---|---|---|
| **Malignant Conditions** | **76** | **45.78%** |
| Adenocarcinoma | 34 | 20.48% |
| Squamous cell carcinoma | 24 | 14.46% |
| Neuro endocrine tumour | 10 | 6.02% |
| Undifferentiated malignancy | 4 | 2.41% |
| Lymphoma | 1 | 0.60% |
| Metastasis from non-pulmonary sites | 3 | 1.81% |
| **Benign Conditions** | **90** | **54.21%** |
| Sarcoidosis | 54 | 32.53% |
| Tuberculosis | 20 | 12.05% |
| Reactive lymph nodes | 16 | 9.64% |

TABLE 2- Statistical parameters of cytology, histology and combined evaluation in overall diagnosis (PPV – positive predictive value, NPV- negative predictive value, CI- confidence interval)

| Parameter | Cytology | Histology | Combined |
|---|---|---|---|
| Sensitivity | 71.02% (95% CI: 63.72%-77.60%) | 87.50% (95% CI: 81.69%–92.00%) | 94.32% (95% CI: 89.80%–97.24%) |
| Specificity | 70% (95% CI: 45.72%–88.11%) | 90.00% (95% CI: 68.30%–98.77%) | 100% (95% CI: 83.16%–100%) |
| PPV | 95.42% (95% CI: 91.38%–97.62%) | 98.72% (95% CI: 95.38%–99.65%) | 100% |
| NPV | 21.54% (95% CI: 15.96%–28.41%) | 45.00% (95% CI: 35.02%-55.39%) | 66.67% (95% CI: 52.28%–78.50%) |
| Accuracy | 70.92% (95% CI: 64.02%-77.17%) | 87.76% (95% CI: 82.33%-91.99%) | 94.90% (95% CI: 90.82%-97.53%) |

Evaluation of needle core specimen histology is statistically significant over smear cytology in terms of sensitivity, specificity and diagnostic accuracy ($p<0.05$). Also, the combined evaluation of cytology and histology improved the negative predictive value of the test than both considered separate ($p<0.05$).

Out of the 166 patients in whom the diagnosis was obtained by EBUS, 90 (54.21%) were diagnosed to have non-malignant conditions and 76 (45.78%) had benign conditions.

**EBUS -TBNA in the diagnosis of malignant conditions**

82 patients were found to have malignant etiology by composite analysis. EBUS-TBNA missed malignant diagnosis in 6 of the 82 patients (7.32%). Out of 76 patients with malignancy diagnosed by EBUS, cytology was diagnostic in 62 cases (81.57%) and histology in 70 cases (92.10%). Adenocarcinoma of lung origin (34 – 44.73%) was the most common diagnosis among malignant conditions (n=76), with squamous cell carcinoma of the lung (24 – 31.57%) closely following it.

TABLE 3- Statistical parameters of cytology, histology and combined evaluation in malignant conditions (PPV – positive predictive value, NPV- negative predictive value, CI- confidence interval)

| Parameter | Cytology | Histology | Combined |
|---|---|---|---|
| Sensitivity | 75.61% (95% CI: 64.88%-84.42%) | 85.37% (95% CI: 75.83%-92.20%) | 92.68% (95% CI: 84.75%-97.27%) |
| Specificity | 99.12% (95% CI: 95.21%-99.98%) | 98.25% (95% CI: 93.81%-99.79%) | 100% (95% CI: 96.82%-100%) |
| PPV | 98.41% (95% CI: 89.77%-99.77%) | 97.22% (95% CI: 89.83%-99.28%) | 100% |
| NPV | 84.96% (95% CI: 79.42%-89.22%) | 90.32% (95% CI: 84.69%-94.03%) | 95.00% (95% CI: 89.79%-97.62%) |
| Accuracy | 89.29% (95% CI: 84.09%-93.24%) | 92.86% (95% CI: 88.31%-96.04%) | 96.94% (95% CI: 93.46%-98.87%) |

The statistical parameters of cytology, histology, and combined evaluation in malignant conditions is given in table 3.

Sensitivity and diagnostic accuracy of histology specimens were higher than cytology in malignant cases. Though cytology had slightly better specificity and positive predictive value compared to histology, the combination of histology with cytology was superior in diagnosis compared to cytology evaluated separately ($p<0.05$).

The needle core specimen obtained from the EBUS TBNA needle aided in a specific diagnosis in many cases. 18 malignant cases were reported as atypical cells suggestive of malignancy by cytological analysis. Histology of needle core specimen yielded specific diagnosis in 16 of them by better visualization of histologic patterns in larger specimens.

Needle-core specimens had an added advantage by aiding in a specific diagnosis in 44 cases by immunohistochemistry (IHC). 28 were positive for IHC markers of adenocarcinoma, 13 were positive for squamous cell carcinoma and 3 positives for neuroendocrine tumor markers.

Molecular testing is currently used primarily for non-small cell carcinoma, particularly for advanced disease requiring targeted chemotherapy. EBUS yielded adequate needle core tissue for molecular testing in 34 patients -6 patients had epidermal growth factor receptor (EGFR-TK) positive, one each for anaplastic lymphoma kinase (ALK), ROS-1 proto onco gene and programmed death ligand-1 (PDL-1) positive thereby aiding in targeted chemotherapy.

**EBUS-TBNA in diagnosis of benign conditions**

Out of the 196 patients, composite diagnosis yielded benign pathology in 94 cases. EBUS diagnosed 90 of these 94 patients. Out of the 90 patients with benign etiology, cytology was diagnostic in 63 cases (70%) and histology in 84 (93.33%). Sarcoidosis (54- 60%) was the most common condition diagnosed, with tuberculosis in 20 (22.23%) and reactive lymph nodes in 16 (17.78%). The statistical parameters of cytology, histology, and combined evaluation in benign conditions are given in table 4.

The diagnostic yield of histology was far higher than cytology in diagnosing benign conditions ($p<0.05$). Procuring needle core specimens for histology has definite advantages over cytology in terms of higher sensitivity, negative predictive value and accuracy ($p<0.05$). Combined evaluation is also better compared to cytology alone ($p<0.05$).

The diagnosis of sarcoidosis was made in 54 patients based on cyto-histological pattern of non-necrotizing granuloma with other supportive evidence like high angiotensin-converting enzyme (ACE) levels, negative tuberculin skin test, and clinical response to therapy. Acquiring needle core for histological analysis improved diagnosis of sarcoidosis since larger tissue was available. This better evaluation potentiated the differentiation of sarcoidosis from tuberculosis, which is significant in a tuberculosis endemic country like India.

Table 4- statistical parameters of cytology, histology and combined evaluation in benign conditions (PPV – positive predictive value, NPV- negative predictive value, CI- confidence interval)

| Parameter | Cytology | Histology | Combined |
|---|---|---|---|
| Sensitivity | 67.02% (95% CI: 56.56%–76.38%) | 89.36% (95% CI: 81.30%–94.78%) | 95.74% (95% CI: 86.48%–97.60%) |
| Specificity | 98.04% (95% CI: 93.10%–99.76%) | 100% (95% CI: 96.45%–100%) | 100% (95% CI: 96.45%–100%) |
| PPV | 96.92% (95% CI: 88.80% to 99.21%) | 100% | 100% |
| NPV | 76.34% (95% CI: 70.72%–81.16%) | 91.07% (95% CI: 85.02%–94.83%) | 96.23% (95% CI: 90.72%–98.52%) |
| Accuracy | 83.16% (95% CI: 77.18%–88.12%) | 94.90% (95% CI: 90.82%–97.53%) | 97.96% (95% CI: 94.86%-99.44%) |

Tuberculosis was diagnosed in 20 patients (22.23%) based on histology findings of necrotizing granuloma supported by other tests. The 21/22-gauge EBUS needle core specimens procured were larger enough to be subjected for tuberculosis liquid culture (AFB culture) and cartridge based nucleic acid amplification test (CBNAAT). The yield of supportive microbiological tests in EBUS specimens are shown in table 5.

Table 5- Yield of supportive microbiological test in EBUS specimens. (AFB: Acid fast bacilli, CB-NAAT: Cartridge based nucleic acid amplification test)

| Test | Specimens send | Specimens positive for tuberculosis | Percentage |
|---|---|---|---|
| Smear for AFB by Ziehl Neelsen staining | 16 | 4 | 25% |
| CB-NAAT | 15 | 4 | 26.67% |
| AFB culture | 14 | 3 | 21.42% |

EBUS TBNA was inconclusive in ten patients out of the 176 patients who had a final diagnosis by composite analysis. The diagnosis in these patients were facilitated by other diagnostic tests. 4 patients underwent mediastinoscopy and 2 had video-assisted thoracoscopic surgery done to diagnose their mediastinal pathology. Another 4 patients had biopsy from other sites. The final diagnosis in those patients was malignant in 6 and benign in 4, hence they were categorized into false-negative groups. Rest 20 patients are under regular follow-up and no new diagnoses were found in those patients. Hence, been categorised as true-negatives.

Histological and cytological reports were discordant in 8 patients. Histological diagnosis was at par with composite diagnosis in 6 of them, with cytological consistent with composite diagnosis only in 2 cases. This finding also signifies the value of histological specimens as relying on conventional cytology alone would have added more false-positive patients.

Among total of 196 patients who underwent the procedure, 186 (94.89%) were done as an out-patient procedure under conscious sedation and only one patient required general anesthesia. The procedures were not associated with any major complications. In a few cases, inadvertent and adrenaline.

**DISCUSSION**

The field of interventional pulmonology evolved when ultrasound was equipped into the bronchoscope. It served as a light into, a rather blind spot of the chest – mediastinum, which was otherwise explored blindly or referred to a surgeon for more invasive techniques. Since its introduction, the evidence has been mounting for superior performance of EBUS-TBNA in sampling mediastinal and hilar lymph nodes and has literally replaced the conventional blind TBNA technique and has drastically reduced the number of patients undergoing mediastinoscopy[14].

The diagnostic yield of EBUS-TBNA in diagnosing mediastinal adenopathy ranges between 74% to 93% from various studies published from India[15,16]. Madan K et.al published initial reports of EBUS-TBNA during 2012-2013 from north India which shows a yield of 74.5% and sensitivity of 81.7%. Another Indian study by Dhooria et.al showed a yield of 65.7% with new needle in EBUS-TBNA[17]. The current study which utilizes histology specimens along with cytology had an overall better diagnostic yield and sensitivity. The overall negative predictive value is also higher compared to prior studies[18].

There is greater preponderance for non-malignant disorders especially granulomatous lymphadenitis (74 patients)

in this series, which is consistent with other studies in a tuberculosis samples obtained by same EBUS-TBNA 21-guage needle. The overall sensitivity and specificity were 89% and 100% with overall sensitivity of EBUS-TBNA-C (cytology) and EBUS-TBNA-H (histology) were 65% and 85%, respectively[18]. Though sensitivity, positive predictive value and negative predictive value were higher in current study, specificity is less than 100% for histology and cytology evaluated separately as there was discordance in 8 cases. The study by Vaidya et.al also highlighted the importance of a combined evaluation rather than cytology alone.

Both cytology and histology samples can be procured from 21- and 22- gauge EBUS-TBNA needles. Our study doesn't compare the efficacy between the two as prior studies do not show any differences between the two[22]. Other studies have shown better preservation of histological structure and increased number of cells within specimens from the 21-gauge needles especially for malignant diseases[24]. New advancements in tissue acquisition of EBUS are into the market including large gauge needles, pro-core needles and EBUS intranodal forceps biopsy (EBUS IFB). The diagnostic yield, accuracy and sensitivity reported in this study is comparable with published studies on EBUS forceps biopsies[25,26]. The utility of such procedure which need costlier needle and additional equipment like cautery, mini forceps, etc. increases financial burden of patients, making it less cost-effective, which is a considerable fact in a developing country like India. The current study is a relief in such aspect that we utilized the same TBNA needle which was primarily used to acquire cytological specimens, to procure core-specimens for histological analysis. And the tissue acquired through this FNAC needles, where larger enough for advanced studies including immune histochemistry, molecular and microbiological studies.

**Limitations of the study**

The current study was limited by a few factors owing to its retrospective aspect. Routine rapid onsite evaluation (ROSE) of cytological preparations were not done. Our center being a referral center would not reflect the disease prevalence in the general population.

**Conclusion**

Adding histologic analysis of tissue cores obtained by EBUS TBNA to cytology improved the overall diagnostic yield, sensitivity, specificity and accuracy than cytology alone. Combined evaluation of cytology and histology has improved the negative predictive value of the test than both considered separate. EBUS TBNA technique has yielded tissue samples from the needle, that were adequate to perform molecular profiling for targeted therapies in lung cancer and to perform various microbiological investigations related to tuberculosis.

**REFERENCES**


1. Detterbeck FC, Jantz MA, Wallace M, Vansteenkiste J, Silvestri GA, American College of Chest Physicians. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007 Sep;132(3 Suppl):202S-220S.
2. Yasufuku K, Chiyo M, Sekine Y, Chhajed PN, Shibuya K, Iizasa T, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspira tion of mediastinal and hilar lymph nodes. Chest. 2004 Jul;126(1):122–8.
3. Bolliger CT, editor. Clinical chest ultrasound: from the ICU to the bronchoscopy suite. Basel; New York: Karger; 2009. 221 p. (Progress in respiratory research).
4. Nakajima T, Yasufuku K, Kurosu K, Takiguchi Y, Fujiwara T, Chiyo M, et al. The role of EBUS-TBNA for the diagnosis of sarcoidosis—comparisons with other bronchoscopic diagnostic modalities. Respir Med. 2009 Dec;103(12):1796–800.
5. Geake J, Hammerschlag G, Nguyen P, Wallbridge P, Jenkin GA, Korman TM, et al. Utility of EBUS-TBNA for diagnosis of mediastinal tuberculous lymphadenitis: a multicentre Australian experi ence. J Thorac Dis. 2015 Mar;7(3):439–48.
6. Erer OF, Erol S, Anar C, Aydoðdu Z, Özkan SA. Diagnostic yield of EBUS-TBNA for lymphoma and review of the literature. Endosc Ultrasound. 2017 Oct;6(5):317–22.
7. Nakajima T, Yasufuku K, Fujiwara T, Chiyo M, Sekine Y, Shibuya K, et al. Endobronchial ultra sound-guided transbronchial needle aspiration for the diagnosis of intrapulmonary lesions. J Thorac Oncol. 2008 Sep;3(9):985–8.
8. Nakajima T, Yasufuku K. How I do it—optimal methodology for multidirectional analysis of endobronchial ultrasound-guided transbronchial needle aspiration samples. J Thorac Oncol. 2011 Jan;6(1):203–6.
9. Varela-Lema L, Fernández-Villar A, Ruano-Ravina

A. Effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration: a system atic review. Eur Respir J. 2009 May;33(5):1156–64.

10. Vaidya PJ, Kate AH, Yasufuku K, Chhajed PN. Endobronchial ultrasound-guided transbronchial needle aspiration in lung cancer diagnosis and staging. Expert Rev Respir Med. 2015 Feb;9(1):45–53.

11. Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guide line from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. J Thorac Oncol. 2013 Jul;8(7):823–59.

12. Dincer HE, Andrade R, Zamora F, Podgaetz E. A new needle on the block: Echo Tip ProCore endobronchial ultrasound needle. Med Devices (Auckl). 2016; 9:467–73.

13. Cheng G, Mahajan A, Oh S, Benzaquen S, Chen A. Endobronchial ultrasound-guided intranodal forceps biopsy (EBUS-IFB)-technical review. J Thorac Dis. 2019 Sep;11(9):4049–58.

14. Clementsen PF, Skov BG, Vilmann P, Krasnik M. Endobronchial ultrasound-guided biopsy per formed under optimal conditions in patients with known or suspected lung cancer may render mediastinoscopy unnecessary. J BronchologyIntervPulmonol. 2014 Jan;21(1):21–5.

15. Madan K, Mohan A, Ayub II, Jain D, Hadda V, Khilnani GC, et al. Initial experience with endo bronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from a tuberculosis endemic population. J BronchologyIntervPulmonol. 2014 Jul;21(3):208–14.

16. Herth FJF, Eberhardt R, Vilmann P, Krasnik M, Ernst A. Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. Thorax. 2006 Sep;61(9):795–8.

17. Dhooria S, Sehgal IS, Gupta N, Ram B, Aggarwal AN, Behera D, et al. Yield of new versus reused endobronchial ultrasound-guided transbronchial needle aspiration needles: A retrospective analysis of 500 patients. Lung India. 2016 Aug;33(4):367–71.

18. Vaidya PJ, Saha A, Kate AH, Pandey K, Chavhan VB, Leuppi JD, et al. Diagnostic value of core biopsy histology and cytology sampling of mediastinal lymph nodes using 21-gauge EBUS-TBNA needle. J Cancer Res Ther. 2016 Sep;12(3):1172–7.

19. Gahlot T, Parakh U, Verma K, Bhalotra B, Jain N. Endobronchial ultrasound-guided transbronchial needle aspiration in diagnosing mediastinal lymphadenopathy. Lung India. 2017 Jun;34(3):241–6.

20. Agarwal R, Srinivasan A, Aggarwal AN, Gupta D. Efficacy and safety of convex probe EBUS-TBNA in sarcoidosis: a systematic review and meta-analysis. Respir Med. 2012 Jun;106(6):883–92.

21. Toth JW, Zubelevitskiy K, Strow JA, Kaifi JT, Kunselman AR, Reed MF. Specimen processing techniques for endobronchial ultrasound-guided transbronchial needle aspiration. Ann Thorac Surg. 2013 Mar;95(3):976–81.

22. Þemaitis M, Musteikienë G, Miliauskas S, Pranys D, Sakalauskas R. Diagnostic Yield of Endobron chial Ultrasound-Guided Transbronchial Needle Aspiration Cytological Smears and Cell Blocks: A Single-Institution Experience. Medicina (Kaunas). 2018 Apr 18;54(2).

