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Pulmon

The Journal of Respiratory Sciences

Mood disorders in asthma - There is more to it than meets the eye

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Mood disorders including major depressive disorders and bipolar disorders are commonly encountered in clinical practice. They affect children, adolescents and adults, with an onset as early as preschool days. Anxiety including panic attacks, generalised anxiety disorders and phobias frequently co-exist with depressive disorders.[1]

Asthma is a chronic medical condition that has been linked with mood disorders and anxiety. A number of studies have investigated the interaction between asthma and mood disorders such as anxiety and depression. Both these are common comorbid conditions in patients with asthma which have an impact on treatment choices, medication adherence, level of asthma control and quality of life. Panic attacks may also be mistaken for asthma.

Asthma was previously thought to be a psychosomatic disease because of the episodic nature of the disease in which symptoms would suddenly appear without an apparent cause. It is however important to note that asthma is primarily not a psychosomatic disorder. Emotional causes have also been thought to produce asthma exacerbations.[2] During stressful times medication adherence may also decrease. Numerous clinical studies have found that patients with asthma suffer from higher rates of depressive and anxiety symptoms than healthy controls.[3] Suicidal ideation has also been shown to be more common among asthmatic adults.[4]

The impact of depression and anxiety on asthma symptoms has been investigated in a large population based study in which it was found that, anxiety and depressive disorders led to significantly more asthma symptom days in the previous 2 weeks than those without anxiety or depression.[5]

A study by Solis and coworkers has shown that asthma heralded the onset of the first depressive symptoms in 62% of patients while depression preceded asthma in 24% and both presented at the same time in 14% of participants studied.[6]

In this edition of the journal Shabna Khader and coworkers have explored the association between depression and level of asthma control. They have identified certain factors which are associated with poor asthma control and these include depression, poor compliance with medication, rhinosinusitis, low socioeconomic status and FEV_1 < 60%. They subdivided their study population into two groups – controlled and uncontrolled asthmatics. Out of the controlled asthmatics 11.9%, and out of the uncontrolled asthmatics 52.3% experienced moderate to severe depressive symptoms.

Pathophysiology that connects asthma and mood disorders

Asthma is a chronic inflammatory disorder of the airways which causes airway hyper responsiveness and bronchial obstruction. Immune responses regulated by T-lymphocytes play a major role in asthma. Th-2 cells play a major role in the allergic inflammatory cascade in asthma. Some data suggests that psychological stress may shift the Th-1/Th-2 cytokine balance towards Th-2 pathway and thereby causes immune dysregulation leading to asthma flare up during periods of high stress.

Psychological stress also activates the hypothalamic-pituitary-adrenocortical axis as well as the sympathetic nervous system, which lead to an increase in cortisol and catecholamine secretion. These in turn, supress the Th-1 cytokines and shifts the immune balance towards Th-2 phenotype.[7]

Asthma is notorious to produce nocturnal symptoms and sleep disturbances. Impaired sleep leads to daytime fatigue, difficulty in concentration, worsened mood and depression as well.[8] The functional impairment caused by asthma leads to reduced participation in physical, social and outdoor activities, the last of which also implies that there is reduced exposure to natural light. All these factors can potentially trigger depression. Apart from this, anxiety has also association with uncertainties associated with asthma symptoms and disease flare-up.[9]

Effects of asthma medications on mood disorders

Controller and rescue medications used for asthma treatment, both can have an impact on mood disorders. Systemic steroids are associated with depression, mania and psychosis. Patients with difficult to control asthma and severe asthma usually need long term or frequent bursts of oral steroids for symptom control. This has been shown to be associated with an increase in depressive symptoms.[10] Inhaled corticosteroids which are the mainstay of asthma treatment have been demonstrated to be relatively safe in children and adults. Leukotriene modifiers like Montelukast have been rarely associated with hallucinations, aggressive behaviour, insomnia and depression.[11]

Bronchodilators used for asthma treatment are known to produce side effects like tachycardia and tremors. These adverse effects have been shown to provoke a sense of anxiety in patients who experience them.

Conclusion

It is very well established that anxiety and depression are comorbid conditions which impair asthma control and make the disease relatively "difficult to control". As has been outlined in the GINA guidelines, it is very important to identify these underlying mood disorders and treat them accordingly to achieve a better control of asthma. Hence it is important to arrange a mental health assessment for all patients with asthma who exhibit symptoms of anxiety or depression. Treatment options for patients having concomitant anxiety or depression include cognitive behavioural therapy, psychoeducation, relaxation, drug treatment and biofeedback.[12] These have been shown to improve symptom control in patients with asthma who have concomitant mood disorders and improve their quality of life.

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Bedside decision making-How can we make the cognitive short cuts more efficient?

C.Sudheendra Ghosh[1], Sarun Ghosh[2,] Sayujya S Ghosh[3].

Abstract

Bedside clinical decision making by expert physicians invloves various cognitive process described under heuristics. Identification of biases and their correction can make these cognitive short cuts more efficient. It is one of the cost effective way of improving basic clinical skills. A thorough understanding and application of evidence based medicine can further strengthen the clinical management capability of the junior doctor at the bedside.

Introduction

Decision-making at bedside is the cognitive process resulting in the selection of a course of action among several alternative diagnostic possibilities.Understanding the process by which experienced clinicians formulate diagnoses and make critical decisions can help future doctors.They may be able to minimize errors in their own judgments as well as build training activities around known strengths and limitations of cognition. Health care decisions are often time consuming and ethically difficult as they require to take into account complex dimensions such as faith, personal beliefs,societal values, cultural and socioeconomic pressures[1] (Figure 1).

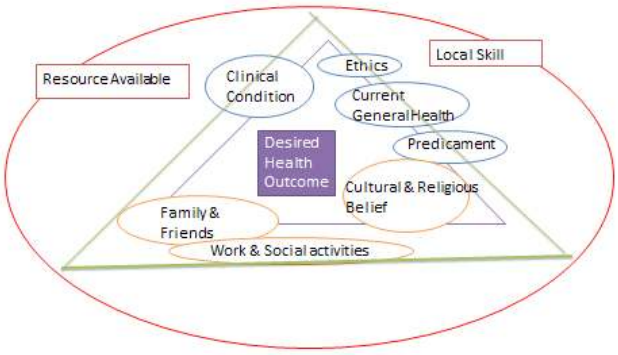

Figure 1 - Variables considered For health Care Decisions

Evolution of Clinical Epidemiology and Evidence Based Medicine (EBM)

William Osler (1849 -1919) portrayed medicine as "a science of uncertainty and an art of probability". The evolution of EBM dates back when AlRhazi, a physician, in early 900 AD has noted his observations regarding the difference between the treated and non-treated. A Scottish doctor, James Lind (4 October 1716 – 13 July 1794) had developed a theory which proves, citrus fruits cured scurvy which was considered as the first ever clinical trials. Pierre-Charles - Alexandre Louis (14 April 1787 – 22 August 1872), a French physician, was considered as the forerunner to epidemiology and the modern clinical trial by initiating the development of the "numerical method". In 1947, Sir Austin Bradford Hill and his colleagues conducted the Streptomycin trial and reported that combination of Streptomycin and PAS resulted in better outcome than either drug alone in the management pulmonary tuberculosis. In October 1951, Sir Richard Doll and Sir Austin Bradford Hill conducted the Lung cancer survey among all registered British doctors to establish the association of smoking and lung cancer. An American clinician, epidemiologist and researcher, Alvin R. Feinstein (December 4, 1925 – October 25, 2001) is considered as one of the fathers of modern clinical epidemiology due to his significant impact on clinical investigations. Prof Archibald Cochrane was a British researcher (1909 - 1988); He wrote in 1979 that our profession is criticized by many because we have not organized a critical summary of all randomized control trials by specialty or subspecialty wise and updated it regularly. The Cochrane Collaboration is named to honour Archie Cochrane.

Alvin Feinstein and David Sackett initiated clinical epidemiology movement which translated epidemiological analytic methods to physician decision making in clinical practice. The EBM movement started in 1981, at

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McMaster University when a group of clinical epidemiologists, headed by David Sackett, published articles guiding the physicians regarding how to appraise the medical literature. It was Gordon Guyatt who coined the actual term "evidence-based medicine". He was the Program Director of Internal Medicine at McMaster University during the period from 1990 to 1997. Evidence-based medicine (EBM) is "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients"[2]. In 1995, David Sacket at McMaster University, using the Evidence cart during his ward rounds looked up 2-3 questions per patient, they were able to modify one third of their clinical decisions within 15-90 seconds[3]. They used the 5 steps for implementing evidence base in clinical practice (Table.1). First step is framing a question related to the health problem of the patient. Next step involve literature search for best evidence related to that question. This is followed by its appraisal. Then apply information in combination with clinical expertise and patient values. Final step involve documentation of the outcome.

Table 1: Stages and activities of ABM

Stages	Action
Step 1	Ask a question
Step 2	Find best evidence from literature
Step 3	Appraisal of evidence
Step 4	Apply information in combination with clinical expertise and patient values
Step 5	Evaluation of outcome

Teaching the Science and Art of Medicine in EBM

Teaching the science and art of medicine is an important consideration for those entrusted with training the next generation of physicians[4]. Use of the "Evidence-based" approach helps to incorporate accurate and appropriate integration of research evidence into patient care. EBM requires precision, attention, and humility. It also needs deliberate, thoughtful, and mentored experience. EBM is considered as an approach to improve the practice of medicine. It also helps to improve decisions by individual physicians about a patient. The EBM aims to integrate the experience of the clinician along with the values of the patient and the best available scientific information to guide decision-making about clinical management in daily clinical practice.