23. Yarmus LB, Akulian J, Lechtzin N, Yasin F, Kamdar B, Ernst A, et al. Comparison of 21-gauge and 22-gauge aspiration needle in endobronchial ultrasound-guided transbronchial needle aspiration: results of the American College of Chest Physicians Quality Improvement Registry, Education, and Evaluation Registry. Chest. 2013 Apr;143(4):1036–43.

24. Nakajima T, Yasufuku K, Takahashi R, Shingyoji M, Hirata T, Itami M, et al. Comparison of 21-gauge and 22-gauge aspiration needle during endobronchial ultrasound-guided transbronchial needle aspiration. Respirology. 2011 Jan;16(1):90–4.

25. Herth FJF, Schuler H, Gompelmann D, Kahn N, Gasparini S, Ernst A, et al. Endobronchial ultrasound-guided lymph node biopsy with transbronchial needle forceps: a pilot study. Eur Respir J. 2012 Feb;39(2):373–7.

26. Darwiche K, Freitag L, Nair A, Neumann C, Karpf-Wissel R, Welter S, et al. Evaluation of a novel endobron chial ultrasound-guided lymph node forceps in enlarged mediastinal lymph nodes. Respiration. 2013;86(3):229–36.

Original article

# Assessment of adherence to inhalers in asthmatics

**Sonia Santhakumar[1], Afsana Ibrahim Kamarunniza[2]**

**Abstract**

**Background**: Asthma is a chronic disorder which affects the quality of life and causes significant morbidity when uncontrolled. Good control of asthma has now become possible with the advent of preventive inhalers and well-established guidelines. But despite all this, a significant number of patients all over the world still has uncontrolled asthma. Suboptimal asthma control is largely due to poor adherence to inhalers and incorrect inhaler techniques. There are very few studies conducted in India to assess the adherence to inhalers using a validated and easily reproducible questionnaire which simultaneously assess adherence as well as psychometric factors associated with non-adherence.

**Materials and Methods**:In this cross-sectional observational single centre study conducted in a tertiary centre in Kerala,India we have assessed the level of adherence to inhalers among 111 patients attending Pulmonology outpatient department between November 2019 to January 2020 using a well-validated Test of adherence to inhalers (TAI) questionnaire.

**Results:**The result showed that good adherence to inhaler was seen only in 28.8%of patients, intermediate adherence in 27% and poor adherence in 45%.Overall, 67% of subjects were women,majority of subjects were older than 20yrs. of age and most of them had education of at least tenth standard and all were literate.

**Conclusion:**Adherence to inhalers is low among asthmatics.There was a significant relation between TAI score and asthma control test score (ACT).The pattern of adherence was mostly erratic and ignorant types and good inhaler technique were seen in only 22.5%

**Keywords**-Test of adherence to inhalers (TAI), Asthma control test score (ACT), Adherence

## Introduction

Good control of asthma is now possible with current guidelines and medications. Inhalers are readily available in both the private and government sectors for asthma control. Despite this, many patients come to our outpatient department with poor asthma control and exacerbations. Causes of exacerbations or poor control vary from poor adherence to ignorance, improper asthma medication, underdosing, phenotype, and lack of proper techniques of an inhaler. Adherence to inhaler has always been an important factor in obtaining asthma control. Many patients who believe they are regular with inhalers are not always adherent. Studies have shown that patients tend to over-report and at times under-report their inhaler use. Hence standard questionnaires[1,2,3]has been validated for assessing the adherence and to find out whether the pattern of non-adherence is deliberate,unwitting, or erratic and to take corrective action according to a pattern of adherence. Test of adherence [2] to inhaler (TAI) developed by Spanish researchers is a 12-point questionnaire with two main domains, the patient (items #1 to #10) and the health professional (items #11 and #12) domain is a well-validated and reliable questionnaire. The 10-items TAI was designed to identify non-adherent patients and to establish the non-adherence level, whereas the 12-items TAI was designed to guide clinically non-adherence patterns.

**Aims of study-**

1. Assessing the adherence of patients prescribed regular preventive inhaler using TAI questionnaire

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2.Assessing pattern of non-adherence in non-adherent patients

3. Assessing the correlation between ACT and TAI score

**Materials and methods**

Study design- This is a cross-sectional observational study in which data pertinent to TAI and ACT questionnaires were collected in a single visit.

**Study Population-**

All asthmatics attending the pulmonology outpatient department who has been on regular corticosteroid inhalers with or without long-acting bronchodilators for at least 3 months were studied regarding their adherence to inhalers using the TAI questionnaire. Patients were simultaneously assessed for their ACT scores. Patients were classified as adherent or non-adherent and patterns of non-adherence were assessed further. Correlation between ACT score and TAI score was also studied

**Inclusion criteria**

1. All asthmatics who have been on preventive inhalers for at least 3 months. All these patients were given instructions to use inhalers properly before starting treatment.

2. Age above 10 yrs. and below 50 yrs.

3. Diagnosis of asthma confirmed by history and spirometry in all patients and categorised accordingly

**Exclusion criteria**

1. Asthmatics not on preventive inhalers

2. Smokers

3. Other comorbid conditions like tuberculosis, bronchiectasis, heart diseases

4. Non-consenting

**Outcome measures**

Primary outcome- Assessment of adherence to asthma inhalers using TAI score

Secondary outcome- Correlation between ACT score and TAI score

Assess pattern and reason for non-adherence

**Data collection and assessment**

A face-to-face interview of each person was conducted. Patients were asked to answer questions 1 to 10 of the TAI questionnaire and their responses were recorded. They were asked to demonstrate their inhaler technique, as well as their knowledge regarding their dose and frequency of inhaler, was tested during the interview for recording the answers of questions 11 and 12. Patients who had not bought their device were asked to demonstrate their technique in a similar placebo device.

We have used the Standard English version of the TAI questionnaire used worldwide for our study to assess the adherence to inhalers. For questions 1 to 10, there are 5 responses, scoring 1 for the worst adherence and 5 for the best adherence. Patients with worst adherence will be given a minimum score of 10 and those with the bestadherence will have a maximum score of 50. A score of 50 will be classified as good adherence and scores between 49 to 46 will be graded as intermediate adherence and scores less than 45 will be graded as non-adherence. Questions 11 and 12 were scored by the interviewer according to the inhaler technique and knowledge. Patients with poor technique were scored 1 and those with good technique were scored 2. So, these questions had a minimum score of 2 and a maximum of 4. To further characterize the psychometric behaviour of patients regarding adherence the results were further classified as follows:

For questions 1to 5, those scoring less than 25 were classified as erratic nonadherence pattern

For questions 6 to 10 score, less than 25 were classified as having deliberate non-adherence pattern.

For questions 11 and 12 scores less than 4 were classified as having ignorant non-adherence pattern.

**Asthma control test (ACT score)**

Control of asthma in these patients was simultaneously assessed using the asthma control questionnaire and results were computed as follows. Scoreless than 19 were classified as poor control and scores above 19 were classified as well-controlled

**Statistical analysis**

Data were entered into a Microsoft excel sheet and were analysed using the Statistical Package for Social Sciences (SPSS) version 16. Descriptive statistics such as frequency, percentage, and mean were used. Univariate analysis was done using the chi-square test. Multivariate analysis was done using binary logistic regression to determine the associated factors with medication adherence.

A p-value of < 0.05 was taken as statistically significant.

**Results**

Of 111 patients recruited 67.6% were women, the median age was 35. All the patients were literate, and the majority had a formal education at least up to the tenth standard,72.1% lived in rural areas and 24.3% were employed.79.2% had been using inhalers for more than 1 year. Test for adherence to inhalers was assessed using an English version of the standard TAI questionnaire. Questions 1 to 10 were used to assess the level of adherence and it was found that out of 111 patients recruited 28.8%were non-adherent, 32% had intermediate adherence and 44.1% were non-adherent. Mean age ofpatients who were found to be adherents was 30.19 and that for non-adherents was 36.82

To get an insight into the type of non-adherence TAI questionnaire with 12 questions were used.Erratic pattern ofnonadherenceis due to lack of awareness of the disease and poor knowledge.This pattern was seen in 70% of participants stressing the need to educate the patients regarding their disease and need for inhaler use.Deliberate nonadherence was seen in about half of the subjects.Deliberate nonadherence was due to financial difficulties, fear of side effects, overconfidence in one's disease status etc.The ignorant pattern of nonadherence was seen in over 75% of participants. They either forget

Table 1 Sociodemographic profile

| | **Adherent** | | **Nonadherent** | |
|---|---|---|---|---|
| **Age group** | **Frequency (n=32)** | **Percentage** | **Frequency (n=79)** | **Percentage** |
| <40 years | 5 | 15.6 | 42 | 53.2 |
| >40 years | 27 | 84.4 | 37 | 46.8 |
| Gender | | | | |
| Male | 11 | 34.4 | 25 | 31.6 |
| Female | 21 | 65.6 | 54 | 68.4 |
| Residence | | | | |
| Rural | 11 | 34.4 | 69 | 87.3 |
| Urban | 21 | 65.6 | 10 | 12.7 |
| Occupation | | | | |
| Employed | 18 | 56.3 | 9 | 11.4 |
| Unemployed | 14 | 43.8 | 70 | 88.6 |
| Education | | | | |
| SSLC | 9 | 28.1 | 47 | 59.5 |
| Above SSLC | 23 | 71.9 | 32 | 40.5 |

Table 2- Level of adherence of patients using inhaler

| **Test of Adherence to Inhalers** | **Frequency** | **Percentage** |
|---|---|---|
| <=45 | 49 | 44.10 |
| 46-49 | 30 | 27.10 |
| 50 | 32 | 28.80 |
| Total | 111 | 100 |

Table 3-Pattern of Non-adherence

| TAI item 1-5 score | Frequency | Percentage |
|---|---|---|
| Erratic pattern (<25) | 78 | 70.30 |
| Non erratic (=25) | 33 | 29.70 |
| TAI item 6-10 score | | |
| Deliberate pattern (<25) | 57 | 51.40 |
| Non deliberate (=25) | 54 | 48.60 |
| TAI item 11-12 score | | |
| Ignorance pattern (<4) | 86 | 77.5 |
| Non ignorant (=4) | 25 | 22.5 |

Table 4 Association between test of adherence to inhalers and asthma control test

| ACT score | Test of Adherence to Inhalers | | | Total | Chi square test | p value |
|---|---|---|---|---|---|---|
| | <=45 | 46-49 | >50 | | | |
| Controlled (>19) | 11(16.4%) | 14(20.9%) | 42(62.7%) | 67(100%) | 15.964 | 0.001* |
| Not controlled (<19) | 22(50.0%) | 9(20.5%) | 13(29.5%) | 44(100%) | | |
| Total | 33(29.7%) | 23(20.7%) | 55(49.5%) | 111(100%) | | |

*p-value is calculated by chi-square test, p<0.05 considered as statistically significant.

Table 5-Univariate analysis

| Variables | TIA | | Chi square value | P value |
|---|---|---|---|---|
| **Age** | Adherence (50) | Non-Adherence(<50) | | |
| <40 years | 5(10.6%) | 42(89.4%) | 13.146 | 0.001* |
| >40 years | 27(42.2%) | 37(57.8%) | | |
| **Gender** | | | | |
| Male | 11(30.6%) | 25(69.4%) | 0.077 | 0.781 |
| Female | 21(28.0%) | 54(72.0%) | | |
| **Residence** | | | | |
| Rural | 11(13.8%) | 69(86.3%) | 31.744 | 0.001* |
| Urban | 21(67.7%) | 10(32.3%) | | |
| **Occupation** | | | | |
| Employed | 18(66.7%) | 9(33.3%) | 24.896 | 0.001* |
| Unemployed | 14(16.7%) | 70(83.3%) | | |
| **Education** | | | | |
| Below SSLC | 9(16.1%) | 47(83.9%) | 8.965 | 0.003* |
| Above SSLC | 23(41.8%) | 32(58.2%) | | |

*p value was calculated by using chi square test, p<0.05 considered as statistically significant.

Table 6: Logistic regression

| Variables | OR | 95% CI | | P value |
|---|---|---|---|---|
| | | Lower | Upper | |
| Age (<40) | 5.270 | 1.491 | 18.632 | 0.010* |
| Residence (Rural) | 6.088 | 1.866 | 19.861 | 0.003* |
| Occupation (Unemployed) | 7.404 | 2.066 | 26.534 | 0.002* |
| Education (Below SSLC) | 2.820 | 0.862 | 9.226 | 0.087 |

the dose or frequency and inhaler technique was suboptimal in most cases.There was a significant association between TAI and ACT which showed that adherent patients had better asthma control when compared to nonadherent patients.

Univariate analysis showed there was a significant association between age,education,place of residence and employment with adherence. Non-adherence was more common with age less than 40, rural residence,lower educationstatus and unemployment. Predictors for nonadherenceby logistic regression included age,occupation, and residence. Education though was an important factor influencing adherence it was not found to be a predictor of nonadherence in our study.

**Discussion**

There have been new insights regarding pathogenesis and treatment of asthma.The advent of inhaled medications especially inhaled corticosteroids has revolutionized the life of asthmatics all over the world. New treatments based on the genomics of patients are now available,but inhaled medications remain the cornerstone for treatment of asthma. Despite vast improvements in knowledge and medications in treating asthma, good control over the disease is seen in very few patients throughout the world[4,5]

As in all chronic disorders, adherence to inhalers in asthmatics is still a major problem. Adherence is defined by WHO asthe extent to which a person's behaviour corresponds with agreed recommendations from a health care provider.A review of literature comprising of 9 studies assessing the level of adherence by different methods showed that overall adherence to inhaler adherence was between 22-63%[6]. In the same review, 6studies were systematically assessed to find out adherence and asthma outcome and it was found that good adherence improves asthma-related outcomes including mortality and exacerbations[6].

Non-adherence to inhalers among asthmaticvaries from 30-70%[7]and at least 50% do not take controller medications as prescribed[8].Majorityof hospitalization due to asthma and about one-fourth ofexacerbations are attributed to poor adherence to inhalers[6]. Non-adherence to inhalers is a known risk factor of asthma-relatedmortality[9].Itwas further observed that poor adherence is common in adolescents, in whom it may be deliberate and in the elderly inwhom it may be nondeliberate. Convenient regimen and reduction in the number of inhalers may helpto improve adherence.[10]

There is no uniformly accepted tool for assessing adherence to inhalers.Subjective, objective, and biochemical monitoring have been used, but assessing adherence to inhalers remain a real challenge[11,12]. Subjective monitoring of adherence can be assessed by patient diaries or questionnaires, while objective monitoring using directly observed treatment and electronic monitoring[12] as well as biochemical monitoring can be done, but they are impractical especially in a crowded resource-limited setting. Though many questionnaires have been developed for this purpose TAI which was developed by Spanish researchers were used for this study because of its specificity[13,14,15]ease of use and its validity measured by many studies as a reliable tool for adherence

Type of adherence was subsequently studied using 12 item TAI questionnaire and the result showed the majority (77. %%) had either erratic or ignorant pattern of nonadherence again stressing the need for repeated patient education regarding disease and checking inhaler technique during each visit. This is again in coherence

with GINA 2020,which says about t80%of patients do not use their inhaler correctly.Erratic pattern adherence was seen in about 70%.The pattern of nonadherence helps us to find out and tackle the causeof nonadherence and develop ways to overcome it like educating the patients and attenders during each visit,help them with their anxiety over disease and to prescribe devices which suit the patient's financial ability while ensuring the ease of use of inhalers and taking into consideration patient satisfaction of the inhaler prescribed. Patients involvement in choosing inhalers and satisfaction towards inhalers go a long way in ensuring adherence[16,17]. But education alone though important was not enough to ensure good self-management ability in asthma according to Hilton *et al*[18]and we did not find education as a predictor of non-adherence in our study.

An asthma control test was conducted, and the majority (64.9%) had poor control. This finding is almost same in many other studies conducted worldwide[4,5,19,20].The significant association between TAI score and ACT score shows the need for ascertaining adherence to prescribed inhalers.Analysis of demographics in nonadherent patients showed that age below 40, poor education and poor economy were important factors influencing non-adherence to inhalers.A similar finding was seen in several studies on adherence among Indian Population[21,22,23]

However, we could not find any significant correlation between adherence and duration of inhaler use and adherence and level of asthma severity. A study conducted on adherence to inhaler among COPD patients showed non-adherent patients had a short duration of disease [24] while a study conducted among multiple sclerosis patients showed there is a significant association between duration of illness and adherence[25]. However, several studies on asthma point out that while being an important disease-related factor, duration of the disease cannot be considered as a significant factor in determining the adherence to inhalers[26,27]

Our main limitation in the study was the sample size when compared with Spanish study. Another limitation is that it is a single hospital study catering to mainly lower and middle-income group and results may vary when applied to the general population. When compared to similar studies on adherence we could not use an objective measurement of adherence using electronic monitoring and pill or puff counting because of economic and practical constraints

**Conclusion**

Our study was designed to find out the level of adherence among patients taking preventive inhalers for asthma as well as for identifying the reasons for non-adherence using TAI questionnaire. Good adherence to inhalers was seen only in 28.8% and good inhaler technique was seen in 22.5%.Assessing the reasons for nonadherenceare important as they help to guide the physician to take corrective steps to improve adherence and help the patients to attain better Asthma control. We found that age, employment status and area of residence may be predictors of non-adherence in our population.

**References**


1. Plaza V,Fernandez-Rodriguez C, Melero C, CosioG,Entrenas L, de Llano L *et al.* Validation of the 'Test of the Adherence to Inhalers' (TAI) for Asthma and COPD Patients. J Aerosol Med Pulm Drug Deliv 2016;29:142–52. https://doi.org/10.1089/jamp.2015.1212
2. Fernandez-Rodriguez C, Plaza V, Bustamante V, Calle M , Contreras F J, Giner J *et al* . Control of asthma, adherence to inhaled therapy and useful ness of the Test of Adherence to Inhalers (TAI). Results of the ASCONA study.European Respirat ory Journal 2017 ;50:PA534. https://doi.org/10.1183/1393003.congress-2017.pa534
3. Cohen JL, Mann DM, Wisnivesky JP, Home R, Leventhal H, Musumeci-szabo TJ, *et al.* Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the medication adherence report scale for asthma. Ann Allergy Asthma Immunol 2009;103:325–31.https://doi.org/10.1016/S1081-1206(10)60532-7
4. KF Rabe, PA Vermeire, JB Soriano, WC Maier. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study.EurRespir J. 2000;16:802-7.https://doi.org/10.1183/09031936.00.16580200
5. Lai CK, De Guia TS, Kim YY, Kuo SH, Mukhopadhyay A, Soriano JB*et al.* Asthma control in the Asia-Pacific region: the Asthma Insights and Reality in Asia-Pacific Study .J Allergy ClinImmunol 2003;111:263-8.https://doi.org/10.1067/mai.2003.30
6. Barnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives.Respir Care 2015;60:455-68**.** https://doi.org/ 10.4187/respcare.03200
7. Global Initiative for Asthma. Global strategy for asthma management and prevention.NIH publica tion no. 02-3659. 2002. National Institutes of

Health/National Heart, Lung, and Blood Institute.Availableat:http://www.ginasthma.com, Accessed 15th Jan 2005

8. Global strategy for asthma management and prevention,2020.Available from:https://ginasthma.org/gina-reports/ (2019), Accessed 3rd Nov 2019

9. HDhruve . Management of asthma: Adherence, inhaler technique and self-management .Practice Nursing 2018, Vol 29, No 10.https://doi.org/10.12968/pnur.2018.29.10.465

10. Mäkelä M, BackerV,Hedegaard M, Larsson K. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. Respiratory Medicine 2013;107:1481-90. https://doi.org/10.1016/j.rmed.2013.04.005

11. López-Campos JL, Quintana Gallego E, Carrasco Hernández L. Status of and strategies for improving adherence to COPD treatment. Int J Chron Obstruct Pulmon Dis. 2019;14:1503-15. https://doi.org/10.2147/COPD.S170848

12. Coutts JA, Gibson NA, Paton JY. Measuring compliance with inhaled medication in asthma. Arch Dis Child. 1992;67:33233. http://dx.doi.org/10.1136/adc.67.3.332

13. JardimJR,NascimentoOA.The Importance of Inhaler Adherence to Prevent COPD Exacerbations. *Med Sci (Basel)* 2019;7:54. https://doi.org/10.3390/medsci7040054

14. Khosravi S, RafieiF,Norozy M, KhanmohamadiHezave A, Ebrahimabadi M. Cross-Cultural Adaptation Of The Persian Version Of Test Of The Adherence To Inhalers (TAI). Patient Prefer Adherence 2019;13:1693–99. https://doi.org/10.2147/PPA.S222096

15 .Montes de Oca M, Menezes A, Wehrmeister FC, Lopez Varela MV, Casas A, Ugalde L *et al.* Adherence to inhaled therapies of COPD patients from seven Latin American countries: The LASSYC study. PLoS One. 2017;12:e0186777. https://doi.org/10.1371/journal.pone.0186777

16. Ngo Q, Phan DM, Vu GV, Dao N, Phan PT,ChuHT*etal*.Inhaler Technique and Adherence to Inhaled Medications among Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease in Vietnam. *Int. J. Environ. Res. Public Health* 2019;16:185. https://doi.org/10.3390/ijerph16020185

17. Gaude G. Factors Affecting Non-adherence in Bronchial Asthma and Impact of Health Education. Indian J Allergy Asthma Immunol 2011;25:1-8.

18. Hilton S, Sibbald B, Anderson HR, Freeling P. Controlled evaluation of the effects of patient education on asthma morbidity in general practice. Lancet 1986;8471:26-9. https://doi.org/10.1016/S0140-6736(86)91904-5

19. Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. BMC Pulm Med 2006;6:13. https://**doi**.org/10.1186/1471-2466-6-13.

20. Rau JL . Determinants of patient adherence to an aerosol regimen. Respir Care 2005;50:1346–56.http://rc.rcjournal.com/content/50/10/1346.abstract

21. Sinha R, Lahiry S, Ghosh S. Suboptimal compliance to aerosol therapy in pediatric asthma: A prospective cohort study from Eastern India. *Lung India* 2019;36:51218. https://doi.org/10.4103/lungindia.lungindia_343_18.

22. Mutha B, Kulkarni G, Dugad S, Borgaonkar S. Study of Aerosol Therapy Compliance in Bronchial Asthmatics. MVP Journal of Medical Sciences 2016;3:37-43http://dx.doi.org/10.18311/mvpjms/2016/ v3/i1/741

23. Gaude GS, Hattiholi J, Chaudhury A. Role of health education and self-action plan in improving the drug compliance in bronchial asthma. J family med prim care 2014;3:33-8

24. Mohsen S, Hanafy FZ, Fathy AA, El-Gilany AH. Nonadherence to treatment and quality of life among patients with chronic obstructive pulmonary disease. Lung India 2019;36:193–8. https://doi.org/10.4103/lungindia.lungindia_340_18

25. Devonshire V, Lapierre Y, Macdonell R, Ramo-Tello C, Patti F, Fontoura P *et al.* The Global Adherence Project (GAP): A multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis. Eur J Neurol 2011;18:69-https://doi.org/10.1111/j.1468-1331.2010.03110.x

26. Lacasse Y, Archibald H, Ernst P, Boulet LP. Patterns and determinants of compliance with inhaled steroids in adults with asthma. Can Respir J. 2005;12:211-7. https://doi.org/10.1155/2005/375454

27. Wells K, Pladevall M, Peterson EL, Campbell J, Wang M, Lanfear DE, et al. Raceethnic differences in factors associated with inhaled steroid adherence among adults with asthma. Am J RespirCrit Care Med. 2008;178(12):1194-201.https://doi.org/10.1164/rccm.200808-1233OC-

Original article

# Analysis of red cell distribution width in patients presented with interstitial lung disease

**Jiss Ann Francis[1], N.A. Arun[2], Rennis Davis[3], T.A. Ajith[4]**

**ABSTRACT**

**Background**: Redcell distribution width (RDW) is a prognostic tool of different clinical conditions and a powerful predictor of mortality in elder adults. Increased RDW values were related to underlying chronic inflammation including interstitial lung disease(ILD). RDW as a biomarker to assess the severity of disease in ILD patients was reported. This study was aimed to evaluatethe change in RDW in ILD patients in late stages of the disease.

**Methods:**A retrospective observational study was conducted among patients who died with ILD. Values of RDW during the later stages of disease (close to and 2 months beforedeath)werecollected from medical records. Variations of RDW in patients with or without smoking habits, occupational exposures, and types of ILD were also studied.Data were statistically analysed.

**Results:** Forty-two patients died with ILD included. The value of RDW at 2 months before death was 15.4 ±1.8, whereas the valueclose to death was 16.1 ±2.4(p=0.030). The change in RDW values during late stages of ILD is significant. There was no association between RDW value 2 months before death with smoking history(p=0.112) or occupation(p=0.119) or types of ILD(P=0.121). But 86% of people with the smoking history presented with abnormal RDW value (>14.5%) at the time of their first presentation itself.No variation in RDW was found among patients with history of smoking status, occupational exposures, or types of ILD

**Conclusion:** Increase in RDW was associated with later stages of ILD. Change in RDW value in later stages of can be used as a biomarker for poor survival.

**Keywords:**Erythropoiesis, interstitial lung disease, prognosis, pneumonia, red cell distribution width

## Introduction

The interstitial lung diseases (ILD) are a heterogeneous group of diffuse parenchymal lung disorders eventually resulting in respiratory failure.[1]The diseases are grouped together because of common clinical, roentgenographic,physiologic and pathologic features.[1-4] Most of the patients present with insidious breathlessness and have a diffuse infiltrative pattern on chest roentgenogram.[5] The interstitial diseases are classically included in the restrictive lung disorders: vital capacity is reduced and respiratory flow rates are preserved.[1-3]These diffuse parenchymal lung diseases consist of disorders of known causes such as environmental or drug-related, collagen vascular disease and disorders resulting from unknown causes. ILD with unknown cause include granulomatous lung disorders (e.g. sarcoidosis), idiopathic interstitial pneumonia, Lymphangioleiomyomatosis, pulmonary Langerhans' cell histiocytosis/histiocytosis X and eosinophilic pneumonia.[4]The pathology of these diseases is characterized by inflammatory cellular infiltration and an apparent increase in the connective tissue of alveolar septae; while in some cases there will be inflammatory cells in alveolar airspaces.[5] Many of the interstitial diseases also have diseases of airways, pulmonary vasculature, and sometimes pleural diseases as well.[1,3,4.]

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Red blood cell distribution width (RDW) is a numerical measurement of the variability in the size of circulating erythrocytes.[6]It is a routine laboratory parameter that indicates the variability in the size of circulating erythrocytes. RDW has been used as a marker in the differential diagnosis of microcytic anaemia. It has been defined as a prognostic tool in different clinical settings such as pulmonary arterial hypertension, congestive heart failure and coronary heart disease.[7-9] It was reported in the general population and older adults that RDW can be used as a powerful predictor of mortality.[10,11] Increased RDW values have been reported to be related to underlying chronic inflammation.[12]Studies connecting the association of RDW with ILD is scant. Recently, Katyal et al. demonstrated that RDW can be used as a biomarker to identify the severity of the disease.[13]Hence,further population-based studies are warranted to establish its role as a biomarker in ILD. This study was aimed to evaluate the variation of RDW values during the later stages of disease among patients who died with ILD.

## MATERIALS AND METHODS

### Study design and procedure

A retrospectiveobservational study was conducted at the Department of Pulmonary Medicine, Amala Institute of Medical Sciences, Thrissur, Kerala, India. The study was started after receiving approval from the institutional research committee and ethical clearance. ILD was diagnosed by a combination of clinical presentation with physiologic testing, lung imaging using high resolution computed tomography of the chest and lung biopsy.All the patients who were diagnosed with ILD and died in the hospital between the time intervals of January 2014-October 2019 were included in the study. Hospital records of these patients were reviewed and data such as RDW values (before death), smoking status, occupation status and type of ILD were collected.Patients with incomplete records were excluded from the study.The value of RDW 2 months prior and close to death was collected and change in value was analysed. The reference value of RDW was taken as 11.5-14.5% which was considered normal and value> 14.5% was taken as abnormal.

### Statistical analysis

Data collected were entered into excel sheets and analysis was done by SPSS software version 23. Non-parametric data were subjected to Chi-square and Fisher's exact test, while the paired t-test was used for quantitative data analysis. pd"0.05 was considered as significant.

## RESULTS

Forty-two patients who died with ILD were included in the study. Among the total cases studied, 15/42 (35.7%) had a history of smoking (Figure 1), while 18/42 (42.9%) were exposed to dust from occupation (Table 1).Usual interstitial pneumonia (UIP) is found in 13/42 (30.9%) cases, while non-UIP was found in only 7/42 (16.7%) cases (Table 2). Among the total cases, abnormal RDW was found in 28/42 (66.7%)cases with 15/28 (53.5%)patients had nosmoking history and 13/28 (46.4%) hada smoking history (Table 3). Among the 15 patients with smoking history,13 (86%)were presented with abnormal RDW at the time of their first presentation itself. The distribution of RDW frequency among patients with and without smoking was found to be statistically significant (p=0.040). Frequency distribution of RDW among the 29/42 patients with known occupation risk (smoke or dust) is given in table 4. Among the total 29 cases, 20 (68.1%) cases had abnormal RDW. Distribution of type of ILD and RDW value 2 months before death is depicted in table 5. Majorities of cases belonging to non-UIP (57.1%) with normal RDW values whereas 10/13 (76.9%) UPI patients were presented with abnormal RDW values.

There was no statistically significant association found between either smoking history (p=0.112) or occupation(p=0.119) or types of ILD(p=0.121) with RDW variation 2 months prior to death. The overall value of RDW at 2 months before death was 15.4 ±1.8 and close to death was 16.1 ± 2.4 (Table 6). The change in RDW values among the total cases was statistically significant (p=0.030). However, among the various group, wise cases no statistically significant change in RDW was found between 2 months prior and close to death.This includescases with distribution based on smoking and non-smoking history (Table 7), occupation exposure to dust or occupation exposure to smoke (p>0.05) (Table 8), types of ILD (Table 9).

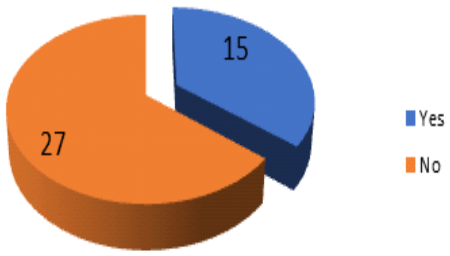

Table 1- Distribution of occupation of patients

| Occupation | Frequency | Percent |
|---|---|---|
| Exposure to dust | 18 | 42.9 |
| Exposure to occupational smoke | 11 | 26.1 |
| Not available | 13 | 31 |
| Total | 42 | 100 |

Table 2-Distribution of interstitial lung disease

| Type of ILD | Frequency | Percent |
|---|---|---|
| UIP(usual interstitial pneumonia) | 13 | 30.9 |
| Non UIP | 7 | 16.7 |
| Not available | 22 | 53.3 |
| total | 42 | 100 |

Table 3.Distribution of smoking status and RDW-CV value 2 months prior to death

| Smoking History | RDW-CV 2 months prior to death | | Total |
|---|---|---|---|
| | Normal value (11.5-14.5%) | Abnormal value >14.5% | |
| Yes | 2 (14.2 %) | 13(46.4%) | 15 |
| No | 12(85.7%) | 15(53.5%) | 27 |
| Total | 14(33.3%) | 28(66.7%) | 42 |

Chi square test p value =0.040

Table 4.Distribution of occupation and RDW value 2 monthsbefore death

| Occupation | RDW-CV 2 month | Prior to death | Total |
|---|---|---|---|
| | Normal value (11.5-14.5%) | Abnormal value >14.5% | |
| Exposure to dust | 5 (55.5%) | 13(65.0%) | 18 |
| Exposure to occupational smoke | 4 (44.4%) | 7 (35%) | 11 |
| Total | 9(31.1%) | 20(68.1%) | 29 |

Fishers exact test p value=0.628

Table 5.Distribution of type of ILD and RDW value 2 months prior to death

| Type of ILD | RDW-CV value 2 months prior to death | | Total |
|---|---|---|---|
| | Normal(11.5-14.5%) | Abnormal >14.5% | |
| UIP (usual interstitial pneumonia) | 3 (42.8%) | 10 (76.9%) | 13 |
| Non UIP | 4(57.1%) | 3(23.0%) | 7 |
| Total | 7 (35%) | 13 (65.0%) | 20 |

Fisher's exact test p-value =0.173

**Table 6 -**Value of RDW variation close to death and 2 months prior to death

| Time of detection of RDW | RDW value (%) | P value |
|---|---|---|
| RDW -CV value 2 month prior to death | 15.4 ±1.9 | 0.030 |
| RDW –CV value close to death | 16.1 ± 2.5 | |

Values are mean ± SD, n= 42

Table 7-Value of RDW variation close to death and 2 months prior to death in smokers

| Cases | Time of detection of RDW | RDW value (%) | P-value |
|---|---|---|---|
| Smokers (n=15) | RDW-CV value close to death | 16.7 ± 2.7 | 0.112 |
| | RDW-CV value 2 months prior to death | 15.8 ± 1.9 | |
| Non-smokers (n=27) | RDW-CV- value close to death | 15.8 ± 2.3 | 0.130 |
| | RDW –CV value 2 months prior to death | 15.1 ± 1.9 | |

Table 8-Value of RDW variation close to death and 2 months prior to death in people with exposure smokeand exposure to occupationalto dust

| Cases | Time of detection of RDW | RDW | P-value |
|---|---|---|---|
| Exposure to Occupational smoke (n=11) | RDW-CV-close to death | 15.9 ± 2.6 | 0.093 |
| | RDW -CV-2 month prior to death value | 15.2 ± 2.5 | |
| Exposure to Dust (n=18) | RDW-CV-close to death | 16.3 ± 2.5 | 0.119 |
| | RDW -CV-2 month prior to death value | 15.3 ± 1.7 | |

**Table 9-**Value of RDW variation close to death and 2 months prior to death in patients with non-UIP and UIP type of ILD

| Type of ILD | Time of detection of RDW | RDW | P-value |
|---|---|---|---|
| Non UIP (n=7) | RDW-CV- value close to death | 15.5 ± 2.1 | 0.428 |
| | RDW -CV- value 2 months prior to death | 14.9 ± 1.4 | |
| UIP (usual interstitial | RDW-CV- value close to death | 16.1± 2.3 | 0.121 |
| Pneumonia) (n=13) | RDW -CV- value 2 months prior to death | 15.3 ± 1.3 | |

**Discussion**

The present study explored the value of RDW in ILD for assessing prognosis.Forty-two patients died with ILD were studied. The value of RDW at 2 months before death was 15.4 ±1.8. The value of RDW close to death was 16.176 ±2.4643(p=0.030). Thus, the change in RDW values during later stages of ILD was found to besignificant. This may probably be due to the terminal ill condition of the patients. There was no association between either smoking history(p=0.112) or occupation(p=0.119) or types of ILD(p=0.121) with RDW. But it was observed that 86% of people with smoking presented with abnormal RDW value(>14.5%) at the time of their first presentation itself.