Why medical information is associated with uncertainty?

Medical decision making can vary as it involves physician's knowledge, experience and judgment[5]. There are also problems with validity and reliability of information with regard to risk, outcomes preferences and perspectives. Medical information is associated with high levels of uncertainty because of biological differences and measurement variations. Quantum of errors that can occur can be reduced by applying probabilistic reasoning and technology based analytic reasoning

How use of Technology helps to improve certainty of clinical context?

To minimise errors in clinical decisions, technology based Artificial Intelligence (AI) and Machine Learning (ML) programs are being widely applied. Two types of reasonings are incorporated in AI and ML technology. Programs of AI and ML use categorical (or deterministic) reasoning at one extreme and probabilistic (or evidential) reasoning at the other. Prototype for categorical reasoning is flowchart and for probabilistic reasoning is decision analysis. To demonstrate expertise in medical consultation these programs will have to use a judicious combination of categorical and probabilistic reasoning. Categorical reasoning helps to establish a sufficiently narrow context and probabilistic reasoning to make comparisons among hypotheses[6]. Programs based on above reasoning eventually lead to better recommendations in therapy. A new era which is variably called as "personalized" or "precision" medicine has emerged as a result of advances in genomics and other 'omic' technologies. This

had taken into account of individual genetic and other sources of variability in disease treatment and prevention[7-8]

Figure 2 - Next Level of EBM

What is the role heuristics at bedside Decisions?

Evidence based decision making is a process of integration of clinical data to decrease diagnostic uncertainty, to reduce risks to patients and to avoid unnecessary costs. It helps in deciding what information to gather, which tests to order, how to interpret and integrate test information to draw diagnostic conclusions and to decide which treatments to give. All are essential for bedside decision making[9]. "Heuristic" is a Greek word meaning "to discover." Heuristics is an intuitive understanding of probabilities that is combined with cognitive processes at bedside. In 1973, Nobel-prize winning psychologists, Daniel Kahneman and Amos Tverskyfirst coined the term Heuristics[10]. They described Heuristics as rules of thumb, educated guesses, or mental shortcuts. It also involves pattern recognition and relies on a subconscious integration of patient data with prior experience. Common Cognitive Heuristics described are Availability, Representative, Anchoring and Adjustments heuristics.

Availability heuristics estimate the prior probability of disease from recent experience. Experiences may often cause overestimation of probability especially when there is memory of a case that was dramatic or a lawsuit involved a patient who fared poorly.

Representative Heuristic – here one may judge the probability of disease based on how closely the patient's findings fit classic manifestations of a disease as described in our standard text books. Typical case of angina pectoris diagnosed at emergency room.

Anchoring and adjustment heuristics regularly modify initial impression as new data accumulate. Consideration of disease prevalence and our prior experience with the condition figure into hypothesis generation. A framework is created by this dominant hypothesis for subsequent data gathering and analysis. Adjustment is done by the process of confirmation and elimination strategies.

What are the common errors committed at bedside?

While we use these cognitive short cuts many types of cognitive errors can occur. Faulty assessment of pre-test probability can result in overestimating or underestimating of disease likelihood. Improper testing (too much or too little) and missed diagnoses may result if all relevant possibilities of a disease is not considered. Identifying the following types of cognitive errors and avoiding it with appropriate corrective measures will help us to increase the efficiency and effectiveness of our patient management[11-12].

Premature closure: Premature closure errors occur when a woman with a long history of migraine presents with a severe headache. We may be tempted to make a quick diagnosis (often based on pattern recognition), and fail to consider other possible diagnoses (brain tumour). Stop collecting further data and jump to conclusions without further confirmation by appropriate testing.

Confirmation bias means selectively accept the clinical data that support a desired hypothesis and ignore other data (cherry-picking). A clinician may steadfastly stick to patient history elements that are suggestive of acute coronary syndrome (ACS) to confirm the original suspicion of ACS even if the serial ECGs and cardiac enzymes are normal.

Attribution errors are errors which include negative stereotypes that minimize or ignore the possibility of a serious disease. For example, clinicians might assume that an unconscious patient with an odour of alcohol is "just another drunk" and miss hypoglycaemia or intracranial injury. A known drug abuser when present with back pain, may be assumed to be simply seeking drugs and hence may miss an epidural abscess caused by use of dirty needles.

Affective errors are errors that occur when avoiding unpleasant but necessary examinations or tests because of sympathy or fondness for the patient. For example: blood cultures on a seriously ill patient who has poor veins or avoiding a pelvic examination on a modest patient.

Strategies for minimising cognitive errors

Cognitive errors can be reduced with the help of some specific strategies. For example after history and physi-

cal examination formulate a working diagnosis based on heuristics. At this point- pause for asking several questions:

1. If it is not the working diagnosis, what else could it be?
2. What are the most dangerous things it could be?
3. Is there any evidence that is at odds with the working diagnosis?

The above questions can help to expand the differential diagnosis that may include things that have been left out due to cognitive errors and remained clinicians to obtain further necessary information.

What are the components of bedside decision making?

Clinical decision making involves the integration of clinical data along with lab evaluation data to decrease diagnostic uncertainty, costs and risks to patients. It is a process that decides what clinical information to gather, which lab tests to order, how to interpret and integrate this information to draw diagnostic conclusions and which treatments to give. Analytic decision making is a quantitative, structured, and analytical methodology that is found to be a better method to decision making for complex cases. Usually pattern recognition provides the most likely diagnostic possibility. Analytic methods may include the application of the principles of evidence-based medicine, use of guidelines and use of various specific quantitative techniques (eg, Bayes theorem).

What is probability estimation?

The probability of a disease in a patient is the frequency with which that disease or event occurs in a population. Probabilities range from 0.0 (impossible) to 1.0 (certain).Disease probabilities (prevalence) are expressed as percentages (from 0 to 100). A disease that occurs in 2 of 10 subjects has a probability of 2/10 (0.2 or 20%)

What is Odds ratio?

Odds represent the ratio of people with disease to people without disease (i.e., the ratio of disease to no disease).A disease that occurs in 2 of 10 subjects as above (probability of 2/10) has an odds of 2/8 (0.25, often expressed as 1 to 4). Probabilities (p) and Odds (Ù) can be converted one to the other. As in the formulae Ù= p/ (1 ″ p) or p =Ù/(1 +Ù). The likelihood ratio can be calculated from experimental test results. This can thus be converted to odds to form the strength of evidence.

How hypothesis generation and hypothesis testing is done during clinical evaluation?

During clinical evaluation of patients at bed side, various hypotheses are generated for testing. Relevant diagnostic possibilities are considered as differential diagnosis. Starting points for the differential diagnosis are from the patient's chief complaint (eg, chest discomfort) and basic demographic data (age, gender, and race) and findings on physical examination. Diagnostic hypothesis are generated by pattern recognition. A presumptive diagnosis is made from the clear-cut pattern obtained from the history and physical examination. Then from the list of possibilities each element is ideally given an estimated number as its likelihood. The probability generated in this way forms the pre-test probability. When uncertainties persist even after the history and physical examination diagnostic testing is used. Once the test results are available the initial diagnostic hypotheses is either accepted or rejected based on the strength of the test result (Post-test probability). This hypothetical-deductive method can improve basic diagnosis and is based on Bayes' theorem on conditional probability[13]. The theorem states that the probability of a diagnosis (the post-test probability) is dependent upon the probability of the diagnosis prior to a test (the pre-test probability) and the strength of evidence added by a test.

Summary

Clinical decisions at bedside, had to be made in the absence of good quality evidence that one treatment modality is better than others. In such situations we have to formulate our decisions based on information derived from observational studies, personal experience or case reports. Understanding the ways by which experienced physicians make critical decisions is useful to minimize errors in our own judgments. This is also important for building training and teaching activities around known strengths and limitations of cognition. Mental templates or scripts of disease processes stored away from prior experiences are helpful at bedside. The prevalence of a condition in the population is often a good estimate of the pre-test probability. We usually anchor at the pre-test probability and modify this probability as new information is collected by testing (Post-test probability).

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Robert Koch & Koch's Bacillus

Deepthi Madhu

Until the 17th century, the probable reason behind *consumption* were wild guesses ranging from poison to curses. The 19th century brought with it the Germ theory of disease. Germ theory was freshly brewed, so to speak, and it was not proving to be everyone's cup of tea. It was during these times that Robert Koch entered society as a practising physician. Robert Koch with his calm disposition and scientific brilliance worked with his patients. He spent a lot of his time and energy on their samples under his microscope. And when it yielded no satisfactory evidence, he turned to death to support him!

It was at this point that Koch came across anthrax which was cursing the lives and livelihood of his common farmer patients. It affected mainly the livestock, and it baffled him that it had such a fatal outcome with a short course of the disease: mildly sick one day, septic the next, dead the day after; respiratory distress and the black blood remained common factors. It was in the black blood collected from these dead anthrax afflicted animals that Koch first observed the causative anthrax bacillus. As a result of purely scientific and ground-breaking experiments, he devised the first-ever specific culture medium, and on this, he grew a pure culture of the bacterium (which, frankly, was the first-ever pure culture of any bacterium). A scientific letter stating these findings left most peers astounded. And he was called for review with the most acclaimed scientist of the time, Virchow. However, Koch's simple, straightforward experiments and findings were scoffed at by Virchow and declared as not noteworthy [#] ([#]Robert Koch's findings were right and on the dot. His research was exemplary. And formed the basis of the life-saving anthrax vaccine formulated later on by Pasteur & team)

Where a lesser man than Koch would have been deterred, Koch rose like a Phoenix. He turned to Consumption next. *Mycobacterium tuberculosis* has roots that can be traced for more than 10,000 years. During all these centuries, this villain of a microbe was associated with severe morbidity and high mortality. The course of the disease being long and drawn out, with cough, haemoptysis, weight loss and eventually death, earned it the rightful name of "consumption". It spared neither man nor beast. Until the 17th century, there was no inkling that the reason for consumption could be a microbe.