The most prevalent interstitial diseases are caused by occupational and environmental inhalants.[5]Of these the inorganic dust disease predominate.[5]The organic dust diseases (hypersensitivity pneumonitis) are caused by inhalation of foreign proteins or complex polysaccharides to which the person has been previously sensitized.[5]Nearly 30 clinical organic dust diseases have been defined by either antigen (aspergillosis) or specific environmental exposure (farmers lung).[1,3]. Most antigens are fungal spores, although bacterial animal proteins have been described, recently synthetic organic compounds have been implicated.[3] In this study, 29/42 patients had a history of occupational exposure to dust and smoke.

The ILD is characterized by inflammatory cellular infiltration and an apparent increase in connective tissue. The clinically significant chronic interstitial disease is most common in mixed connective tissue disorder, rheumatoid arthritis and progressive systemic sclerosis. In contrast, interstitial diseases are rare in polymyositis, systemic lupus erythematosis and Sjogren's syndrome.[5]Regardless of the aetiology, majority of the interstitial diseases have common pathogenesis.[1,3] Initially there is some type of injury to lung cells.[5]Many of the known agents are found directly toxic to alveolar or capillary endothelial cells.[5]Other agents cause injury tothe lung through the generation of free radicals in the inflammatory cells.Many of the interstitial diseases of unknown aetiology are associated with alterations in immune mechanism.[5]The organic dust and some drugs injure lung through immune mechanisms.[5]As a result of injury to lung cells, there is an influx of inflammatory and immune effector cells into alveolar septa resulting in alveolitis.[5]The alveolitis will become chronic and structural derangements will result.[1,3]The final common pathway for most interstitial diseases is the end-stage (honeycomb) lung.[5]Injury, alveolitis and repair coexist; fibrosis is a result of the inflammatory and reparative process.[1] Increased RDW can be due to the underlying chronic inflammation which promotes red blood cell membrane deformability and changes in erythropoiesis.[12]

A study conducted by Katyal et al. on RDW as a biomarker of disease severity in ILD patients in 24 patients with ILD were evaluated in whom baseline complete blood count was available.[13]The study demonstrated that CT score was found to be high in subjects with RDW value > 15 whereas cases with RDW >20 had dyspnoea score V. Furthermore, patients with normal RDW (<14%) values had a less CT and dyspnoea scoreswhen compared with those with RDW >15. Thus,RDW can be used as a biomarker to identify the severity of disease or pulmonary compromise in ILD patients.[13]In our study, patients who died withILD were showed significant variation in RDW at the end stages of their life.

A study conducted by Rahimirad et al. in patients with AECOPD in two referral teaching hospitals of East Azerbaijan and West Azerbaijan, Iran found that increased mortality among patients with higher RDW values even after applying the correction for thrombocytopenia, age, leukocyte count, mean corpuscular volume and

anaemia.[14] The study concludes that RDW on admission day found to be a useful indicator to predict in-hospital death in AECOPD.In our study, the patients who died of ILD showed an increase in RDW value close to death than 2 months before death.The prognostic value of RDW is also proved in patients with pulmonary embolism and heart failure.[6,15]Ozsu et al. demonstrated that an elevated RDW was associated with adverse outcomes of heart failure and pulmonary hypertension. The optimal cut-off value of RDW for predicting in-hospital mortality was >15%. The multivariable regression analysis showed RDW remained associated with an increased odd of death (odds ratio: 1.2, 95% CI: 1.1-1.4).

Limitations of the study: Small sample size due to a single centre study is the major limitation of the study. The variations in each type of ILD and demographic patterns need more sample size. Therefore, the study period and sample size need to be augmented for better results. Confounding parameters like co-morbid illness, family history, other blood values (Hb, WBC, Platelet Count etc.) were not included in the study.Furthermore, the dyspnoea indices and CT scoring need to be incorporated along with RDW variation to assess prognosis in ILD in the future.

**Conclusion**

Increase in RDW was associated with later stages of ILD. Change in RDW value can be used as a biomarker for poor survival in ILD patients. No variation in RDW found among patients with history of smoking status, occupational exposures,or types of ILD. RDW in smokers with ILD showed abnormal high values at the time of first presentation itself.

**References**


1. Talmadge E King Jr. Clinical advances in the diagnosis and therapy of the interstitial lung diseases.Am J Respir Crit Care Med. 2005;172(3):268-79.
2. Weinberger SE, Kelman A, Elson NA, Young RC, Reynolds, Fulmer JD, et al. Bronchoalveolar lavage in interstitial lung disease. Ann Intern Med. 1978; 89:459-66
3. Crystal RG, Gadek JE, Ferrans VJ, Fulmer JD, Line BR, Hunningbalce GW. Interstitial lung disease: current conceptsof pathogenesis, staging and therapy. Am J Med

   1981;70:54-67
4. ATS board of Directors and ERS executive committee. American thoracic society/European respiratory society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med.2002;165:277–304.
5. Fulmer JD.The interstitial lung diseases. Chest, 1982;2:172-178.
6. Salvatori M, Formiga F, Moreno-Gonzalez R,Chivite D,De Amicis MM, Cappellini MD, et al. Red blood cell distribution width as a prognostic factor of mortality in elderly patients firstly hospitalized due to heart failure.kardiologia polska.2019;77:632-638.
7. Hampole CV, Mehrotra AK, Thenappan T, Gomberg-Maitland M, Shah SJ.Usefulness of red cell distribution width as a prognostic marker in pulmonary hypertension. Am J Cardiol. 2009; 104:868-872
8. Allen LA, Felker GM, Mehra MR, Chiong JR, Dunlap SH, Ghali JK, *et al.*Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. J Card Fail. 2010;16(3):230-238.
9 Tonelli M, Sacks F, Arnold M, Moye L, Davis B, Pfeffer M. for the Cholesterol and Recurrent Events (CARE) Trial Investigators.Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. Circulation. 2008;117:163-168.
10. Perlstein TS, Weuve J, Pfeffer MA, BeckmanJA. Red blood cell distribution width and mortality risk in a community-based prospective cohort. Arch Intern Med. 2009;169:588-594.
11. Patel KV, Semba RD, Ferrucci L, Newman AB, Fried LP, Wallace RB, et al.Red cell distribution width and mortality in older adults: a meta-analysis. J GerontolABiol Sci Med Sci. 2010; 65:258-265.
12. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, GuidiGC.Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med. 2009;133:628-632.
13. Katyal R, Janmeja A, Ku V. Red cell distribution width (RDW) as a biomarker of disease severity in ILD patients. Eu Respir J.2015;46:PA3689.
14. Rahimirad S,Ghafari M,Ansarin K,Rashidi F,Rahimi-Rad MH. Elevated red blood cell distribution width predicts mortality in acute exacerbation of copd.Pneumolgia.2016; 65:85-89.

# Radiology Pearl

**Venugopal Panicker[1], Preethi Augustine[2], Shahina S[2], Arjun Suresh[3]**

A 19-year-old male who is a diagnosed case of obstructive uropathy with subsequent chronic renal failure on hemodialysis presented with progressive breathlessness for the last 3 months.On examination he had tachypnea and respiratory examination revealed bilateral basal crepitations. There was resting hypoxia and exercise desaturation.

His Xrays and CT (both HRCT and mediastinal window without contrast) pictures are given below.

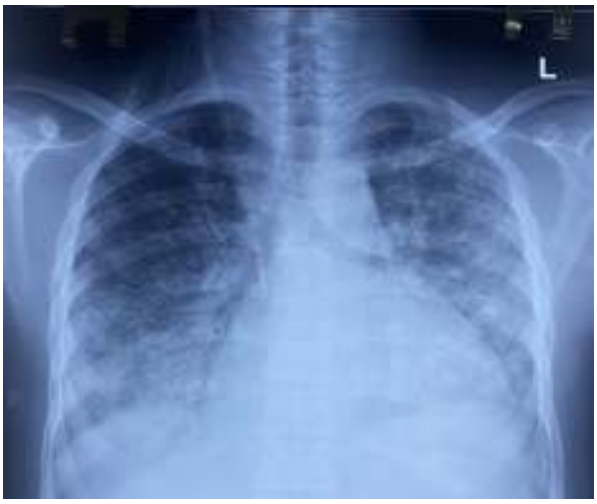


Fig 1: X-ray chest PA view

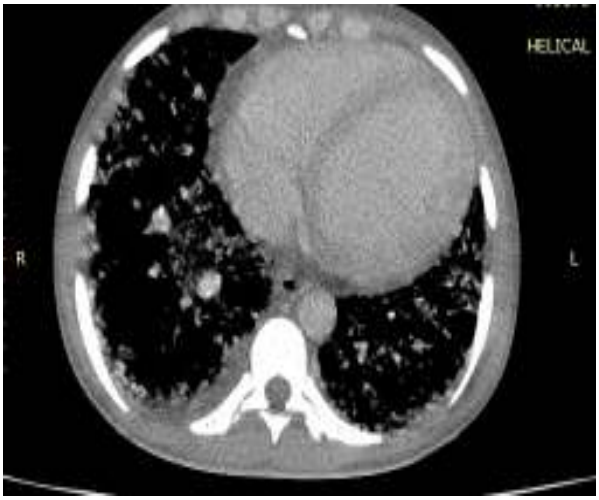


Fig 2: Mediastinal window without contrast

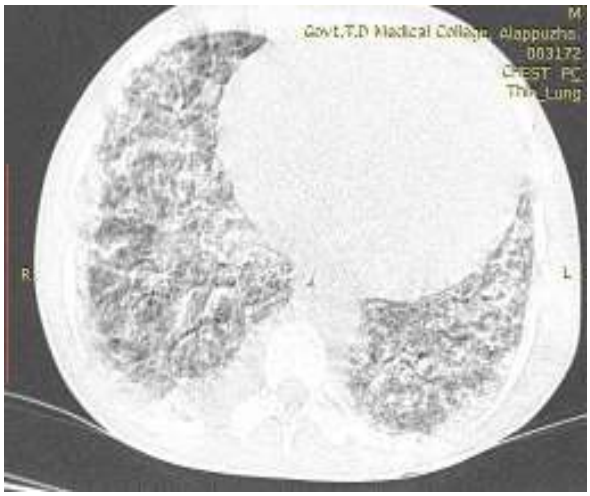


Fig 3: Lung window- HRCT

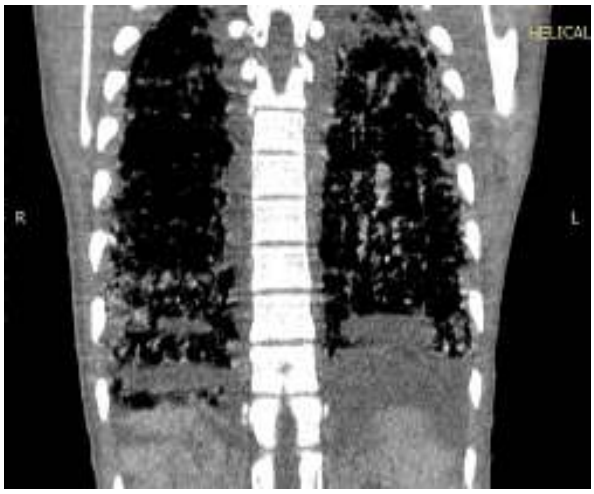


Fig 4: Coronal section CT

**What is the diagnosis?**

[1]Professor & HOD, [2]Junior Resident, [3]Senior Resident, Department of Pulmonary Medicine, Government TD Medical College, Alappuzha

Answer: METASTATIC PULMONARY CALCINOSIS (MPC) with evidence of volume overload secondary to renal failure

X-ray (fig 1) shows cardiomegaly (probably due to volume overload) and bilateral diffuse air space opacities more in the mid and lower zones.

CT (fig 2-4) shows multiple air space ground glass opacities with some amount of conglomeration in the subpleural region. The non contrast mediastinal window shows areas of calcifications in many nodules as well as minimal pleural effusion in the right side.

**Discussion**

Metastatic pulmonary calcication (MPC) is a metabolic lung disease where there is deposition of calcium in normal lung tissue. This can occur under conditions that directly or indirectly result in hypercalcemia[1]. Causes of MPC include long-term complication of chronic renal failure like secondary hyperparathyroidism, primary hyperparathyroidism, excessive exogenous administration of calcium and vitamin D, orthotopic liver transplantation, massive osteolysis from metastases or multiple myeloma and heart surgery.

The term "metastatic" suggests a malignant process, but in fact here it purely refers to the spread to and deposition of the excess calcium in the lungs. In fact, malignancy is only very rarely the etiology.

**Pathology**

There are two types of tissue calcification one where calcium is deposited in previously normal tissue as in MPC , in contrast to dystrophic calcification that occurs in previously damaged tissue. In MPC there is interstitial deposition of calcium salts, predominantly in the alveolar epithelial basement membranes with a particular affinity for elastic tissue . Alveolar capillary walls, bronchial walls, bronchioles and media of pulmonary arterioles are the other sites where calcium deposition occur. Although the condition is less commonly diagnosed, antemortem histological changes of MPC are encountered on autopsy in many patients who received hemodialysis and has been seen in up to 60-80%. Poor sensitivity of standard chest radiographs for the identification of small calcifications, the lack of awareness among clinicians of the imaging manifestations of MPC, and the benign clinical course of the disease all play a role in causing the situation.

Microscopic examination shows widening of the alveolar sept due to fibrosis, with infiltration of the walls by multiple areas of calcification and a few lymphocytes. The alveolar lumen is filled with exudate or calcification and may be surrounded by fibroblast proliferation. A foreign-body giant cell reaction to the calcium may be seen. In mild cases, calcium deposits are present along the alveolar epithelial basement membrane and in alveolar capillary walls without significant desmoplasia or septal thickening. However, when calcification is severe, a desmoplastic reaction may occur and result in interstitial fibrosis. This fibrosis, rather than the calcium *per se*, is thought to account for the development of respiratory symptoms and disturbed pulmonary function.

MPC is associated most frequently with an increased calcium-phosphate product as a result of hypercalcemia and/or hyperphosphatemia. This product is about 40 mg/dl in normal subjects, and metastatic calcifications are most likely to develop when it exceeds 70 mg/dl.

**Causes**

A variety of disorders can be the cause of metastatic pulmonary calcinosis.

- Chronic renal failure: considered as the commonest cause
- Primary and secondary hyperparathyroidism
- Vitamin D intoxication
- Sarcoidosis
- Intravenous calcium therapy
- Milk-alkali syndrome
- Multiple myeloma
- Massive osteolysis caused by metastases

**Distribution**

Metastatic pulmonary calcification occurs predominantly in the upper lobes. This is thought to be due to a higher ventilation-to-perfusion ratio in the apices, hence less $CO_2$ pressure and a more alkaline environment.

**Clinical features**

Usually patients with MPC are asymptomatic. When symptomatic, they present with nonspecific symptoms which include dyspnea and non-productive cough. Restrictive lung function, decreased diffusing capacity and hypoxemia may also occur. Rarely acute respiratory failure has also been described in patients with MPC. Thus, diagnosis is usually made only on strong clinical suspicion in the background of persistent pulmonary infiltrates despite treatment in the presence of hypercalcemia.

Chest Xrays are often normal or demonstrate nonspecific findings. High-resolution computed tomography

(HRCT) is more accurate than chest radiography for delineating parenchymal opacities and calcification and may allow a presumptive diagnosis of MPC, thereby avoiding invasive procedures like lung biopsy.

MPC usually has a chronic course but it may occur relatively acutely within several weeks to months .In chronic renal failure resolution of pulmonary calcification may occur after parathyroidectomy, renal transplantation, or dialysis. Spontaneous resolution of changes has also been described in patients with MPC

**Radiographic features**

**Plain radiograph**

The plain chest radiograph has low sensitivity in detecting small quantities of calcium and therefore appears normal in most of the cases. Non-specific air space consolidation, mimicking pulmonary edema or pneumonia is the most common pattern seen if the chest radiographs are abnormal.

**CT**

Metastatic Pulmonary Calcification is usually characterized by centrilobular nodular fluffy ground-glass opacities that may or may not appear calcified. Patterns of pulmonary calcifications can be punctuate within nodular opacities, ring-like, or diffuse, involving the entire nodule or consolidation area .These findings suggest the deposition of calcium salts in the alveolar walls around the terminal bronchioles.CT described patterns include multiple diffuse calcified nodules, diffuse or patchy areas of ground-glass opacity or consolidation, and confluent dense parenchymal consolidation with lobar distribution[2,3].

Other patterns seen are:

- Peripheral reticular opacities associated with small, calcified nodules
- Pleural effusion
- Vascular calcification within the chest wall.

Even though the primary pathology in MPC is purely interstitial, interlobular septal thickening is not seen in MPC. This is because the predominant sites of calcium deposition are the alveolar septa, the pulmonary arterioles and bronchioles.

**Magnetic resonance imaging**

A signal void or reduction in signal intensity is the most common finding. MPC appears hyperintense on T1-weighted images and to have a higher lesion/muscle signal-intensity ratio on T1-weighted than on T2-weighted images

**Bone scan**

Increased uptake in pulmonary opacities is diagnostic of MPC.This. may help in early diagnosis as these findings appear before plain radiographic abnormalities.

**Nuclear imaging**

Nuclear imaging with technetium-99m–methylenediphosphonate (Tc99m-MDP) may be a more specific and less expensive method for diagnosis. Radionuclide imaging is probably the most sensitive technique for the early detection of MPC. Some authors have recommended the use of scintigraphy as part of the evaluation of dyspnea in patients with chronic renal failure[4].