As he did with his cases of anthrax, Robert Koch spent hours studying his patients, and he spent every drop of sample he could extract from his patients, under the microscope. The microbe seemed to be evasive. No matter what Koch tried he could not pin it. He needed more clinical material. So, where his live patients could no longer help him, he turned to death to aid him. Autopsies provided answers, evidence, and support. But even autopsies could guarantee a supply of clinical material to last his research work only for upto a week. And it frankly was not sufficient, because this was after all a rogue bacillus. So, he started injecting this caseation into few laboratory animals to ensure a lasting supply of clinical material. To use these animals as experimental beings was far from his mind at this point. This proved to be a pivotal moment in the budding of Koch's postulates. When the same caseating lesions were noted in the autopsy of these laboratory animals, it was the birth of Koch's postulate1.

Koch, through rigorous and meticulous trial and error method, chalked out the nutritional requirements of this fastidious and finicky bacterium. Considering its minimum incubation period of ~15 days, this was no simple feat. He devised solid and liquid culture media which served pivotal roles in serving his experimental objectives.

To determine the method of transmission of the organism, he sprayed pure liquid culture of the organism into a box containing otherwise healthy animals. And successfully demonstrated lung caseation in these laboratory animals' post-mortem.

As he set about in his work to thoroughly and meticulously thwart any doubts that may arise in anyone's

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minds or any arguments that may arise in any forum, the ground-breaking Koch's postulates, which went on to become the backbone of bacteriology, were born one by one!!!

He inspected his work from every angle and covered every loophole with a scientifically meticulous zest. No stone was left unturned. It was possible, probably because he was not trying to drive the experiments to a particular answer. He did not have a working hypothesis, to begin with. He was getting answers on the go. And the system worked; for he was a patient researcher and a meticulous observer. When all his questions were answered through experiments, he took his results to the public.

His work on tubercle bacilli was briefly interrupted when he was deputed by his nation to determine the cause of the deadly cholera outbreak in India, which he successfully narrowed down to the comma-shaped bacterium we now know as *Vibrio cholerae*.

He suffered from a heart attack at the age of 66 but honoured a previously committed lecture on Tuberculosis at the Prussian Academy of Sciences. 3 days after delivering the lecture he passed away. Why I say about his death is, *firstly*, I think that, that final academic commitment resuscitated him that one last time. *Secondly*, to point out that he did not pass away from anthrax, tuberculosis or cholera (or the many other deadly microbes he dealt with, without knowing anything about them at the outset). Facilities were short, sponsorship were quite unheard of for out-of-the-box-thinking (which sadly continues exactly the same even one and a half centuries later), scientific know-how was bare minimum, and in the case of tubercle bacilli, non-existent. That is a level of infection control par excellence. Salute'!

Among the 1000s of microbes that dwell and thrive, I cannot help being amazed and awestruck at the greatness and uniqueness of *Mycobacterium tuberculosis*. Pandemics of SARS-CoV, SARS-CoV2, H1N1 or even the Bubonic Plague have been able to get attention more because of the element of surprise than anything else. *Mycobacterium tuberculosis* makes the above-mentioned pathogens seem like amateurs. *Mycobacterium tuberculosis*, if you ask me is the king of pathogenic microbes, and Robert Koch the ultimate microbe slayer. For these, and many other reasons, *Mycobacterium tuberculosis* is rightfully called the "**Koch's bacillus**".

We have come much farther in Mycobacterial research especially in the last few decades, but all of it has been built on the firm and solid foundation built by Dr.Robert Koch. All that we currently know about *Mycobacterium tuberculosis*, we owe to the magnificent head start that Robert Koch gave us. Without whose guidance and findings, there is no saying how much longer we would have continued in the dark regarding consumption.

Points I would like to get across:

1. Come pandemic, go pandemic, *Mycobacterium* is here to stay. Give it its due attention, resource, and energy.

2. The potential role of livestock and other ani mals in the propagation of *Mycobacterium*, to be given its due importance always.

3.Resource limitation is a myth. However, if an institutional or ethical sanction is not available, that is a whole different thing.

4.Don't back everything on existing studies; if you do, where you are now, is where you shall always be.

5.Think outside the box. Hypothesize. If it turns out to be a null hypothesis, so be it, If it is a negative correlation, it is still a finding.

6.Research without a hypothesis is not essentially a bad thing.

Year after year, March 24th is observed as Tuberculosis Day, World over. 24 March commemorates the day in 1882 when Dr Robert Koch **astounded** the scientific community by announcing to a small group of scientists at the University of Berlin's Institute of Hygiene that he had discovered the cause of tuberculosis, the TB bacillus.

Forever an ardent Robert Koch admirer.

Diagnosis of allergy – old vs new methods

Ajoy Samuel Mammen

Allergic diseases are a worldwide health problem. The incidence and prevalence of hypersensitivity reactions are increasing day by day. Personalised medicine and precision treatment are the need of the hour. Here, we review the old and novel methods in the diagnostic workup of allergic diseases.

Old methods

1.Skin Prick Test (SPT)

Skin prick test confirms sensitisation in IgE mediated allergic diseases. In 1850, Henry Salter, described the formation of wheals following scratches in patients with asthma and exposed to cats [1]. In 1907, Clemens Von Pirquet modified Koch's subcutaneous procedure based on abrasion of the skin to evaluate for tuberculin response[2].

In 1909 first case of anaphylactic response after exposure to allergen was reported[3]. Practical application of a standardized procedure was put forward by Schloss[4].Several techniques to evaluate allergic sensitisation have been described e.g., Intracutaneous test[5], conjunctival test[6], intracutaneous test by serial dilution[7].

The best technique to evaluate with safety allergenic sensitisation is SPT. It is based on presence of sensitized cells, mainly mast cells in the skin and the resultant cutaneous reactivity is used by the clinician as a surrogate biomarker for sensitisation in eyes, nose, lungs, gut and skin. The test requires both a positive and negative control. A positive result is defined as wheal >= 3mm diameter after 15 to 20 minutes[8,9]. Thus skin prick test is a fundamental technique to study to explore allergen sensitization in patients.

2.Intra dermal skin test (IDST)

IDST when compared to SPT and is more sensitive. It is performed only when the SPT is negative for a particular antigen. The test uses 25–27-gauge needles and allergy syringes. A small amount of antigen (0.02 – 0-05ml) is injected into the skin in order to raise a small wheal of 2 - 3mm in diameter. A minimum distance of 2cm should be present between the test sites. Concentration used for IDST is generally 1:1000 or 1:500 fold more dilute than the concentration used for SPT. IDST when compared to SPT are riskier and adverse reactions such as anaphylaxis have been reported.

3.IgE and allergy

The discovery of reaginic activity in the IgE antibody by Ishizaka in 1967 led to a revolution in the knowledge of allergy. Patients with allergy tends to produce high levels of IgE antibodies[10]. Total IgE concentration does not correlate with clinical manifestations of the atopic conditions. Therefore, it is preferable to measure specific IgE (sIgE)[11,12]. Total IgE concentration is the addition all the specific IgE(sIgE) to the different allergens the individual has been exposed to. Specific IgE levels are below the level of detection (0.35kU/L)in non-allergic individuals[13].

The quantification of sIgE can be done based on antigen antibody reaction

E.g., Radio allegro sorbent assay (RAST), Enzyme linked immune sorbent assay (ELISA) and Fluorescence Enzyme Immuno Assay (FEIA).

New methods

4.Radio allergo-sorbent assay (RAST)

RAST was the first laboratory method developed for invitro detection of specific IgE(sIgE)[14] in atopic individuals. It is the second most used test after SPT, although it is gradually being replaced by newer methods like ELISA. The main advantage over SPT is the safety of the patient. In SPT, the allergen is administered in the cutaneous layer of the skin which can lead to sensitization to new allergens. In some cases, it may trigger anaphylaxis. These were avoided by in vitro tests like RAST. Also RAST may be helpful when the patient's skin is unsuitable for SPT or

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IDST, as in extensive atopic dermatitis or eczema.

4.1.Enzyme-linked immunosorbent assay (ELISA)

ELISA is one of the most common immune-assays used in clinical and experimental procedures. It allows detection of allergy-related analytes, e.g., IgE or Th2 cytokines. Fast performance, improved biosafety when compared with radioimmunoassay, low reagent cost, affordability for the patient, and simple methodology [15] are the advantages of ELISA.

4.2.Fluorescent enzyme immune assay (FEIA)

These are based on the same principle used for ELISA and RAST but differs in the way the read out is made. In FEIA, the secondary antibody is linked to an enzyme that permits the activation of a fluorochrome, the fluorescence of which is measured by a fluorometer[18].