**Treatment and prognosis**

Overall prognosis will depend on the underlying cause. Majority of patients with renal failure and non-progressive asymptomatic MPC do not require any treatment specific to MPC. Treatments used with some success in patients with symptomatic disease include attempts to normalize calcium and phosphate biochemistry by using bisphosphonate , curative parathyroidectomy, renal transplant, or definitive dialysis

**Acknowledgement:**

Dr Suma Job, Additional Professor, Radiodiagnosis, Government TD Medical College, Alappuzha. Dr. Gomathy S, Professor & HOD, Nephrology, Government TD Medical College, Alappuzha

**References:**

1. Patrick Duncan, Stephanie Cull, Palmi Shah, MD; Amie Gamino. A 59-year-old man with chronic kid ney disease after kidney transplantation presents with chronic dyspnea. CHEST 2020; 157(1):e9-e12
2. Hartman TE, Müller NL, Primack SL, Johkoh T, Takeuchi N, Ikezoe J, Swensen SJ. Metastatic pulmo nary calcification in patients with hypercalcemia: find ings on chest radiographs and CT scans. AJR Am J Roentgenol. 1994 Apr; 162(4):799-802.
3. Luciana Camara Belém, 1Glaucia Zanetti, ,Arthur Soares SouzaJr, Metastatic pulmonary calcification: State-of-the-art review focused on imaging findings. Respiratory Medicine Volume 108, Issue 5, May 2014, Pages 668-676
4. Luciana Camara Belém1, Carolina A. Souza2, Arthur Soares Souza Jr.3, Radiol Bras. 2017 Jul/ Ago;50(4):231–23

# Localised hypertranslucency in AECOP

**Vishnu Sharma. M.**

**Case summary**

A 65-year-old gentleman who is a known case of COPD, on regular inhaled medication was admitted with a sudden increase in breathlessness and right-sided chest pain since one day. There was no history of an increase in cough, purulent sputum or other respiratory symptoms. He had no cardiac or GI symptoms.

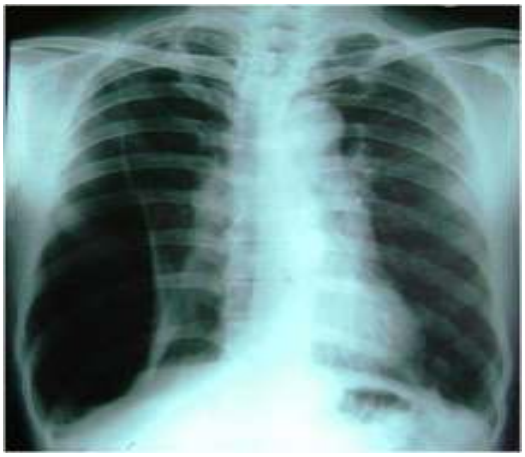

Fig 1: Chest x-ray PA view

What is the diagnosis from the Chest X-ray ?

A. Large bulla on the right side.

B. Encysted pneumothorax right side.

C. Massive pulmonary embolism on the right side.

D. Artefact mimicking pneumothorax on right side.

E. Swyer-James (MacLeod) syndrome.

**Answer –** B.

On the right side,there is a hyper translucent area devoid of bronchovascular markings which is medially bounded by visceral pleural line. Collapsed lung is seen medial to this.This is characteristic of pneumothorax[1]. In a typical pneumothorax,the lung will collapse towards the hilum in a curvilinear fashion, maximum air being collected at the apex[2]. In encysted pneumothorax,the air is trapped in a localized area of the pleural cavity due to pre-existing pleural adhesions.

Encysted pneumothorax should be differentiated from other causes of a localized area of hyper translucency. In a patient with COPD, skinfold artefact and emphysematous bulla will closely mimic encysted pneumothorax. In pneumothorax, the visceral pleural line will be a thin, sharply defined white line. There may shift of the mediastinum to the opposite side in tension pneumothorax.In skin fold artefact the line is usually broad, ill-defined medially and will be outlined by a sharp linear lucent (dark) line later In bulla visceral pleural line is not seen. Instead,a thin margin of the bulla is seen all aroundthe area of hyper translucency.HRCT thorax will show air outlining both sides of the bulla wall parallel to the chest wall. This is known as double wall sign[5].Bulla does not conform to the contour of costophrenic sulcus. Bulla is concave toward the chest wall.

Massive pulmonary embolism with occlusion of the main pulmonary artery can lead oligemia. The affected lung field may appear hyper translucent. Pulmonary artery proximal to occlusion will be dilated which may be visible in the radiograph[6].Westermark sign is a radiographic sign in pulmonary embolism which represents oligemia. In pulmonary embolism decreased vascularization at the lung periphery may be seen due to embolus or reflex vasoconstriction[7].But these signs of pulmonary embolism can be differentiated from encysted pneumothorax because of the absence of other radiological signs of pneumothorax.

Swyer-James-MacLeod syndrome is a rare entity associated with post-infectious bronchiolitis obliterans occurring in childhood. It is characterized by hypoplasia and/or agenesis of the pulmonary arteries resulting in hypoperfusion of pulmonary parenchyma. Chest radiographs show the affected part of the lung is smaller and

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hyper translucent. The majority are diagnosed in childhood[8].

The most common cause for pneumothorax in a patient with COPD is rupture of paraseptal emphysematous bulla[9]. Bulla is common in COPD patients. A careful history, physical examination, comparison of previous radiographs and HRCT thorax will help to differentiate bulla from encysted pneumothorax[10].

Most common cause for exacerbation of breathlessness in COPD is airway infection. When a patient with COPD presents with acute exacerbation without symptoms or signs of airway infection other causes for breathlessness should be evaluated. These include cardiac causes like left ventricular dysfunction, acute myocardial infarction, cardiogenic pulmonary oedema, cardiac arrhythmia, pneumothorax, pleural effusion, pulmonary embolism, bronchogenic carcinoma,collapse of lung, pneumonia, and metabolic acidosis. These conditions can coexist with COPD and hence all hospitalized AECOPD patients should be screened for this conditions[10].

Most of the pneumothorax in COPD occurs during exacerbation. This may be due to hyperinflation due to airway obstruction or positive pressure ventilation. Most often chest x-ray will help to make the diagnosis. Majority of COPD patients with a pneumothorax will be symptomatic even if the air collection is small and encysted. Hence intercostal tube drain is usually indicated[11]. Recurrence of pneumothorax is common in COPD patients due to the underlying bulla. Hence pleurodesis is indicated in these patients[11].

In the case of encysted pneumothorax, the site for intercostal tube drain insertion mustbe decided after a careful clinical and radiological examination. A lateral chest radiograph is essential. When chest x-ray shows multiple encystments HRCT of thorax and thoracoscopy may be needed[12].

**Learning points.**

` Pneumothorax is one of the causes for acute exacerbation of breathlessness in COPD. Encysted pneumothorax needs to be differentiated from bulla and other causes for localizedhyper translucency. Most of these patients will require intercostal tube drain and pleurodesis.

**References**


1. A R O'Connor, W E Morgan, Radiological review of pneumothorax, BMJ. 2005 Jun 25; 330(7506): 1493–1497
3. M. Obadah Kattea, Omar Lababede, Differentiating Pneumothorax from the Common Radiographic Skinfold Artifact, Ann Am Thorac Soc Vol 12, No 6, pp 928–931, Jun 2015
4. Buckle CE, Udawatta V, Straus CM. Now you see it, now you don't: visual illusions in radiology. Radiographics 2013;33: 2087–2102
5. Aramini B, Ruggiero C, Stefani A, Morandi U. Giant bulla or pneumothorax: How to distinguish. Int J Surg Case Rep. 2019;62:21–23. doi:10.1016/ j.ijscr.2019.08.003 –
6. Worsley DF, Alavi A, Aronchick JM, et al. Chest ra diographic findings in patients with acute pulmo nary embolism: observations from the PIOPED Study. Radiology 1993; 189:133–13
7. Algýn O, Gökalp G , Topal U. Signs in chest imag ing . Diagn IntervRadiol 2011 ; 17 :18 –29
8. Tortajada M, Gracia M, García E, Hernández R. Diag nostic considerations in unilateral hyperlucency of the lung (Swyer-James-MacLeod Syndrome) AllergolImmunopathol (Madr) 2004;32:265–270
9. Tanaka F., Itoh M., Esaki H., Isobe J., Ueno Y., Inoue R. 1993.Secondary spontaneous pneumothorax. Ann Thorac Surg,55(2):372–76.
10. Barnes PJ. Future treatments for chronic obstructive pulmonary disease and its comorbidities. Proc Am Thorac Soc 2008;5:857–864
11. Baumann MH, Strange C, Heffner JE, Light R, Kirby TJ, Klein J, et al. Management of spontaneous pneu mothorax. An American College of Chest Physicians Delphi consensus statement. Chest 2001;119: 590-602
12. O"Connor AR, Morgan WE. Radiological review of pneumothorax. BMJ. 2005;330:1493–1497.

## Case Report

# Anthraco-fibrosis–A masquerader?

**Mithali Panwala[1], Sharada Nair[2], V. Kesavan Nair[3]**

**Introduction**

Anthraco fibrosis is a rare condition which has many clinical and radiological features mimicking or masquerading as pulmonary tuberculosis, carcinoma bronchus and silicosis. The biopsy from the lung lesion is the clincher in the diagnosis.

**Abstract**

We are presenting here a case of anthracofibrosis in a manual labourer who was working in the stone –cutting and tiles industry. He was engaged in the job actively for years though he was having co- morbidities like diabetes mellitus, tuberculosis etc. A heavy smoker with a smoking index of 600, he presented with chronic cough, dyspnoea, chest pain and melena. His investigations showed ECG changes suggestive of coronary artery disease and chest X-ray with right upper lobe cavitation and nodules in both lungs. Bronchoscopy revealed bluish pigmentation and nodules in the air ways and narrowing of the bronch in certain areas suggestive of bronchial stenosis. Bronchoscopic biopsy revealed only chronic inflammatory cells. Subsequently, CT guided tru-cut biopsy from the right upper lobe lesion confirmed features of anthracofibrosis. Though there are lakhs of people in India working in the construction industry with work involving stone and tile cutting etc., reports about anthraco fibrosis have been few and far between. Hence this report.

**Key words:** Anthracofibrosis, tru cut biopsy, silicosis

**Case report**

A 48-year-old gentleman, manual labourer for years and who had cut stone and tiles for most of his working life, presented with cough and dyspnoea of 2 years duration, and acute-onset left sided chest pain of 1-day duration. No recent h/o fever, haemoptysis or weight loss. He was a diabetic for more than 5 years and had taken 2 courses of anti-tuberculous treatment one for 2 months and later for 8 months in view of chronic cough with mucopurulent expectoration and X-ray lesions suggestive of tuberculosis, from local hospital although his sputum was never positive for AFB.

He had no hypertension, Ischemic heart disease, major surgery or asthma in the past. He used to smoke 20 cigarettes per day for about 30 years and also consumed ethanol regularly.

On examination, the patient was alert, PR- 104/min- 20/min, BP- 124/80mmhg, Spo2- 94% on room air. Pallor and clubbing were present but no lymphadenopathy, icterus or oedema. Respiratory system examination revealed bilateral wheeze and crackles over the bases. The heart sounds were normal with no murmur. The abdomen was soft with no tenderness or any free fluid.

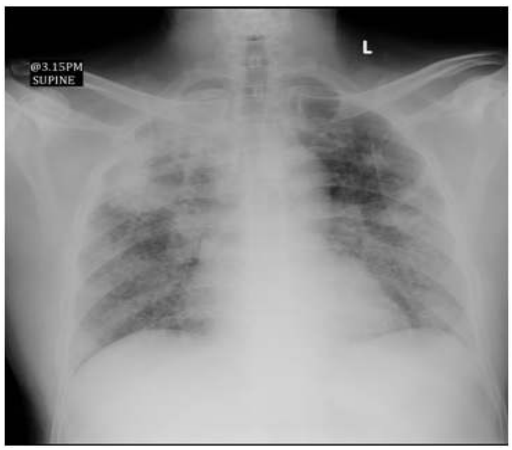


Figure 1 X-ray Chest showing cavitating mass right upper lobe and nodules in both lungs.

CT thorax (figure 2a, 2b) showed thick irregular walled cavity, along with nodules in both lungs. Interstitial fibrosis with traction bronchiectasis was seen in the lower lobes.

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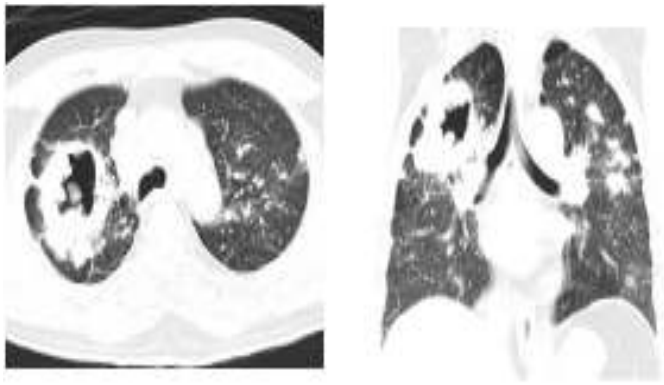

Figure 2a, 2b: CT chest showing thick walled cavity in right upper lobe with multiple speculated nodules in both lung fields.

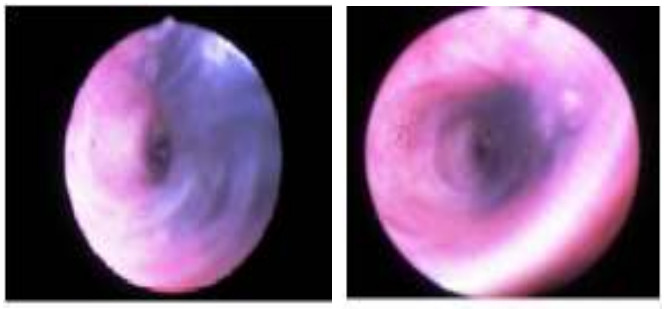

Fig 3. Bronchoscopy showing narrowing of the bronchus and the bluish pigmentation

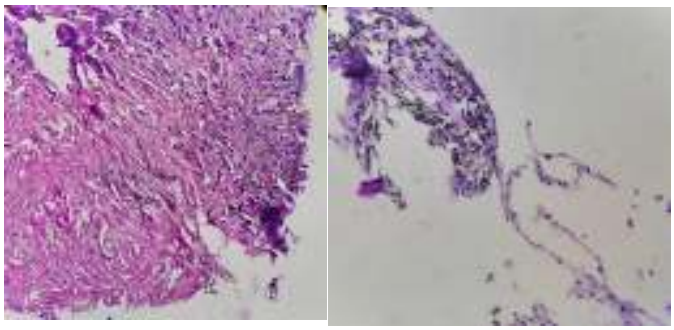

Fig 4: Histopathology slides showing focal collection of spindle cells simulating microgranuloma and fibrosis, with no evidence of malignancy. Black pigment granules were seen in some histiocytes

**Investigations**

His routine blood investigations including liver and renal functions were normal. X ray chest (figure 1) showed a cavitating mass in the right upper zone and bilateral nodules and fibrosis.

Bronchoscopy (figure 3) showed bluish black pigmentation of mucosa in right intermediate bronchus with narrowing of the lumen which was suggestive of anthraco-fibrosis. In view of the history of working with marbles and tiles, anthraco-silicosis was also thought of.

Bronchoscopic biopsy showed bronchial mucosa with chronic inflammation and suspicious foci of microgranuloma. Black pigment granules were seen in some histiocytes. There was no evidence of any neoplasm.

CT guided tru-cut biopsy from the right upper lobe lesion was suggestive of pneumoconiosis, probably carbon pigment related (Anthracosis with fibrosis and necrosis). There was no evidence of silicosis in the specimens studied.(Fig 4)

Whole body PET CT showed moderate degree of increased FDG uptake in right upper lobe cavitary lesion, multiple parenchymal nodular lesions and mediastinal lymph nodes–reported likely to be benign in nature with no evidence of active disease in lung at present.

**Discussion**

Anthracosis refers to blackish pigmentation of the tracheobronchial tree (involving both mucosal and submucosal layers) and lung parenchyma, or black pigmentation in macrophages which is caused by the deposit of carbon, silica, and quartz particles. When anthracosis is associated with mucosal proliferation resulting in luminal obliteration and/or obstruction, it is referred to as anthracofibrosis. This was first described by Chung et al. in 1998 as a disease that was associated with tuberculosis in Korea.[1] However; later reports suggested a strong association with biomass fuel smoke exposure, and exposure to mineral dusts, coal, silica, and mica.

It is a benign condition which may progress very slowly, and can finally lead to gradually progressive bronchial stenosis. According to Han FF, Yang et al[2] the pathogenesis and diagnosis of bronchial anthracofibrosis (BAF) are currently not clear, although it may be related to tuberculosis or bio-fuel inhalation. The study by Virendra Singh et al[3] concluded that there is a strong association of Anthracofibrosis with pulmonary tuberculosis and not with biomass fuel exposure. But later, studies came from Ladakh, in Jammu and Kashmir, India which is at a high level above sea. The houses in Ladakh have fireplaces inside the house, which use partially burnt wood/dung with smoke. People usually remain indoors during winter and cooking is also usually done in the same room.

Hence, they get exposed to smoke, soot etc. and develop anthracofibrosis.[4] Occupational anthracofibrosis was described from U.K. in 2008[5] and from U.S.A in 2014.[6] In India also, there must be a high incidence of anthracofibrosis, as there are lakhs of workers in the building-construction industry who do not use any kind of protective wear.BAF is also seen in elderly ladies in India who spend long hours cooking with firewood, getting exposed to dense smoke in poorly ventilated kitchens[7] Several studies show that there is no gender predisposition for this condition.[8]

The diagnosis is important because most of the patients have clinical, radiologic and bronchoscopic changes that suggest malignancy. Hence, unnecessary thoracotomies can be avoided if diagnosis by biopsy is available.

Diagnostic criteria for bronchial anthracofibrosis adopted by several other authors include: (a) prolonged history of biomass fuel smoke exposure (b) bronchial narrowing on HRCT and (c) bronchoscopy by visualization of bluish-black mucosal anthracotic pigmentation along with narrowing/distortion of the affected bronchus. Bronchoscopy in Anthracofibrosis usually reveals inflammatory bronchial stenosis with overlying deep blue (anthracotic) pigmentation. Microscopy shows carbon pigment in alveolar and interstitial macrophages, in connective tissue and lymphatics.[9]

The radiological picture of anthracofibrosis in our case is similar to that of several other cases described in literature. It includes multifocal bronchial narrowing [10], per bronchial soft-tissue thickening/cuffing, fibrosis with traction bronchiectasis and/orinterstitial involvement in the form of nodular or reticulonodular opacities. [11] Among this fibrosis with interstitial thickening in the lower parts of the lungs were present in our case.

Anthracofibrosis has been noted to be associated with malignancy, chronic obstructive pulmonary disease (COPD), recurrent pneumonias, and tuberculosis, hence all affected patients need close follow-up. [12]

No established treatment has been reported so far for anthracofibrosis. Bronchodilators (short or long acting), corticosteroids (inhaled or systemic) and antibiotics may be given as empirical treatment.[13] In cases of severe localized bronchial obstruction of large airways, bronchial stents may be used. [14]

The possibility of anthracosis or anthraco-fibrosis to be thought of, in any patient with long standing history of working with marble/tiles/coal/stone cutting. Anthracofibrosis must be much more common than what is reported. This patient also had malignancy elsewhere in the stomach but a second primary in the lung could not be proved and had cavitation and nodules which are most commonly seen in tuberculosis. The clinical and radiological differential diagnoses were Silicosis with PMF, carcinoma bronchus, pulmonary tuberculosis in view of the presence of cavitating mass in the right upper lobe, nodules and the interstitial fibrosis in the lower lobes. The diagnosis was missed during the initial stages. It is the lung biopsy from the right upper lobe mass which confirmed the diagnosis. This case is presented because this rare condition may masquerade as tuberculosis, silicosis or lung malignancy which are much more common in India.

**Acknowledgement**

We would like to thank the department of Pathology in the Kerala Institute of Medical Sciences (KIMS), Trivandrum for their help in the histopathologic di agnosis of this case.

References

1. Chung MP, Lee KS, Han J, Kim H, Rhee CH, Han YC,et al. Bronchial stenosis due to anthracofibrosis. Chest. 1998 Feb;113(2):344–50.

2. Han F, Yang T, Song L, Zhang Y, Li H, Guan W, et al. Clinical and pathological features and im aging mani festations of bronchial anthracofibrosis: the findings in 15 patients. Chin Med J (Engl). 2013 Jul;126(14):2641–6.

3. Singh V, Meena H, Bairwa R, Singh S, Sharma BB, Singh A. Clinico-radiological profile and risk fac tors in patients with anthracosis. Lung India. 2015 Mar 1;32(2):102.

4. Spalgais S, Gothi D, Jaiswal A, Gupta K. Nonoccupationalanthracofibrosis/anthracosilicosis from Ladakh in Jammu and Kashmir, India: A case series. Indian J Occup Environ Med. 2015 Sep-Dec;19(3):159-66

5. Wynn GJ, Turkington PM, O'Driscoll BR.

Anthracofibrosis, bronchial stenosis with overlying anthracotic mucosa: possibly a new occupational lung disorder: a series of seven cases from one UK hospi tal. Chest. 2008 Nov;134(5):1069–73.

6. Rangelov K, Sethi S,The first described case of occu pational anthracofibrosisin the USA: Case Reports in Pulmonology.2014.Volume 2014, Article ID 460594.3

7. Gupta A, Shah A. Bronchial anthracofibrosis: an emerging pulmonary disease due to biomass fuel exposure. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. 2011 May;15(5):602–12.

8. Kim YJ, Jung CY, Shin HW, Lee BK. Biomass smoke induced bronchial anthracofibrosis: presenting fea tures and clinical course. Respir Med. 2009 May;103(5):757–65.

9. Afridi F, Ashraf A. A Bronchial Mark: A Case of Bron chial Anthracofibrosis. Chest. 2017 Oct 1;152(4): A723.

10. Kala J, Sahay S, Shah A. Bronchial anthracofibrosis and tuberculosis presenting as a middle lobe syn drome. Prim Care Respir J J Gen PractAirw Group. 2008 Mar;17(1):51–5.

11. Kunal S, Pilaniya V, Shah A, Bronchial anthracofibrosis with interstitial lung disease: an association yet to be highlighted. BMJ Case Rep. 2016 Jan 11;2016.

12. KunalS,Shah A, The concomitant occurrence of pulmo nary tuberculosis with bronchial anthracofibrosis. Tuberculosis: Volume, January 2017, Pages 5-9

13. No TM, Kim IS, Kim SW, Park DH, Joeng JK, Ju DW, et al. The clinical investigation for determining the aetiology of bronchial anthracofibrosis. Korean J Med. 2003 Dec 1;65(6):665.

14. Gómez-Seco J, Pérez-Boal I, Guerrero-González J, Sáez-Noguero F, Fernández-Navamuel I, Rodríguez-Nieto MJ. Anthracofibrosis or

## Case Report

# An unusual case of granulomatous pleural effusion

**Sujith Varghese Abraham[1], Ameer K.A[2], Padmanabhan Arjun[3]**

**Abstract**

A 56 year old female, a case of EPTB – left sided pleural effusion was evaluated for lack of response to ATT. She underwent pleuroscopy which showed multiple discrete greyish lesions on parietal pleura and biopsy revealed granulomatous lesion. Despite the continuation of ATT for another 2 weeks, the chest tube inserted post pleuroscopy drained 500ml/day. PET CT showed metabolically active mediastinal adenopathy and splenomegaly. She underwent mediastinoscopy and biopsy of the mediastinal node which revealed non-necrotizing granulomas highly suggestive of sarcoidosis. Steroid was initiated and ATT medications were stopped considering sarcoidosis as the diagnosis. Her effusion subsided subsequently and became asymptomatic. She has had no recurrence on follow up so far.

**Introduction**

Sarcoidosis is a multi-system granulomatous disorder of unknown etiology, which was first described by Hutchison in 1878. It usually presents in patients between 20 and 60 years of age. Mediastinal lymph nodes and lung parenchyma are the most frequently affected. Pleural involvement in the form of pleural thickening, chylothorax, pneumothorax and effusion are rare manifestations. Though pleural effusions are seen rarely in sarcoidosis patients during their natural course of diseases, effusion as a presenting symptom is very unusual. Here, we are presenting a case of a 56-year-old female who presented with massive left-sided pleural effusion which was later confirmed to be sarcoidosis as per the histology and treatment response to steroids.

**Case Report**

A 56-year-old female, non-smoker, with no prior history of any respiratory or cardiac illness presented to our department with complaints of intermittent fever, chest pain and exertional dyspnea of two-month duration. She had a history of significant weight loss of about 10 kg in 3 months with loss of appetite. She did not have any history suggestive of connective tissue diseases, or history of any chemical or organic exposures orradiation or any prolonged drug intake. For the same complaints, she was started on empirical anti-tubercular chemotherapy (ATT) from elsewhere, after a diagnostic pleural aspiration which showed lymphocyte-predominant, exudative effusion. Since symptoms persisted despite ATT for 1 month, she was referred to our centre for further management.

On examination, she was found to have features of left-sided massive pleural effusion, while examination of other systems was unremarkable. Her complete blood count, hepatic and renal panels were normal. Thyroid function test was also normal. Postero-anterior view of her chest radiograph showed massive effusion of the left side with mediastinal shift (Figure 1). Contrast-enhanced CT scan of the chest showed massive left-sided pleural effusion. Sputum smear examination for acid-fast bacilli by ZN staining and MTB-PCR CBNAAT were negative. Diagnostic pleural aspiration revealed pauci-cellular, lymphocyte rich exudative effusion with high protein (4.16 g/dl) and low adenosine deaminase (ADA) of 19.3. The patient underwent pleuroscopic evaluation. Multiple discrete greyish nodular lesions were seen in the parietal pleura (Figure 2). Histopathology reports of the biopsy specimens were suggestive of granulomatous inflammation. Based on the biopsy reports, anti-tuberculous chemotherapy was continued with pleural tuberculosis as the primary diagnosis. However, a low ADA was a point against tubercular etiology.

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Despite another 2 weeks (total one and half months) of ATT, her symptoms persisted and an intercostal tube inserted post pleuroscopy drained average 500ml/day. Hence, further investigations to rule out other diagnosis were done. Her electrocardiogram was normal and echocardiography showed good biventricular function with normal ejection fraction. Ultrasound scan of the abdomen was normal with no ascites or organomegaly. Serum angiotensin-converting enzyme(ACE) levels was normal -32.52 U/L (normal 12-68 U/L), while her serum calcium was low -7.5 mg /dl(normal 8.6 to 10.2 mg/dl) with a high 24-hour urinary calcium was 226 mg/dl (normal 50 to 150 mg/dl). Her connective tissue work-up which included rheumatoid factor, anti-nuclear antibody, antineutrophil cytoplasmic antibodies and Anti-ds-DNA were negative.A tuberculin skin test was done and was negative. An 18-FDG whole-body positron emission tomography/CT was done to rule out metastatic malignancy. It showed moderate left pleural effusion, mildly metabolic mediastinal lymphadenopathy and metabolically active moderate splenomegaly with no evidence of metabolically active distant lymph node/liver/skeletal/any other organ involvement (Figure 3). The differential diagnosis considered at this point of time were granulomatous disease/infection like tuberculosis and malignancy probably lymphoma but less likely lung cancer. Based on the PET CT, it was decided to proceed with mediastinoscopy and biopsy of the mediastinal nodes to arrive at a definite diagnosis. The histology of the excised mediastinal lymph node station 7 showed closely arranged non-caseating granuloma composed of epithelioid histiocytes and several multinucleated giant cells with star-shaped eosinophilic inclusions "asteroid bodies", highly suggestive of sarcoidosis. Special stains- Ziehl Neelsen for AFB and PAS stain for fungal organisms were negative. CBNAAT of the excised lymph node sample was also negative. A QuantiFERON TB gold test done was also negative. Thus, the diagnosis of sarcoidosis, as the etiology of the pleural effusion was inferred. She was started on appropriate dose of steroids and discharged after removal of ICD tube.

On follow-up imaging with Chest X-ray PA view after 2 months, (Figure. 4), there was complete resolution of effusion and she was clinically better. Her anti-tuberculous chemotherapy was stopped following negative AFB culture reports and continued on steroids. She was then follow-up for 8 months and found to have no recurrence of effusion/other systemic features of sarcoidosis.

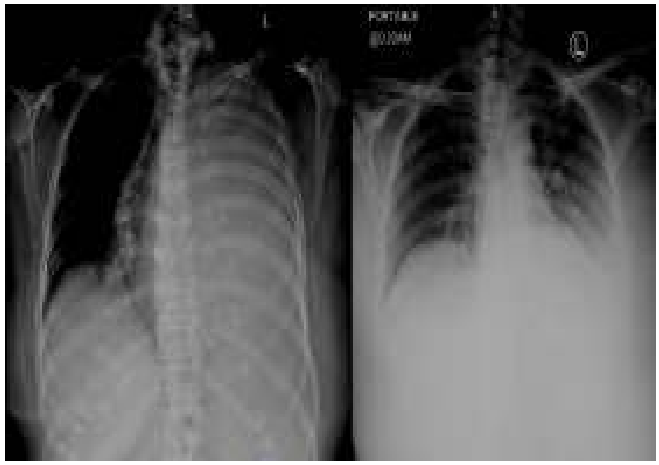

Figure 1: Chest X-ray showing left massive effusion in the first image and post pleuroscopy - ICD in-situ in the second image.

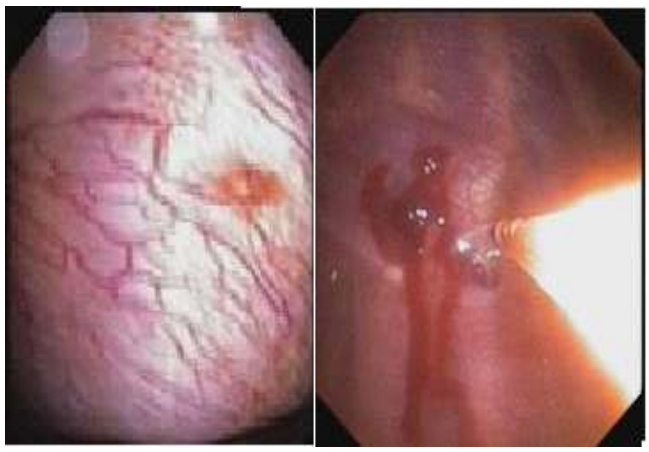

Figure 2: Greyish nodules visualized during pleuroscopy with the biopsy forceps

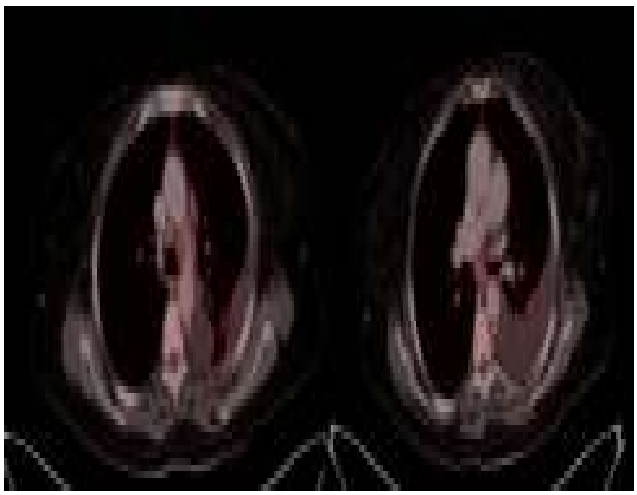

Figure 3: Metabolically active mediastinal nodes in PET CT

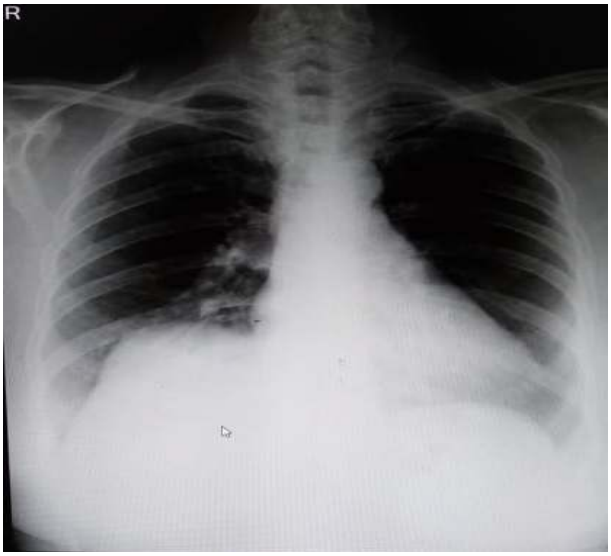


Figure 4: chest x-ray showing complete resolution of left effusion after 2 months

**Discussion**

Sarcoidosis is a disease that is known to the medical fraternity for more than 100 years. Features can usually mimick many diseases including malignancy and other granulomatous diseases like tuberculosis. Sarcoidosis usually presents with non-specific symptoms and are asymptomatic in 20-50% of patients. The diagnosis is mostly incidental when an abnormality is detected on a chest radiograph obtained for unrelated reasons[1]. Though it is a multi-organ disease, 97% of affected patients have intra-thoracic involvement[2]. Bilateral hilar adenopathy (50-85%), pulmonary parenchymal infiltrates (25-60%) are the characteristic radiographic findings in sarcoidosis [3,4]. Pleural involvement (including pneumothorax, chylothorax, effusion and thickening) is found in 5-10% of cases. Sarcoidosis with effusion is extremely rare with an incidence ranging from 0.16% to 4% 5-7. Pleural effusion is so rare in sarcoidosis, that it usually excludes the diagnosis.

Huggins et.al screened 181 outpatient sarcoidosis patients with ultrasonography to diagnose pleural effusion in 2.8% cases, out of which only 1.1% was attributed to sarcoid pleural involvement[7]. Another series by Szwarcberg and colleagues' studies 61 patients of sarcoidosis with computed tomography and found to have pleural effusion in 5 patients (8.2%), however, none of them have tissue diagnosis to prove sarcoid involvement of pleura[8].

The presence of pleural effusion cannot be attributed to sarcoidosis per se in many cases. Pleural effusion in sarcoidosis can be due to direct sarcoid involvement of pleura leading to increased capillary permeability or inflammation of both pleura caused by peripheral lung granulomas, in which case it will be exudative. Transudative effusion can also occur due to indirect causes like a congestive cardiac failure due to direct cardiac sarcoidosis, trapped lung[9], endobronchial sarcoidosis leading to bronchial stenosis and lobar atelectasis[10], lymphatic obstruction leading to chylothorax[11] and superior vena cavalobstruction[12]. Sarcoid effusions are typically paucicellular, lymphocytic-predominant, and exudative. Another characteristic feature described is protein-LDH discordance i.e., exudative by protein criteria and transudate by LDH criteria, supporting the view of increased capillary permeability with minimal pleural space inflammation being the causative mechanism in the formation of pleural fluid in sarcoidosis[7]. Even, pleural fluid CD4/CD8 ratio was also utilized in the diagnosis of sarcoid pleural effusion. Kumagai et.al utilised CD4/CD8 ratio of pleural fluid obtained by thoracocentesis, which was increased to 5.62 (higher than the ratio of mean +2 standard deviation value of pleural tuberculosis) to substantiate the diagnosis already made by histological examination of more than one organ specimen [13].

To the best of our knowledge, there is only one case in literature, which reports pleural effusion as the presenting symptom of sarcoidosis. However, in that case, the effusion was bilateral and was not exclusively attributed to sarcoidosis alone, as the patient had congestive heart failure also, which could have accounted for effusion[14]. A review of sarcoidosis from our centre, out of 66 patients with biopsy-proven sarcoidosis diagnosed from June 2016 to April 2020, this was the only case having pleural effusion. Sarcoidosis was not considered among the various differential diagnosis as an effusion in a case of sarcoidosis was very unlikely. Sarcoidosis is a diagnosis of exclusion. In a tuberculosis endemic country like India, biopsy finding of granuloma almost always points towards to tuberculosis, unless proved otherwise. This was a diagnostic dilemma as she did not respond to ATT, which made investigations to rule out other granulomatous conditions, a necessity. The diagnosis of sarcoidosis, in this case, was affirmed by histopathological evidence of sarcoidosis from two different organ systems and all microbiological investigations and investigations on malignancy being negative. After initiation of oral steroids, the patient reported significant clinical improvement with

complete resolution of pleural fluid, which also confirms sarcoidosis as the etiology of pleural effusion in this case.