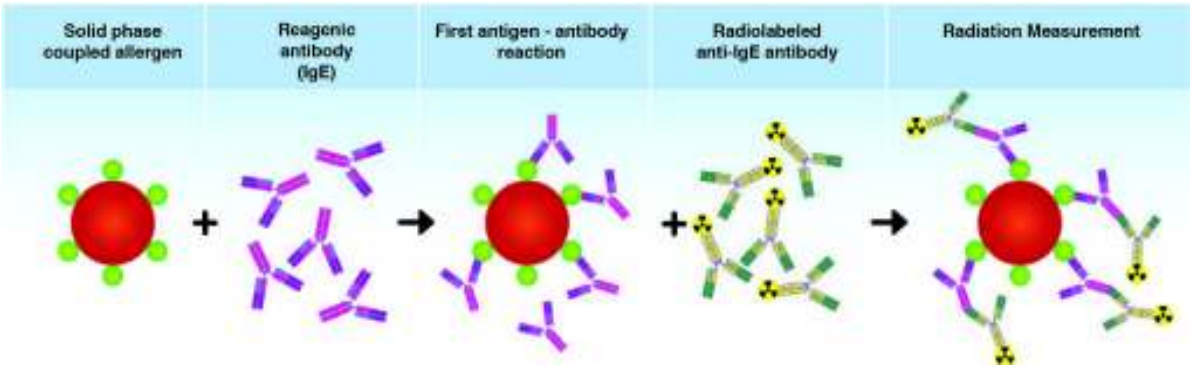

Fig 1 - RAST methodology. An allergen is absorbed covalent to a solid particle,then serum of the patient is added to react with the allergen. Next, a radio labeled IgE antibody identifies the previous formed immune complexes.The radiation generated is measured by a radiation detector.

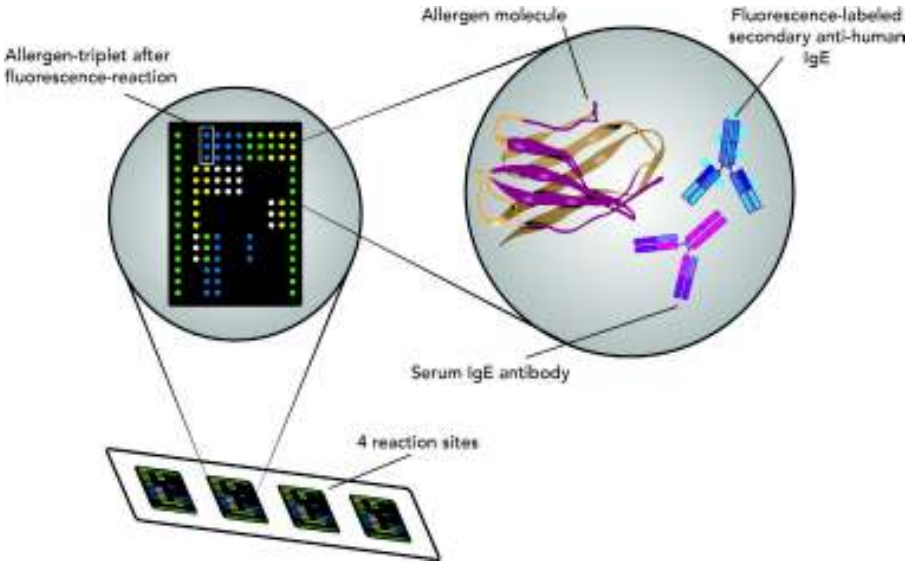

Figure 2. Immuno CAP-ISAC. The recombinant allergens are recognized by sIgE from serum samples; a secondary antibody fluorescent-labelled interacts with IgE. Fluorescence is measured by a biochip. Recombinant allergen diminishes the risk of cross-reactivity

The biotin streptavidin system is the most common substrate used in ELISA method. Due to its safer and faster performance, with a similar sensitivity and specificity it has replaced other methods like RAST[16,17].

Fluorometric assays have paved way to the development of automatized systems, which resulted in improved reproducibility, diminished operator involvement, with reduction of mistakes, and increased sensitivity and specificity [19,20]. FEIA technology can screen specific IgE to

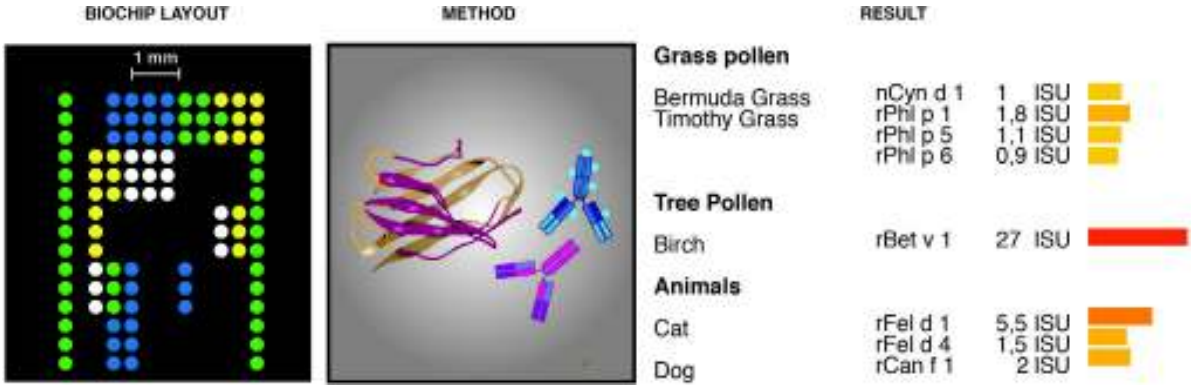

Figure 3. ISAC biochip layout. Results are reported in arbitrary units named ISAC-Standardized Units (ISU).

several allergens at the same time and with minimal amount sample[21].

4.3.ImmunoCAP-ISAC (Immuno solid-phase allergen chip)

SPT has the risk of sensitisation or anaphylaxis in the patient while innovative and non-invasive techniques can lead to the identification of many sIgE to different allergens at the same time, with a minimum sample volume (~50 µL)[22]. ISAC is the first multiplex diagnostic tool commercially available, to evaluate sIgE directed against 112 well-characterized antigens.

First, the sIgE from serum samples interacts with the recombinant allergen previously adsorbed to the solid phase. A secondary anti-human IgE antibody labelled with fluorochrome recognizes sIgE-recombinant allergen complex (**Figure 2**). Fluorescence is evaluated using a biochip and reported in arbitrary units named ISAC Standardized Units (ISU) (**Figure 3**)[23].

ISAC multiplex assay has been proposed to guide therapeutic decisions, e.g., the discontinuation of restrictive diets, the content of allergen-specific desensitization immunotherapy and even to analyse the sensitization profile in multi-sensitized patients to define whether they can receive a specific immunotherapy[24].

4.4.Western blot

It combines different techniques to identify new antigens related to allergy.

Certain allergens share amino acidic sequences that can be recognized by the same IgE antibody and it is known as cross reactivity. Aeroallergens and food allergens have cross reactivity. So, laboratory blood tests may give false positive results even if the patient has never been exposed to them [25].

Cross-reactivity can occur between allergens from the same family eg: nut allergens or in different species of house dust mite. It can also be present in diverse phylogenetic sources eg: house dust mite and shrimp, birch and apple, or fish and chicken meat

5.Functional tests

5.1. FACS (Flow cytometry and Fluorescence activated cell sorting)

The use of flow cytometry is to determine the expression of cell surface markers, to know absolute or relative numbers of cells, to determine intracellular proteins, to quantify soluble proteins.

Isolation of cells by FACS is performed in complete steril ity, and sorted cells are used for therapeutical interventions[26].

5.1.1. Basophil activation test (BAT)

Basophils are activated *in vitro* by the suspicious drug, which lead to upregulation of two molecules CD63 and CD203con their surface. CD63 is an intracellular lysosomal protein. CD203c is an ectoenzyme located both on the plasma membrane and in the cytoplasmic compartment of basophils. The sensitivity and specificity of BAT is up to 92% and 86–90% respectively [27,28]

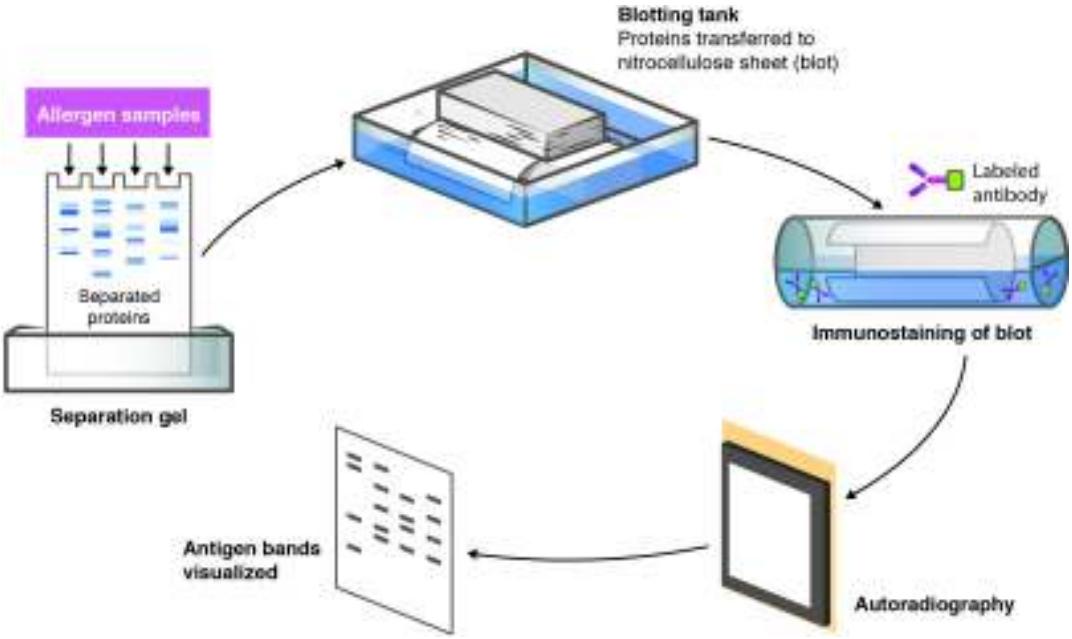

Figure 4. Western-blot methodology. Allergen mixtures are separated in an SDS-PAGE according to the molecular size. Then it is transferred to a nitrocellulose or PVDF membrane. Then, by adding the antibodies from the serum samples sIgE will bind to their specific antigen.

Adverse drug reactions (ADR) constitute a major health problem worldwide. The incidence of fatal ADR occurs in 5% in hospitalized patients in Europe [29]. ADR can be Type A (augmentation of normal drug effects), Type B (bizarre effects), Type C (chronic effects), Type D (delayed effects), and Type E (end of drug use effects). BAT can be used to determine drug sensitisation in an individual.

Other tests worth mentioning include:

Patch test

This is the gold standard test for identification of a contact allergen. It is indicated in any patient with acute and chronic pruritic, eczematous, lichenified dermatitis if underlying or secondary allergic contact dermatitis is suspected. Allergens are placed in chambers that are applied to the skin (usually on the back and away from the spine) and good adhesion between the allergens and the skin is necessary. Topical corticosteroids and calcineurin inhibitors should be withheld 1 week prior to the test. Oral corticosteroids greater than 20mg prednisolone daily or its equivalent should be discontinued 3 to 4 weeks prior to patch placement and to avoid false negative result. Oral antihistamines need not be discontinued during the patch test.

Patch should be removed and read in 48 hours. Tests are read 30 minutes after the removal of the patch. Since 30 percent of the reactions may be negative at day 2, additional readings should be performed at 72 to 96 hours and sometimes after 7 to 10 days after the initial application.

Prick on Prick test

It is a skin test used for food allergy testing. In this test, a fresh antigen obtained by pricking the fruit or vegetable is tested on patient's skin. Although the technique used is crude and non-standardized, this test yields reliable results. A control subject is needed to rule out non-specific reactivity.

6. Conclusions

All the allergen-based diagnostic methodologies are grounded in the antigen-antibody reaction; recognizing the advantages and disadvantages of each analytic method is essential to make accurate choices. The understanding of these techniques could be easy, but to make therapeutical decisions based on the findings are not as

easy. Therefore, precision medicine is need for management of allergic diseases.

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Orginal article

Predictors of post discharge home oxygen therapy and Bilevel positive airway pressure therapy in stable hypercapnoea : an experience from tertiary care health center in South India

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Abstract

Background: Hospital admission for acute exacerbation of COPD (AE-COPD) accounts for 70% of total costs of COPD treatment, and treatment cost is related to the duration of hospital stay. If post-discharge supportive care is required an extra cost will be added. The objectives of this study are to determine the predictive factors of post-discharge supportive care (Domiciliary oxygen, Bi-level positive airway pressure) in known COPD patients who got admitted with acute exacerbation. This is likely to help the treating physician to prime the family and plan an early discharge of the patient with supportive care instead of waiting for the patient to be off oxygen or BiPAP support.

Methods: This is a retrospective study done at the pulmonology department of tertiary care hospital from January 2018-Jan 2019. Data sources were electronic medical records and the hospital discharge minimum data set. This study included 89 known COPD subjects who were not on prior supportive care (Long term oxygen therapy or home BIPAP) and were admitted for the management of acute exacerbation. Clinical parameters like symptoms at onset and the duration of symptoms (cough, fever, breathlessness, sputum production),comorbidities, initial blood investigations(complete blood counts, serum creatinine, arterial blood gas analysis,sputum culture reports)radiological findings, treatment details, pulmonary function test were evaluated with appropriate statistical tests. Parameters associated with post-discharge supportive care were evaluated.

Results:A total of 89 patients were included in the study. Four patients were excluded because of the death. Presence of type II respiratory failure related findings like respiratory acidosis PH (P=0.02), elevated bicarbonate HCO3 (P=0.01), elevated carbon dioxide level PCO2 (p=0.007) in the ABG, and the requirement of non-invasive ventilation (P=0.00), Chest X-ray finding of hyperinflation (P=0.03) and treatment-related variables like prolonged duration of hospitalization (P<0.01) were associated with post-discharge supportive care (Home oxygen therapy and BiPAP support) in univariate analysis. In the multivariate analysis hyperinflation (Odds ratio OR-4.73; 95% confidence interval; 1.37-16.33), noninvasive ventilation (OR-4.9; 95% CI: 1.29-18.47), and prolonged duration of hospitalization (OR-1.32; 95% CI: 1.05-1.66) remained significantly associated with post-discharge home oxygen therapy and home BiPAP therapy.

Conclusion: This study results conclude that severe disease as marked by hyperinflation on Chest X-ray, presence of type II respiratory failure related changes in the ABG and requirement of non-invasive ventilation, and longer duration of hospitalization predicts the post-discharge supportive care. These findings can help the clinician to prepare for earlier discharge with post-discharge supportive care.

Keywords - COPD-Chronic obstructive pulmonary disease; ABG- Arterial blood gas analysis; BiPAP- Bi-level positive airway pressure, HOT-Home oxygen therapy

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Introduction

Acute exacerbations of COPD (AE-COPD) are the main cause of hospital admission and mortality in COPD patients. Existing data show marked variation in hospital mortality (2.5-30%), due to variation in the model of recruitment and availability of healthcare facilities.[1] Up to 90% of exacerbations (mild and moderate) can be managed on an outpatient basis. Only 10% of the exacerbations require hospitalization.[2] Exacerbations are associated with reduced pulmonary function which in turn lead to reduced physical activity and quality of life and increased mortality.[3] Exacerbation-related hospital admissions account for more than 70% of the direct cost generated by COPD.[4] Additional costs will be added if the patient requires post-discharge supportive care like domiciliary oxygen or BiPAP support.

Previous studies identified the risk factors associated with hospital admission and mortality. The predictors of in-hospital mortality are age, male gender, low BMI, cardiac failure, renal failure, confusion, long-term oxygen therapy, lower limb edema, severe disease, elevated troponin levels.[5] More recently biomarkers of inflammation are considered as important predictors to identify the exacerbation (CRP, fibrinogen, eosinophils, leukotriene-B4, interleukin-8, tumor necrotizing factor, endothelin, adrenomodulin,etc).[6]

The current study is intended to identify the variables associated with post-discharge respiratory care in terms of home oxygen therapy and the home BiPAP therapy which help the clinicians plan an early discharge of the patients instead of waiting for the patients to be off the supportive treatment (BiPAP, oxygen) before discharge. It will be helpful to reduce the hospital stay and the cost of treatment.

Material and methods

This is a retrospective study conducted at a tertiary care health center from January 2018 to January 2019. The study protocol is approved by the institute's ethics committee. A consent waiver was allowed as the study involved the use of anonymized retrospective patient data extracted from the medical records. COPD Subjects who were hospitalized for acute exacerbation and went home alive were included in this study. Total 89 known COPD subjected who were not on prior supportive care (long term oxygen therapy or on home BIPAP) and now admitted with acute exacerbation to the pulmonology department were included in the study. During the study period, there were four deaths, hence these patients were excluded from the study. The final analysis was done for 85 patients.

An exacerbation was defined by the presence of an increase in at least one of the following three symptoms: dyspnea, cough, and increased sputum amount, and sputum purulence severe enough to warrant hospital admission. All these patients were documented cases of COPD previously confirmed with spirometry (FEV1/FVC <0.7 and irreversible airway obstruction) and were requiring a combination of various bronchodilators. During admission, patients were treated with a standard protocol consisting of intravenous administration of corticosteroids (0.5 mg/kg), nebulized salbutamol and ipratropium bromide, and antibiotics as per their requirement. Oxygen support was initiated when room air saturation was <90% either at rest or on exertion or ABG showed Pao2 <55 m.m Hg) with target saturation of 88-92%.

Patients who were drowsy or hemodynamically unstable requiring inotropic support or history of respiratory or cardiac arrest at the emergency department were admitted to the intensive care unit. Patients who had severe respiratory acidosis (PH<7.25 and Paco2>45 mm.Hg) and /or persistent hypoxia (Pao2<40 mmHg) despite supplemental oxygen and non-invasive ventilation were also admitted to the intensive care unit for invasive ventilation. Patients who were conscious, able to protect the airway, hemodynamically stable, and arterial blood gas analysis showed PH<7.35 and >7.25 and Paco2> 45 mmHg were managed with non-invasive mechanical ventilation in the pulmonology ward. Serial ABG was performed to assess the improvement in the PH and Paco2 levels.