**References**


1. Lynch JP, Kazerooni EA, Gay SE. Pulmonary sarcoi dosis. Clin Chest Med. 1997 Dec;18(4):755–85.
2. Ungprasert P, Carmona EM, Utz JP, Ryu JH, Crowson CS, Matteson EL. Epidemiology of Sarcoidosis 1946-2013: A Population-Based Study. Mayo Clin Proc. 2016 Feb;91(2):183–8.
3. Hoang DQ, Nguyen ET. Sarcoidosis. Semin Roentgenol. 2010 Jan;45(1):36–42.
4. Sones M, Israel HL. Course and prognosis of sarcoi dosis. Am J Med. 1960 Jul;29:84–93.
5. Tommasini A, Di Vittorio G, Facchinetti F, Festi G, Schito V, Cipriani A. Pleural effusion in sarcoidosis: a case report. Sarcoidosis. 1994 Sep;11(2):138–40.
6. Judson MA. The Clinical Features of Sarcoidosis: A Comprehensive Review. Clin Rev Allergy Immunol. 2015 Aug;49(1):63–78.
7. Huggins JT, Doelken P, Sahn SA, King L, Judson MA. Pleural effusions in a series of 181 outpatients with sarcoidosis. Chest. 2006 Jun;129(6):1599–604.
8. Szwarcberg JB, Glajchen N, Teirstein AS. Pleural in volvement in chronic sarcoidosis detected by tho racic CT scanning. Sarcoidosis Vasc Diffuse Lung Dis. 2005 Mar;22(1):58–62.
9. Heidecker JT, Judson MA. Pleural effusion caused by trapped lung. South Med J. 2003 May;96(5):510–1.
10. Poe RH. Middle-lobe atelectasis due to sarcoidosis with pleural effusion. N Y State J Med. 1978 Nov;78(13):2095–7.
11. Bhattarai B, Schmidt F, Devkota A, Policard G, Manhas S, Oke V, et al. A case of chylothorax in a patient with sarcoidosis: a rare and potentially fatal complication. J Community Hosp Intern Med Perspect. 2015;5(4):28300.
12. Morgans WE, Al-Jilahawi AN, Mbatha PB. Superior vena caval obstruction caused by sarcoidosis. Tho rax. 1980 May;35(5):397–8.
13. Kumagai T, Tomita Y, Inoue T, Uchida J, Nishino K, Imamura F. Pleural sarcoidosis diagnosed on the basis of an increased CD4/CD8 lymphocyte ratio in pleural effusion fluid: a case report. J Med Case Rep. 2015 Aug 14;9:170.
14. Rivera E, Gesthalter Y, Vardelaan P, Chee A, Majid A. Sarcoidosis With Pleural Effusion as the Present ing Symptom. J BronchologyIntervPulmonol. 2018 Apr;25(2):148–51.

## Case Report

# Yellow Nail Syndrome

**Sharada Nair[1], V. Kesavan Nair[2]**

**Abstract**

The 'Yellow Nail Syndrome' is a condition characterized by yellowish- brown finger and toe nails, lymphedema of the legs and pleural effusion. It is a rare condition, reported infrequently in literature. This report is of a case of yellow nail syndrome in a 32-year-old female, native of Maldives. She had noticed yellowing of nails along with symptoms of allergic rhinitis ten years ago. She was diagnosed to have asthma with cor-pulmonale from elsewhere. She came here for surgical treatment of leg edema. She was also found to have yellow nails with allergic rhinitis and asthma. There was no evidence of bronchiectasis or pleural effusion which are the usual reported associations. Cardiac evaluation done revealed no abnormality. Bilateral inguinal nodo-venous shunt was done which relieved her edema to a large extent. Her diagnosis was delayed for nearly ten years entailing a lot of financial burden and mental strain.

**Key words**: Yellow nails, lymphedema, pleural effusion, allergic diathesis

**Introduction**

We are presenting a case of 'Yellow nail syndrome' with yellow finger and toe nails, and lymphedema in a 32-year-old female. She came to the hospital for the surgical management of her lymphedema which was refractory even after medical management. She had coexistent allergic rhinitis and asthma. There was no pleural effusion. As it is a rare condition, the diagnosis was missed by physicians in India and Sri Lanka.

**Case Report**

A 32-year-old house-wife from Maldives presented to the Plastic surgery department of our hospital for complaints of edema of legs of ten years duration. The swelling had not subsided in spite of treatment from various physicians. Though the swelling never increased beyond a certain level, she found it difficult to use footwear and hence wanted to undergo surgical treatment for the edema. As she was having recurrent attacks of allergic rhinitis and recurrent breathlessness, she was referred to the Respiratory medicine department for pre-operative evaluation.

Patient had noticed yellowing of fingers and toe nails for 10 years, concurrently she also noticed symptoms of allergic rhinitis with episodic breathlessness with wheezing. She had a battery of tests done in Sri Lanka and later in India by physicians, chest physicians and cardiologists over a period of nine years. Though none of the tests were conclusive, the final verdict was 'reactive airway disease with cor pulmonale', even though no echocardiographic evidence of cor pulmonale.

General examination showed a moderately built lady with no respiratory distress. There was no clubbing or cyanosis but the finger and toe nails were yellowish with increased curvature(Figures 1&3). The toe nails were deformed, with onycholysis and absence of cuticle. The lymphedema of legs was without much lichenification.(Fig.1&2).

Respiratory system examination showed presence congested nasal mucosa with no polyps. There was bilateral wheeze but no crackles.

Routine examination of blood and urine did not reveal any abnormality except a mild eosinophilia of 9%. The serum IgE level was normal,(140IU/ml). The X-ray chest was normal. The sputum AFB was negative and the sputum did not grow any organism. HRTC was done, but revealed no abnormalities.

The ECG and the echocardiogram were within normal limits. The lung function test showed obstructive

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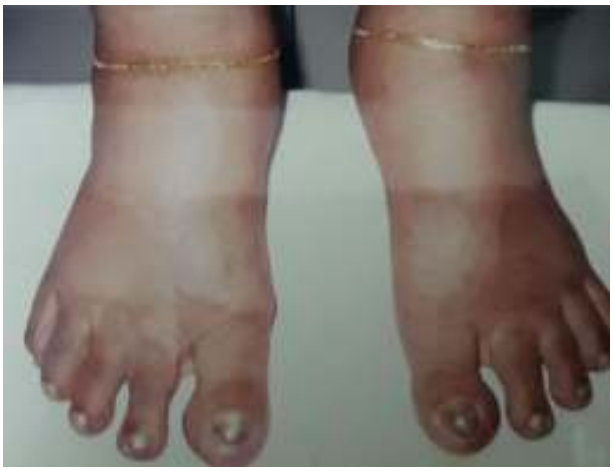

Figure 1& 2: The legs and feet showing oedema legs and yellowish brown toe nails

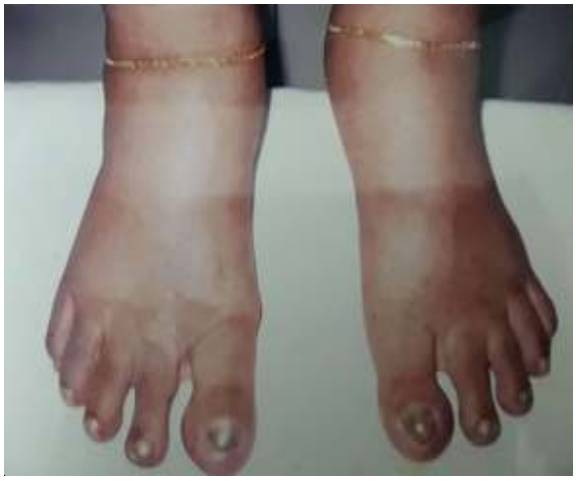

Figure2: Showing odema legs and yellowish brown toe nails

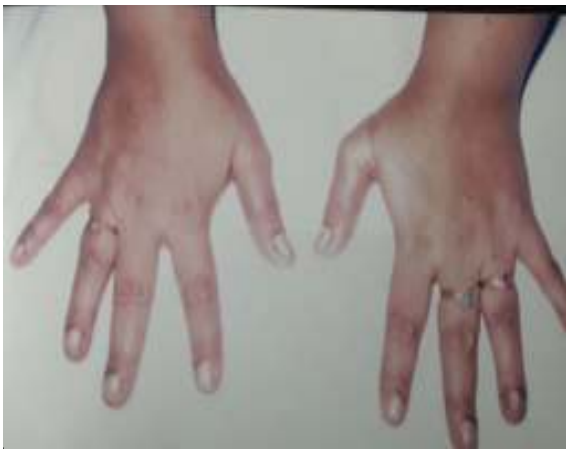

Fig:3 Finger nails showing yellow brown colour

abnormality with good reversibility to inhaled bronchodilator.

The lympho-scintigraphy showed reduced lymphatic drainage in the lower limbs with hold-up at the ankle and popliteal levels.

The patient underwent bilateral nodo-venous anastomoses where the inguinal lymph nodes were anastomosed to the adjacent veins, under spinal anesthesia, after controlling her respiratory symptoms. Her lymphedema legs showed good improvement at 2 months' follow up.

**Discussion**

The association of primary lymphedema of legs and yellow nails was initially reported by Samman and White in 1964.[1] Pleural effusion was later noted by Emerson.[2] The case reported by the author [3] in 1996, was in a 40-year-old male who had all the three classical features but the diagnosis may have been missed as he came from a place where filariasis was rampant. The present case differs in the fact that it was detected in a Maldivian female and the features are yellow nails and intractable lymphedema. Though most of the cases have been reported in Caucasians, cases have been seen in Indians also. The diagnosis was delayed probably because of lack of awareness of this rare condition. This case is presented to create awareness about this rare condition.

Yellow nails syndrome is classically described with a triad of yellow and thickened nails, lymphedema and respiratory manifestations (bronchietasis/pleural effusion / chronic cough). How ever only two out of the three is essential for diagnosing this condition, with nail abnormality being mandatory.

It is more frequently an isolated condition, but may be associated with other diseases implicating the lymphatic system, autoimmune diseases or cancers. Though the exact etiology of the association of signs is debated, it is believed to be due to lymphatic hypoplasia at the sites of involvement.[4] The other conditions which may be associated are bronchiectasis, sinusitis etc[5].It is possible that these conditions could be due to recurrent infections as a sequelae of an allergic diathesis as in the present case. We could not gather any literature implicating atopy in such patients. Another rare association is pericardial effusion.[6]

Although, spontaneous remission of the nail changes has been observed in up to 30% cases, most pa-

tients desire treatment due to its unaesthetic appearance. Oral vitamin E, topical triazole antifungals, oral zinc sulphate, intralesional corticosteroids have been tried alone or in combination. Treatment of lymphedema comprises of several components which include elastic low-stretch bandaging, skin/nail care (to reduce infection) and exercises to aid lymph drainage. Pulmonary manifestations may also be managed conservatively. Recurrent and/or large pleural effusions may need medical pleurodesis/ decortication/ pleural–peritoneal shunts.

**References**


1. SammanPD, White WF. The yellow nail syndrome. Br.J. Dermatol 1964; 76: 1553 — 157.
2. Emerson PA. Yellownails, lymphoedema and pleu ral effusion. Thorax 1966, 21 :247 - 253. 3.
3. Kesavan Nair V, Sukumaran, P. Yellow nail syn drome: A rarity in Indians? Ind Chest Dis.& Allied Sciences. 1996; 38: 39 — 43.
4. Rama Prasad T. Yellow nail syndrome. Chest 1980; Vol77. issue4. page 580
5. Woodfield G, Nisbet M, Jacob J, Mok W, Loebinger MR, Hansell DM, et al. Bronchiectasis in yellow nail syndrome. Respirology. 2017; 22:101–7.
6. Reidel.M. Multiple effusions and lymphedema in yellow nail syndrome. Circulation 2002. 105.
7. Valdés L, Huggins JT, Gude F, Ferreiro L, Alvarez-Dobaño JM, Golpe A, et al. Characteristics of patients with yellow nail syndrome and pleural effusion. Respirology. 2014;19: 985–92.

## Case Report

# Pulmonary vasculitis as initial manifestation of Rheumatoid arthritis

**Suhas H S[1], Sundaram P[2]**

**Abstract**

Rheumatoid arthritis (RA) is an autoimmune disorder of unknown aetiology that characteristically causes progressive, symmetric erosive destruction of bone and cartilage which can lead to deformities that may be often debilitating.

Although joint involvement is the primary manifestation of rheumatoid arthritis, there have been many instances where it can primarily present with extra articular manifestation in the form of subcutaneous nodule formation, vasculitis, inflammatory changes in the eyes, pericardial involvement and lung involvement.

Involvement of respiratory system may be seen in 30-40% patients of rheumatoid arthritis and in 10% of the patients, involvement of the respiratory system may be the initial manifestation and may precede the articular manifestations. It may present in the form of parenchymal involvement manifesting as interstitial lung disease, airway abnormality or with pleural involvement presenting as pleural effusion and rarely may present as pulmonary vasculitis.

We present a rare case of 60-year-old man presenting with pulmonary vasculitis in the form cavitating nodule with effusion with high levels of anti-cyclic citrullinated peptide (anti CCP) and RA levels.

**Keywords:** Pulmonary vasculitis, Rheumatoid arthritis, Cavitating nodule

**Introduction**

Pulmonary involvement in rheumatoid arthritis is seen in 30-40% patients and in 10-12% patients it might be the initial presentation of RA [1]. It is associated with significant morbidity and is the second leading cause of RA-associated mortality. Pulmonary vasculitis, a rare manifestation of RA, is typically identified in those with long-standing severe forms of RA [2]. A recent study has demonstrated that anti-cyclic citrullinated peptide (CCP) positive individuals with airways or interstitial lung disease may represent a pre-articular RA phenotype[3]. In this report, we describe a patient who presented with cavitating nodule with pleural effusion secondary to pulmonary vasculitis with a positive anti-CCP antibody as initial presentation of RA.

**Case Report**

60-year-old man presented to us with complaints of progressive dyspnoea and cough associated with copious expectoration and fever since 4-5 months. There was no history of joint pain, rashes or Raynaud's phenomenon. He had been initially diagnosed as left sided pleural effusion based on Chest X ray (Figure 1) and pleural fluid ADA being high, was initiated on ATT (Anti tuberculous therapy) in another hospital. Despite intake of ATT, the pulmonary complaints persisted and there was worsening clinically and radiologically and hence followed up with us for further management.

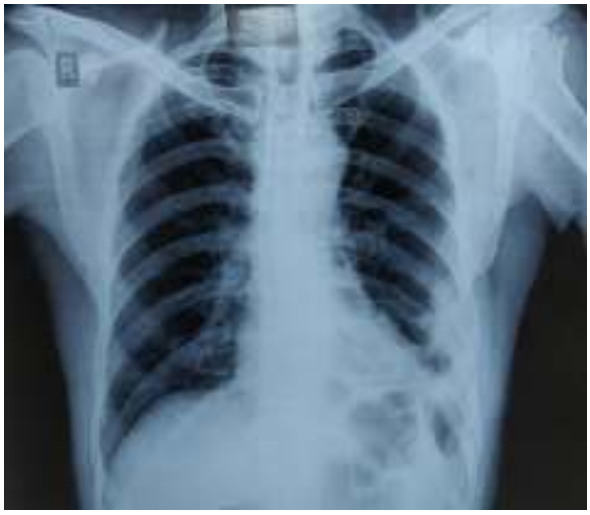

Figure 1 : Chest X ray showing presence of left sided pleural effusion with left lower zone patchy opacity.

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On general examination, vitals were stable. On respiratory system examination, there was presence of crackles on left infrascapular and left infraaxillary area. Other systemic examination was unremarkable.

He was evaluated with Chest radiograph which revealed presence of left lower zone cavitating nodule (Figure 2). High resolution computerised tomography of thorax (HRCT) done showed the presence of left lower lobe cavitatory lesion (Figure 3). Sputum investigations were negative for tuberculosis and other infections. Renal function test and urine microscopy was normal. ENT evaluation for upper airway was normal. Hence subjected to CT guided biopsy of the cavitating lesion which revealed necrotising pneumonia with no evidence of malignancy or granulomas. Bronchoscopy was done and subsequently biopsy was taken from left lower lobe which revealed perivascular neutrophilic infiltration involving the three layers of vessel in a background of necrotising pneumonia (Figure 4).

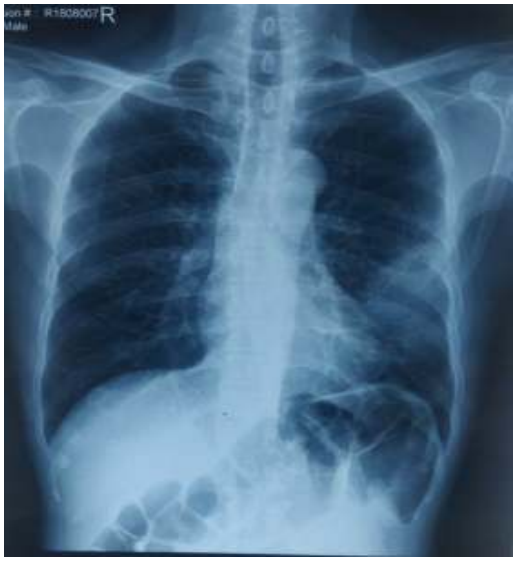

Figure 2 : Chest x ray showing the presence of left lower zone cavitating nodule

As there was perivascular infiltration with neutrophils on biopsy, the patient was investigated to find out the aetiology of vasculitis. RA factor and anti CCP were highly positive for him, while the other factors of ANA profile and ANCA were negative. Hence a diagnosis of cavitating pulmonary nodule secondary to rheumatoid arthritis was made. Patient was referred to rheumatology services and initiated on immunosuppressive therapy with steroids. Following 6 weeks of administration there was complete resolution of left lower lobe cavitating nodule (Figure 5).