Discharge criteria

Patients were discharged as per GOLD guidelines. Patients were discharged after a full review of clinical and laboratory data. Discharge was planned when the patients were able to understand and to take the maintenance therapy. The inhaler technique was reassessed before discharge. Home nebulization was prescribed to the patients till follow-up for the patients who were not able to take the inhalers properly. Home oxygen was advised to the patients who had exertional desaturation (Spo2<9o %) or when the arterial blood gas analysis showed Pao2<55mm.Hg or Pao2 <60 mm.Hg in the presence of pulmonary hypertension. Discharge with BiPAP was planned in the patients who were not able to tolerate ≤ a 4hrs break (off BiPAP) either because of the breathless-

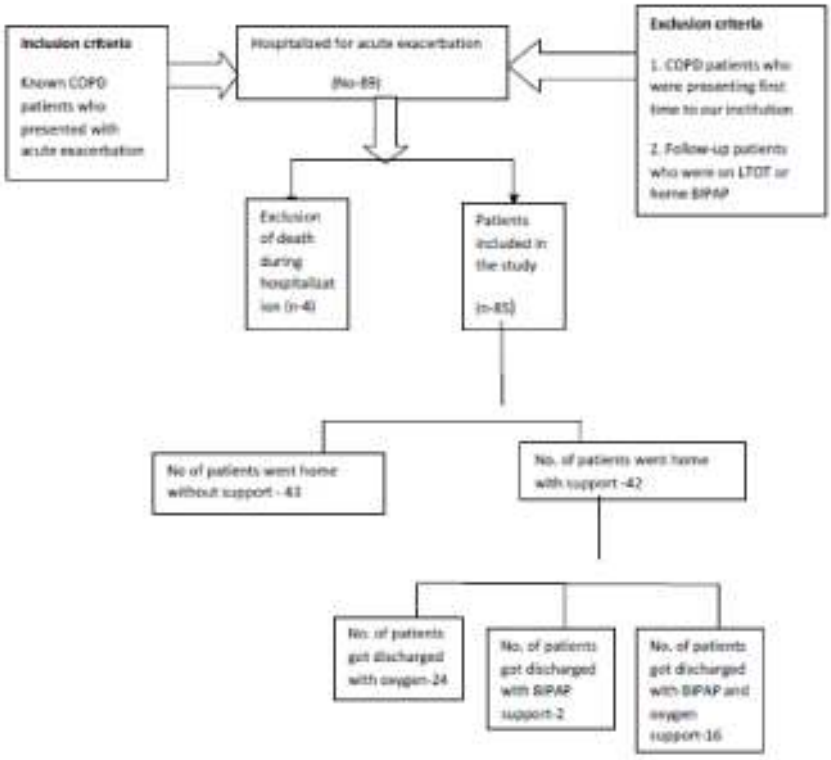

Fig 1: Patient recruitment data and outcomes

ness or when ABG showing a rise in Paco2 ≥ 50mm.Hg/ drop-in ABG PH ≤ 7.35 from the baseline. Patient recruitment data and their outcomes were found in Figure 1.

Statistical analysis

Data were entered in Microsoft Excel and analyzed using Statistical Package for Social Sciences (SPSS) software, version 26.0 (SPSS, Chicago, IL, USA). Frequency distribution with percentage was presented for categorical variables and descriptive statistics like mean with standard deviation (SD) was given for continuous variables. Univariate analysis was done to check for association between the sociodemographic, lab, medical, and treatment-related variables and discharge with supported ventilation either with BIPAP or Oxygen using appropriate statistical tests. Multivariate analysis was done with a step back logistic regression with variables that were significant in univariate analysis. For all the analysis P-value <0.05 was taken for statistical significance.

Results

Total 89 patients were admitted for the management of AE-COPD during the study period. Four patients were excluded because of the death. The final analysis was done for 85 patients who went home alive. Demographic data, baseline variables, and lab investigations, initial chest X-ray findings along with the treatment details, and outcomes are mentioned in Table1. The mean age of our study population is 66.31(sd- 9.58). Male predominance is observed in our study group with male to female ratio is 16:1 (80:5). Hypertension (40%) was the most commonly observed co-morbidity in our study population followed by diabetes (31.8%), ischemic heart disease (16%), chronic kidney disease (1.2%), and cerebrovascular accident (1.2%). The most common presenting symptoms were breathlessness and cough.

Blood investigation showed neutrophil predominant leukocytosis and there was no peripheral eosinophilia (Absolute eosinophil count <2%). Sputum culture positivity is observed in 22.23% exacerbations and the most common isolate was pseudomonas followed by klebsiella at our setting. Initial chest x-ray showed consolidations in 30 (35.3%) patients, hyperinflation in 55(64.7%) patients, bronchiectasis, and old pulmonary tuberculosis changes were present in 7(8.2%), 10(11.9%) patients.

Two-thirds (64) of the patients had respiratory failure. Hypercapnic respiratory failure was the predominant finding 41 (48.2%). Hypoxic respiratory failure was observed in 24(28.2%) patients. The number of patients who received invasive ventilation and non-invasive ventilation were 4(4.7%), 31(36.27%). The mean duration of hospital stay was 6.27±3.68 days. Nearly half 42 (49.4%) of our study population got discharged with supportive care of which 24(28.23%) went home with supplementary oxygen, 16(18.72%) patients got discharged with BIPAP and supplementary oxygen, and 2(2.34%) patients with BiPAP alone.

Type 2 Respiratory failure associated findings in ABG like respiratory acidosis (PH<7.35), elevated serum bicarbonate (HCO3 >27 mm.Hg), raised carbon dioxide level (PCO2>45mm.Hg), the requirement of non-invasive ventilation, and advanced disease indicators like the presence of hyperinflation in the chest x-ray and treatment-related variables like prolonged duration of hospitalization were associated with post-discharge supportive care (Home oxygen therapy, BiPAP requirement) in univariate analysis. In the multivariate analysis hyperinflation, non-invasive ventilation, and duration of hospitalization remained significant associations. However we accepted the model in multivariate analysis with Serum Bicarbonate level despite it not achieving statistical significance due to the sense it makes clinically, given that a cluster of findings in type II respiratory failure was significant in univariate analysis. Table 2 describes the results of univariate and multivariate analysis.

In this study population,there was male predominance with advanced age. The probable reason could be the high prevalence of co-morbidities and the decline of lung function with the advancement of age, the cumulative effect of smoking in this group. The mean age and sex of our study population are similar to the other studies.[7]The mean FEV1 of our study population is 0.89±0.38 liters (38% of the predicted) which indicate severe COPD.

Medical co-morbidities often coexist with COPD. The prevalence of each type of co-morbidity or combination varies across the studies. Cardiovascular diseases are the most commonly observed comorbidities in the COPD population.[8]Forty percentage of this study population were hypertensive, while the rest of the 60% was contributed by diabetes, ischemic heart disease and chronic kidney disease, cerebrovascular accident.

Like the rest of the studies, the most common symptom experienced by this study population was dyspnoea during exertion.[9] In the ECLIPSE study 37.4% of patients had peripheral eosinophil count >2% but in our study population, none of our patients showed absolute eosinophil count >2%.[10] The mean eosinophil count observed in our study population is 0.12±0.2.

Exacerbations are mainly caused by respiratory viral infections although bacterial infection and environmental factors such as pollution and change in ambient temperatures also initiate or provoke these events.[11] When exacerbations are associated with sputum production and purulence, the studies have demonstrated the increased bacterial yield in the sputum. Increased sputum production was observed in 62.4% of our study population and sputum culture positivity was seen in 22.23% of the patients. As culture isolates vary from center to center. In this study, pseudomonas and klebsiella were the main pathogens isolates.

The European COPD audit reported consolidation in 19.2% of the COPD exacerbation.[12] In our study initial chest x-ray showed consolidations in 30(35.3%) patients. Hyperinflation was observed in 55(64.7%) patients. The sensitivity and specificity of chest x-ray for the diagnosis of COPD are 35% and 87% respectively.[13] According to Ghobadi et al, there was evidence of lung hyperinflation on the chest x-ray which was significantly associated with PFT parameters.

Respiratory failure is an important complication of COPD and hospitalization with acute episodes being poor prognostic markers. The presence of hypercapnia during an acute episode of respiratory failure is associated with significantly higher mortality are both initially and during follow-up.[14] Nearly half of our study population 41(48.2%) presented with type 2 respiratory failure; hypoxic respiratory failure waspresent in 24(28.2%) patients.

Enough data is available in regards to prolonged hospital stay and mortality in acute exacerbation of COPD.[1,5,15,15-18] According to Diamantea et al Antonisen type of exacerbation, Charlson comorbidity index score, oxygenation at admission (P:F ratio), and PaCO2 in ABG and presence of chronic respiratory failure predict the duration of hospital stay.[17] There is no data available in the aspect of post-discharge supportive care in terms of home oxygen therapy or BiPAP support.In thisstudy, we evaluated variablesthat predict post-discharge supportive care (Domiciliary oxygen support, BiPAP). Presence of