**Discussion**

Rheumatoid arthritis is a chronic inflammatory disorder of autoimmune aetiology characterised by symmetrical erosive destruction of cartilage and bone. Usual manifestation is symmetrical involvement of small joints in hand and feet, which may subsequently lead to deformities. Extra articular manifestation may often be the initial presentation of Rheumatoid arthritis which may be in the form of lung involvement, eye involvement, subcutaneous nodule formation, neurological involvement and cardiac involvement [4,5].

Lung involvement often contributes to significant morbidity and mortality. It may manifest with the airway involvement, parenchymal involvement, pleural involvement or pulmonary vasculature involvement. Lung parenchyma is most often affected manifesting in the form of interstitial lung disease. Pleural involvement may manifest in the form of pleural effusion, pleural nodules. Both the upper airway and the lower airway may be involved. It may present as cricoartenoid joint arthritis or glottis stenosis and may present as bronchiectasis or obliterative bronchiolitis.

Vasculitis is a well-recognized extra-articular manifestation of RA; however, it is usually associated with long-standing, severe sero-positive disease[6,7]. Vasculitis associated with RA may present in the skin with pyoderma gangrenosum, nervous system with mononeuritis multiplex, or may involve other organs such as the lungs. In the lungs, vasculitis may present with nodular opacities which may often cavitate often masquerading as infection or a lung abscess. However due to advances in the current era and with availability of more effective disease modifying anti-rheumatic drug therapies including monoclonal antibodies, RA-vasculitis is less commonly seen.

Rheumatoid vasculitis is characterized by features of vessel wall destruction often, including necrosis, leukocytoclasis, and disruption of the internal and external elastic lamina. An important observation is that inflammation of greater than three cell layers of the vessel is a sensitive and specific finding to distinguish rheumatoid vasculitis from RA without vasculitis or rheumatoid nodules[8].

In our case, patient initially presented as pleural effusion and subsequently developed left lower lobe cavitating nodule. We believe that development of effusion

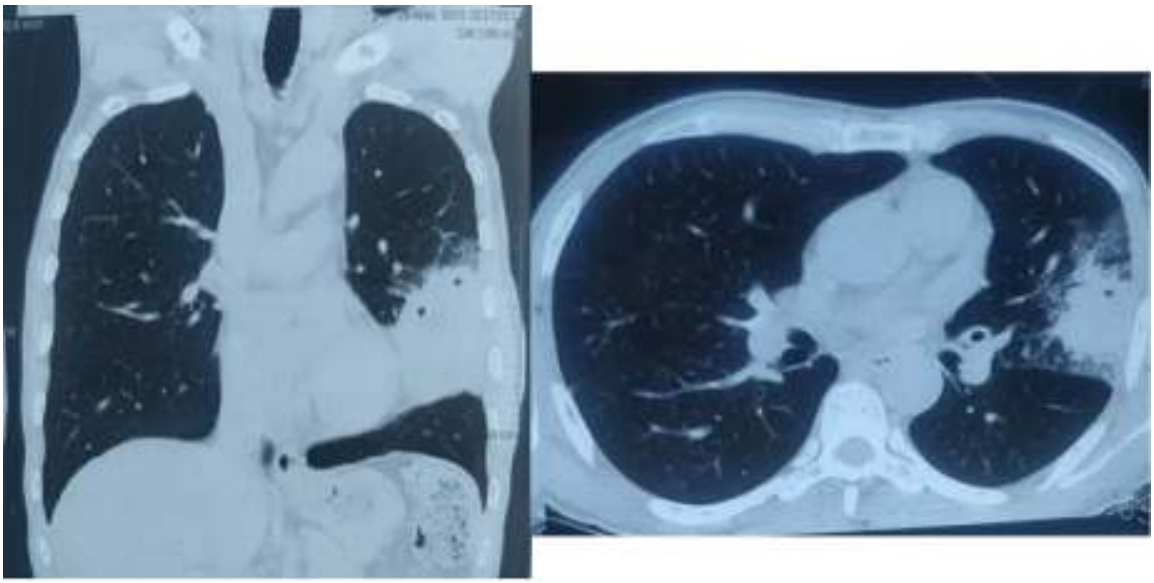

Figure 3 : CT thorax showing Left lower lobe cavitating nodule

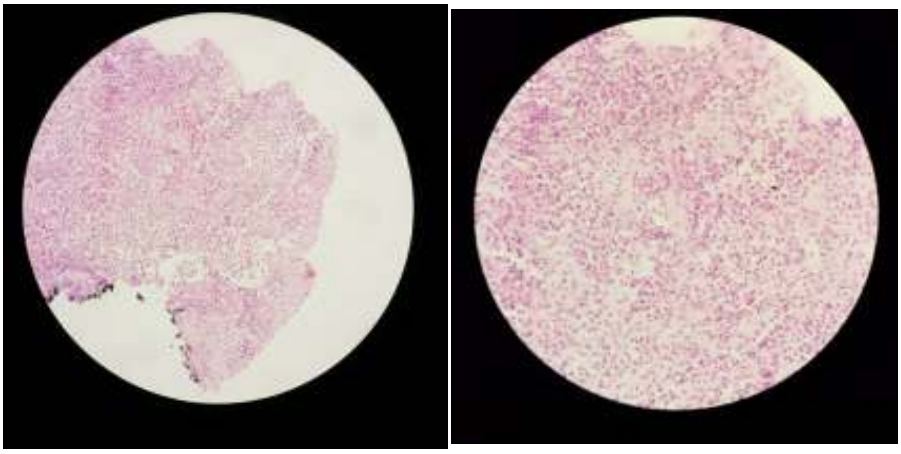

Figure 4 : Histopathology showing perivascular neutrophilic infiltration in a background of necrotising pneumonia

and cavitating nodule is more likely to be secondary to pulmonary vasculitis which might have been the initial presentation of rheumatoid arthritis. Because of the high levels of anti CCP and Rheumatoid factor in serum with other autoimmune profile being negative and with absence of clinical features of RA, this might be an extra articular manifestation of rheumatoid arthritis. There is an increasing evidence that high levels of anti CCP is more specific for rheumatoid arthritis and the lung disease may predate the articular manifestations.

Subsequently on therapy with immunosuppressive agents there was complete resolution of left lower cavity.

While evaluating any cavitating lesions in the lung, after ruling out more common infective causes initially, one should consider connective tissue disorders. Often they have associated systemic manifestations. A comprehensive approach to rule out connective tissue

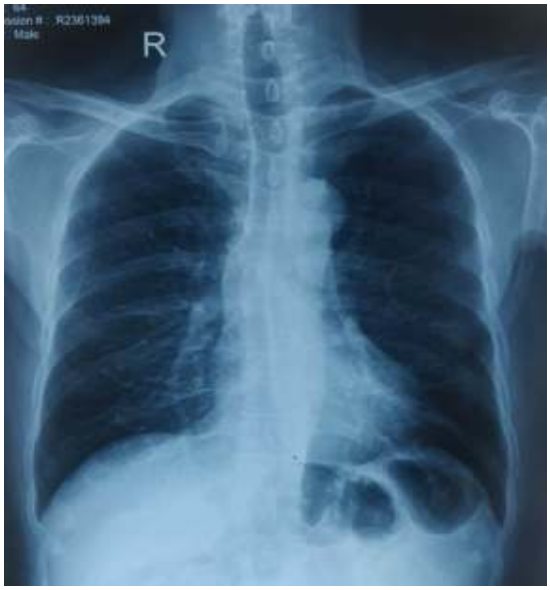


Figure 5 : Complete resolution of left lower zone nodule

Table 1: Differential diagnosis of cavitating pulmonary lesions

| | |
|---|---|
| Infection | Pulmonary tuberculosis |
| | Bacterial abscess or cavitating pneumonia |
| | Septic pulmonary emboli |
| | Other rare infectionsPulmonary coccidioidomycosis<br>Pulmonary actinomycosis / thoracic Actinomycosis<br>Pulmonary nocardiosisMelioidosis<br>Pulmonary cryptococcosis |
| Malignancy | Adenocarcinoma |
| | Small cell carcinoma |
| | Sarcoma |
| Non infective granuloma | Rheumatoid arthritis |
| | Wegener's granulomatosis |
| Vascular causes | Pulmonary infarct |
| Trauma | Pneumatoceles |
| Congenital | CCAM(Congenital cystic adenomatoid malformation) |
| | Sequestration |
| | Bronchogenic cyst |

disorders including clinical, radiological and serological tests needs to be done.

Rheumatoid arthritis may present with initial manifestation as pulmonary vasculitis and subsequently patient may develop arthritis. To our knowledge this is only the second case that has been reported where the initial manifestation of rheumatoid arthritis may be pulmonary vasculties.

**References:**


1. You-Jung Ha, Yun Jong Lee, and Eun Ha Kang, Lung Involvements in Rheumatic Diseases: Update on the Epidemiology, Pathogenesis, Clinical Features, and Treatment, BioMed Research International, vol. 2018, Article ID 6930297, 19 pages, 2018. https://doi.org/10.1155/2018/6930297.
2. Schneider H.A, Yonker R.A, Katz P, Longley S, Panush R.S. Rheumatoid vasculitis: experience with
13 patients and review of the literature. Semin Arthritis Rheum. 1985 May;14(4):280–286. [PubMed] [Google Scholar]
3. Fischer A, Solomon J.J, du Bois R.M, Deane K.D, Olson A.L, Fernandez-Perez E.R. Lung disease with anti-CCP antibodies but not rheumatoid arthritis or connective tissue disease. Respir Med. 2012 Jul;106(7):1040–1047. [PMC free article] [PubMed] [Google Scholar]
4. Alessia Alunno, Roberto Gerli, Roberto Giacomelli, and Francesco Carubbi, Clinical, Epidemiological, and Histopathological Features of Respiratory Involvement in Rheumatoid Arthritis, BioMed Research International, vol. 2017, Article ID 7915340, 8 pages, 2017. https://doi.org/10.1155/2017/7915340.
5. Yunt, Zulma X, and Joshua J Solomon. Lung disease in rheumatoid arthritis. Rheumatic diseases clinics of North America vol. 41,2 (2015): 225-36. doi:10.1016/j.rdc.2014.12.004
6. Tourin O, de la Torre Carazo S, Smith DR, Fischer A. Pulmonary vasculitis as the first manifestation of rheumatoid arthritis. Respir Med Case Rep. 2013 Feb 5;8:40-2. doi: 10.1016/j.rmcr.2013.01.003. PMID: 26029614; PMCID: PMC3920422.
7. Megan Shaw, Bridget F. Collins, Lawrence A Ho, Ganesh Raghu. Rheumatoid arthritis-associated lung disease. European Respiratory Review Mar 2015, 24 (135) 1-16; DOI: 10.1183/09059180.00008014.
8. Voskuyl AE, van Duinen SG, Zwinderman AH, et al. The diagnostic value of perivascular infiltrates in muscle biopsy specimens for the assessment of rheumatoid vasculitis. *Ann Rheum Dis.* 1998;57:114–117.

## Obituary

# Remembrance - Dr. P.Ravindran

Saturday 3rd April 2021 is an unforgettable day in the history of Pulmonary Medicine of Kerala when we lost Dr. P.RAVINDRAN, a Doyen in Pulmonary Medicine of International acclaim quite unexpectedly. It was a sad moment for all who loved and respected him , both in the medical community and the public.

Dr. P.RAVINDRAN who was born on 20th June 1942 had his early medical education at Government Medical College , Calicut. After passing MBBS in 1965, he joined the Government Medical College, Trivandrum to pursue post graduate study in General Medicine. After his post graduation, he joined the Medical Education Department, at Government Medical College , Calicut as tutor in TB and Chest Diseases. He was soon deputed for DTCD ( at that time there was no MD in TB and Chest Diseases) to BANARAS Hindu University. After the successful completion of the course, he was appointed Asst.Prof. of TB and Chest Diseases in Government Medical College, Trivandrum.

While striving to improve the care of his tuberculosis patients, he took active interest to start post graduate diploma in TB and Chest Diseases (DTCD) to impart training for students. His persistent efforts in this direction was materialised in 1977 with the starting of DTCD course in Government Medical College, Trivandrum. In an effort to further broaden the scope of the speciality, he could convince the then government for the need for MD course in TB and Respiratory Medicine and was formally launched in the Government Medical College, Trivandrum in 1984.

He became the professor, later Director and Professor of TB and Respiratory Medicine Government Medical College, Trivandrum. His dedicated work in the realm led to the establishment of the first ever Allergen Manufacturing Centre, in the state.

He became the first person from India to be selected for USAID fellowship in Management of Professionals in Medical Colleges and clinical epidemiology in Toronto in 1988. He underwent special training in Biostatics , Health Economics , Health Social Sciences from the Institute of Medical Sciences, Toronto and McMaster university. On return he took steps to set up the INDIACLEN , he being the founder secretary and later it's president. Soon Clinical Epidemiology Unit (CEU) was started at Government Medical College, Trivandrum. Later it was converted into Clinical Epidemiology Resource and Training Centre (CERTC) in 1990. He was the Founder , Director of both . This gave tremendous momentum to clinical research in the state.

Soon he became elevated to the Vice Principal of Government Medical College , Trivandrum which could reveal the managerial and administrative potentials of P.Ravindran . He has served University of Kerala as Chairman of Doctoral Committee, Chairman Post Graduate Committee, Member Faculty of Medicine , Member MBBS pass board , Member Health Science Standing Committee.

He had been the Post Graduate examiner for various universities across the country and National Board of Examinations.As a brilliant research scholar he had done several original research work and got them published in national and international journals . He had also served as the editor- in- chief of Lung India.

The Government of Kerala has honoured him with 'The Best Doctor Award' in 1996 to reciprocate his accomplishments as a doctor in the public sector. He earned the visiting professorship in Yale University, USA in 1990 and 1994. Other noteworthy recognitions include the Best Alumini Award of Government Medical College Calicut, OMShivpuri Oration 1997 , Raman Viswanathan Oration 2020 (both National Awards).

He had been conferred Lifetime Achievement Awards by several organisations like Indian Chest Society and National College of Chest Physicians (India) , Academy of Pulmonary and Critical Care Medicine, Paediatric Allergy and Immunology Association, Coimbatore Pulmonary Society , International Asthma Services , Colarado – USA , World TB Day Lifetime Achievement by the Trivandrum Association of Pulmonary and Critical Care Medicine.

Amidst his hectic academic, clinical and administrative responsibilities, he was in the fore front of many organisational activities as well. He was president of the Indian Chest Society , President of National College of Chest Physicians (India) , President of Indian College of Allergy, Asthma and Applied Immunology , President of Academy of Pulmonary and Critical Care Medicine (APCCM), President of Trivandrum Association of Pulmonary and Critical Care Medicine (TAPCCM). He was an active member of American College of Chest Physicians (ACCP). He was the founder patron of Pulmonary Research Initiative of Trivandrum (PRIOT) .

In 1997, he retired as Vice Principal of Government Medical College , Trivandrum. Soon after retirement, he joined the Cosmopolitan Hospital, Trivandrum of which he was also a shareholder. As in the public sector, here again he immersed in developing the pulmonary, sleep and critical care medicine as a trend setter speciality. He initiated steps to start DNB course in pulmonary Medicine and was soon entrusted the task of running DNB courses in other specialities as well.Board.

Dr P Ravindran was a multifaceted personality with tremendous potentials. He was an astute clinician, a prolific genius, a teacher par excellent, a brilliant researcher and a superb academician. He used to take care of his ailing patients with empathy and compassion.

When Novel Coronavirus outbreak happened in China, he was the first to arrange a session exclusively on 'Novel Corona Virus' at Cosmopolitan Hospital. Since it became a pandemic, he was instrumental in conducting regular bimonthly webinars under PRIOT as 'Chasing Covid19'. The last session he moderated was on 17th March 2021.

We, individually and collectively are immensely indebted to Dr P. Ravindran, a giant in Pulmonary Medicine, a Master Clinician and above all a magnificent personality, for transforming and popularising the TB and Chest diseases in to the high profile pulmonary, sleep and critical care medicine. It is quite befitting that he is affectionately called as the 'Father of Pulmonary Medicine in Kerala'. But in reality he was an erudite pulmonologist of international acclaim. He was capable of identifying talents and fostering them.

Though he has left us physically the legacy he left behind will continue to glow inspiring generations of pulmonologists to come. We join his family sharing the sorrow and agony due to his sudden unexpected demise.

Let us pray for his soul to rest in peace and harmony.

To quote his saying ' If you choose to be a practising clinician , be prepared for lifelong learning' . 'You should be reading and learning till you go to the graveyard.'

Dr. P. Ravindran Sir's glorious innings in the field of Pulmonary Medicine will be scripted in golden letters in the annals of Pulmonary Medicine of the State as a legend.

With PRANAMAM and Floral tributes to the fond memory of Dr. P.Ravindran Sir

Long Live Dr. P. Ravindran Sir

M. Raveendran Nair

Senior Consultant Pulmonologist

Cosmopolitan Hospital , Trivandrum

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Only such data as are essential for understanding the discussion and main conclusions emerging from the study should be included. The data should be arranged in unified and coherent sequence so that the report develops clearly and logically. Data presented in tables and figures should *not* be repeated in the text. Only important observations need to be emphasized or summarised. The same data should not be presented both in tabular and graphic forms. Interpretation of the data should be taken up only under the Discussion and *not* under Results.

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