Table 1: Baseline data and descriptive statistics

		Unsupported Discharge	Supported Discharge
Variables	**Mean±SD/N (%)**	**Mean±SD/N (%)**	**Mean±SD/N (%)**
Age	66.31±9.58	65.51±9.53	67.12±9.68
Sex (Male: Female)	80:5	39:4	41:1
BMI	21.36 ± 5.47	20.36 ± 5.57	22.37± 6.23
FEV1 in liters	0.8953 ±0.383	0.98 ±0.40	0.80 ±0.35
FVC	1.51±0.67	1.63±0.86	1.40±0.41
Co morbidities Diabetes	27 (31.8%)	12 (27.9%)	15 (35.7%)
Hypertension	34 (40%)	18 (41.9%)	16 (38.1%)
Chronic kidney disease	1 (1.2%)	1 (2.3%)	0(0%)
Ischemic heart disease	14 (16%)	7 (16.3%)	7 (16.7%)
Cerebrovascular accident	1 (1.2%)	0 (0%)	1 (2.4%)
Presenting complaints			
Fever	35(41.2%)	23(53.5%)	12(28.6%)
Cough	78 (91.8%)	40 (93%)	38 (90.5%)
Increased sputum production	53 (62.4%)	29(67.4%)	24 (57.1%)
Breathlessness	83(97.6%)	41(95.3%)	42(100%)
Blood investigations (Means)			
WBC count	13.16±4.28	12.92±4.36	13.40±4.24
Haemoglobin	13.25±1.76	12.95±1.97	13.57±1.48
Differential count(Neutrophil			
predominance)	85(100%)	43(100%)	42(100%)
Absolute eosinophil count	0.124±0.20	0.116±0.19	0.133±0.23
Serum creatinine	1.10±0.7	1.11±0.74	1.09±0.67
Sputum culture positivity) n (%)	19(22.23%)	8(18.6%)	11(26.2%)
Klebsiella	6(7.02%)	2(4.6%)	4(9.52%)
Pseudomonas	7(8.19%)	2(4.65%)	5(11.9%)
Streptococcus	1(1.17%)	1(2.32)	0(0%)
H.Influenza	2(2.34%)	1(2.32%)	1(2.38%)
Others	3(3.51%)	2(4.6%)	1(2.3%)
Normal upper respiratory flora	54(63.5%)	31(72.1%)	23(54.8%)
Arterial blood gas analysis (Mean)			
PH	7.35±0.81	7.37±0.06	7.33±0.09
Paco2	51.42±18.34	44.83±13.07	56.92±20.36
Pao2	96.51±53.9	90.57±52.97	101.46±54.82
HCO3	27.26±5.60	25.37±4.60	28.83±5.92
Chest X-ray findings n (%)			
Consolidations	30(35.3%)	19(44.2%)	11(26.2%)
Hyperinflation	55(64.7%)	23(53.5%)	32(76.2%)
Bronchiectasis	7(8.2%)	4(9.3%)	3(7.1%)
Old pulmonary tuberculosis			
changes	10(11.9%)	6(14%)	4(9.5%)
Respiratory failure n (%)	65(76.4%)	24(55.8%)	41(97.6%)
Type 1 respiratory failure	24(28.2%)	12(27.9%)	12(28.6%)
Type2 respiratory failure	41(48.2%)	12(27.9%)	29(69%)
Treatment details n (%)			
Oxygen supplementation	66(77.6%)	24(55.8%)	42(100%)
Antibiotics	76(89.4%)	37(86%)	39(92.9%)
Steroids	66(77.6%)	30(69.8%)	36(85.7%)
Invasive ventilation	4(4.70%)	1(2.3%)	3(7.3%)
Non invasive ventilation	31(36.27%)	6(14%)	25(59.5%)
Duration of hospital stay	6.27±3.68	4.95±2.08	7.62±3.37
No. of patients discharged with			
home oxygen therapy	24(28.23%)	0(0%)	24(28.23%)
No. of patients discharged with			
home BiPAP therapy	2(2.34%)	0(0%)	2(2.34%)
No. of patients discharged with			
home BiPAP and oxygen therapy	16(18.72%)	0(0%)	16(18.72%)

Table 2: Univariate and Multivariate analysis for post-discharge home oxygen or BiPAP therapy

Selected Variables	**Univariate analysis**		**Multivariate analysis**	
	Odds ratio (SD)	*P value*	*Odds ratio(SD)*	P value
Age	1.01 (0.97-1.06)	0.43		
BMI	1.07 (0.94-1.22)	0.28		
Old pulmonary tuberculosis	1.71 (0.382-7.66)	0.48		
Presenting complaints				
Cough	1.4(0.29-6.68)	0.67		
Increased sputum production	0.64(0.266-1.55)	0.32		
Breathlessness€	0.95(0.89-1.02)	0.49		
Blood investigations				
Hemoglobin	1.24(0.94-1.62)	1.15		
White blood cell count	1.02(0.92_1.13)	0.61		
Absolute eosinophil count	1.45(0.18-11.7)	0.72		
Sputum culture positivity	0.64(0.23-1.80)	0.40		
Arterial blood gas analysis				
PH	0.00(0.00-0.32)	0.02*		
Paco2	1.04(1.01-1.08)	0.07		
Hco3	1.13(1.03-1.25)	0.01*	1.08(0.95-1.21)	0.23
Chest x ray findings				
Consolidation	0.44(0.18-1.11)	0.85		
Bronchiectasis	0.75(0.15-3.57)	0.71		
Hyperinflation	2.78(1.09-7.04)	0.03*	4.73(1.37-16.33)	0.01*
Pulmonary function test				
FEV1	0.25(0.93-1.02)	1.71		
Co morbidities				
Diabetes	1.43(0.57-3.5)	0.44		
Hypertension	0.85(0.35-2.03)	0.72		
Treatment details				
Oxygen supplementation				
Antibiotics	2.10(0.49-9.05)	0.31		
Steroids	2.6(0.881-7.67)	0.83		
Invasive ventilation	3.31(0.33-33.2)	0.30		
Non invasive ventilation	9.0693.14-26.1)	<0.01*	4.9(1.29-18.47)0.02*	
Hospital stay	1.16(1.19-1.8)	<0.01*	1.32(1.05-1.66)	0.02*
Respiratory failure				
Type 1 respiratory failure	1.03 (0.40-2.65)	0.94		
Type 2 respiratory failure	5.76(2.26-14.66)	<0.01*		

type II respiratory failure in the ABG (respiratory acidosis(PH<7.35), elevated bicarbonate(HCO3>27 mm.Hg)) and the requirement of non-invasive ventilation, presence of hyperinflation in chest x-ray (a surrogate marker for severe COPD) and treatment-related variables like prolonged hospitalization was associated with post-discharge supportive care. This study concludes that severe disease as marked by longer duration of hospitalization and hyperinflation on Chest X-ray, presence of type II respiratory failure related changes in the ABG, and the requirement of non-invasive ventilation in the hospital predicts the post-discharge supportive care. These findings can help the clinician to prepare for earlier discharge with post-discharge supportive care. Our study was not powered to find a significant association with the other findings in type II respiratory failure. The relatively small sample size is a limitation of the study.

Conclusion

Evidence of type II respiratory failure in the ABG (PH<7.35; HCO3> 27 mm.Hg), presence of hyperinflation in the chest x-ray, a requirement of non-invasive ventilation, and longer hospital stay predict the requirement of post-discharge home oxygen therapy and the BiPAP requirement.

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Association between depression and level of asthma control

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Abstract

Background and objectives: Asthma and depression are two highly prevalent chronic diseases in India and worldwide, imposing unacceptable social and economic burdens on the public health care system. Asthma has long been considered an illness in which mood and emotions contribute to poor control of symptoms. The contribution of psychiatric diseases especially, depression towards poor asthma control was not been widely studied in Indian scenario. Therefore, this study was conducted to find out the potential relationship between the level of asthma control and depression in the Indian scenario.

Materials and methods: This was a case control study with controlled and uncontrolled adult asthma patients as controls and cases, respectively. The sample size calculated was 168 (84 controlled and 84 uncontrolled) asthma patients. Those with concomitant Asthma COPD overlap/diagnosed psychiatric disorders were excluded. Control of asthma was determined using the GINA 2016 adult asthma control tool and depressive symptoms with Patient Health Questionnaire 9. Data analysis was done using Epi Info 7 software. Results: Of the 168 asthma patients in this study, 134(79.7%) were females; mean age was 43.8±16years and mean BMI was 23.5±4. Out of the controlled asthmatics 10(11.9%), and out of the uncontrolled asthmatics 44(52.3%) experienced moderate to severe depressive symptoms (Odds Ratio-8; p<0.001). Other factors associated with poor asthma control included poor medication compliance (p<0.001), rhinosinusitis (p=0.004), low socioeconomic status (p=0.005) and FeV1<60% (p=0.001). Conclusion: Depression is associated with poor control of Asthma. Various other factors associated with poor asthma control were also determined.

Key words: Depression, Control of asthma

Introduction

Asthma is a major health problem; with a global prevalence of 3.8 percent[1]. It is the 24th leading cause of death in the world, causing about 6.48 deaths per 100, 000 population[1]. About 30 million people are affected by asthma in India and it's the eighth leading cause of death in India, causing 18.46 deaths per 100,000 population[1]. In the Kerala scenario, about 3.4 percent are affected by asthma, which amounts to about 11.9 lakh asthma cases[1]. Asthma is the 19th leading cause of death in Kerala, causing 2845 deaths every year[1].One of the major goals of asthma treatment is to achieve and maintain symptom control. The level of asthma control is determined by the interaction between the patient's genetic background, underlying disease processes, the treatment that they are taking, environment, and psychosocial factors[2]. Approximately 5%[3] of asthma cases are difficult to control, do not remain symptom-free despite maximal inhaled therapy, and may require maintenance treatment with oral corticosteroids. Patients with inadequately controlled asthma are particularly at high risk of exacerbations, hospitalization, and death, and often have severely impaired quality of life.

There are multiple established risk factors[3] for poor asthma control - poor compliance with treatment, incorrect inhaler technique, associated comorbidities, ongoing sensitizer exposure, etc. All of these problems are well addressed in the usual scenario. But the impact of psychiatric disorders, especially depression, on the control of asthma is not well recognized, at least in our setting.

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Major depressive disorder is the most common mood disorder, with lifetime prevalence in the general population, estimated to be about 10.8%[4]. About 45 million people are affected by depression in India[1]. In Kerala, it affects about 1.3 million people[1]. Depression is a debilitating disease that can cause severe functional impairment and emotional anguish. It is associated with significant income loss, absenteeism from work, and increased health care burden. Depression appears to be particularly more common among people with chronic health impairment and asthma is no exception. A study conducted in France[5] in 2010 showed 12.3% depression in controlled asthma patients and 30% depression in uncontrolled asthma patients. Another study conducted in Poland[6]concluded that individuals with depression were characterized by a significantly lower degree of asthma control compared to depression-free individuals ($p<0.001$).

While there are studies regarding the aforementioned issues in the literature, it is not known how much; depression contributes to poor control of asthma in our setting. In this background, the present study has been undertaken to determine the potential relationship between the level of asthma control and depression in the Indian scenario.

Materials and Methods

This was a case-control study conducted in the Department of Pulmonary Medicine, from January 2017 to August 2018. All adult asthma patients who gave written informed consent were included in the study. Those with concomitant Asthma COPD overlap and already diagnosed psychiatric diseases were excluded from this study. The sample size calculated was 168 (84 controlled and 84 uncontrolled) asthma patients.

Control of asthma was determined using the GINA 2016 assessment of adult asthma control tool. Those with well-controlled asthma were taken as control, and those with partly controlled and uncontrolled asthma were taken as cases. Depressive symptoms were assessed with the Patient Health Questionnaire 9 tool. A structured questionnaire was used to collect the data. All the data collected were entered in a Microsoft excel sheet and analyzed with Epi Info Version 7 software.

Quantitative variables were summarized as mean and standard deviation and categorical variables as percentage and 95%confidence interval. The difference in proportions between groups was analyzed using the Chi-square test and change in quantitative variables were assessed using paired t-test. The correlation was determined using logistic regression for qualitative variables. This study was approved by the institutional Ethics Committee with an ethical clearance number of IEC.No.07/24/2016/MCT on 29th December 2016.

Results

During the 18 months study period, 168 asthma patients (84 patients with controlled asthma as control and 84 patients with uncontrolled asthma as cases) as diagnosed by pulmonologists based on GINA 2016 were recruited. OR-odds ratio, CI-confidence interval, GERD-gastroesophageal reflux disease

Depression was significantly associated with poor asthma control after bivariate and multivariate logistic regression analysis with an odds ratio of 11.2(95% CI-3.2-39) and a p-value of <0.001. The figure 1-box plot depicts how depression is associated with poor asthma control in the study population.

Discussion

84 controlled asthma patients and 84 uncontrolled asthma patients as diagnosed by pulmonologists (based on GINA 2016 guidelines) were recruited in this study over a period of eighteen months. The mean age of the study population was 43.8±16 years. The mean age of uncontrolled asthmatics (49.01±14.3 years) was higher when compared to controlled asthmatics (38.76±17.06 years). This is in agreement with other similar studies[7]. In our study, 63(75%) of uncontrolled asthmatics and 38(45.2%) of controlled asthmatics were aged above 40 years (odds ratio-3.6;95% CI:1.8-6.9). The burden of asthma is more significant in the elderly than in their younger counterparts, particularly with regard to mortality, hospitalization, medical costs, and health-related quality of life[8].Asthma in older adults is superimposed on a background of age-related changes in respiratory physiology, and often on multiple diseases common in older age.

134 females and 34 males were included in this study. Among controlled asthma population 61(72.6%) were females, and among uncontrolled asthma population 73(86.9%) were females (odds ratio-2.5; 95% CI: 1.1-5.5).Asthma is a disease that has a higher prevalence in boys, than in girls before puberty and a higher prevalence in women than in men in adulthood. Important differences between men and women with asthma have also been reported, with women describing more symptoms and worse asthma-related quality of life, despite having similar pulmonary function[9]. In this study, 61(72%) of

Table 1-Profile of study participants

Variables	**Controlled asthma(n=84)**	**Uncontrolled asthma(n=84)**
Mean age	38.76±17.06	49.01±14.3
Mean Body mass index	23.01±3.6	24.02±4.4
Female sex	61(72.6%)	73(86.9%)
Below poverty line	42(50%)	61(72%)
Firewood smoke exposure	45(53.57%)	68(80.95%)
Passive smoke exposure	19(22.62%)	37(44.05%)
Smoker	6(7.14%)	8(9.52%)
Ongoing allergen exposure	3(3.57%)	7(8.3%)
Poor medication compliance	25(29.76%)	54(64.29%)
Incorrect inhaler technique	28(33.3%)	57(67.8%)

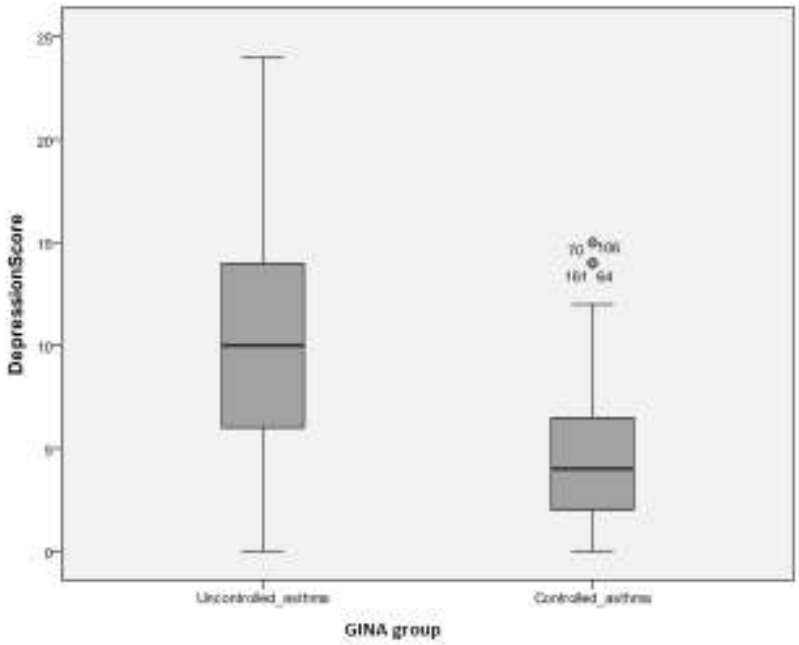

Figure 1- Association between depression and asthma control

Table 2-Risk factors for Uncontrolled Asthma

	Bivariate analysis				Multivariate analysis			
Risk factors	**OR**	**95% CI**		**P value**	**OR**	**95% CI**		**P value**
Age>40 years	3.6	1.8	6.9	<0.001	2.8	0.9	8.9	0.06
Female sex	2.5	1.1	5.5	0.02	0.98	0.18	5.1	0.98
Low Socioeconomic status	**2.6**	**1.3**	**5**	**0.002**	**4.5**	**1.5**	**13.2**	**0.005**
Firewood smoke exposure	3.6	1.8	7.3	<0.001	0.89	0.19	4.1	0.88
Passive smoke exposure	2.6	1.3	5.2	0.003	1.4	0.5	4.1	0.47
Poor compliance	**4.2**	**2.2**	**8.1**	**<0.001**	**14.8**	**4**	**46**	**<0.001**
Wrong inhaler technique	4.2	2.2	8	<0.001	1.7	0.5	4	0.3
Rhinosinusitis	**2.5**	**1.17**	**5.48**	**0.01**	**6.6**	**1.7**	**24.4**	**0.004**
GERD symptom	4.3	2.1	8.58	<0.001	0.96	0.3	3	0.95
Obesity	2.4	0.6	9.8	0.19				
OSA symptoms	3.2	0.8	12.4	0.07				
Depression	**8.14**	**3.7**	**17.8**	**<0.001**	**11.2**	**3.2**	**39**	**<0.001**
Diabetes	3.7	1.6	8.5	0.001	1.1	0.2	4.8	0.84
Dislipidemia	6.6	1.4	31.5	0.005	9.08	0.6	120	0.09
Pulmonary TB	8.7	1.06	71.4	0.01	3.9	0.6	23.9	0.14
FeV1<60%	3.3	1.7	6.2	<0.001	5.2	1.8	14.9	0.001

OR-odds ratio, CI-confidence interval, GERD-gastroesophageal reflux disease

uncontrolled asthmatics and 42(50%) of controlled asthmatics were having low socioeconomic status (odds ratio-4.5; p-value=0.005).

Firewood smoke exposure was present in 45(53.5%) of controlled asthmatics and 68(80.9%) of uncontrolled asthmatics (odds ratio-3.6; 95 % CI:1.8-7.3). J.R. Swiston et al[10]states that wood smoke exposure induces a state of pulmonary and systemic inflammation and can trigger asthma exacerbations. In our study population, passive smoke exposure was present in 19(22.6%) of controlled asthmatics and 37(44%) of uncontrolled asthmatics (odds ratio-2.6; 95% CI: 1.3-5.2). Britton et al[11] noted that passive smoke exposure is likely to be bad for all people with asthma.

Comorbidities like diabetes, hypertension, dyslipidemia, and coronary artery diseases were found in higher proportions in uncontrolled asthmatics compared to controlled asthmatics. Diabetes was present in 9(10.71%) of controlled asthmatics and 26(30.9%) of uncontrolled asthmatics (odds ratio-3.7;95% CI-1.6-8.5). Dyslipidemia was present in 2(2.38%) of controlled asthmatics and 12(14.2%) of uncontrolled asthmatics (odds ratio-6.6; 95% CI: 1.4-31.5). In poorly controlled asthmatics the use of systemic corticosteroids, reduction of activities and exercise, and possibly poor sleep quality may contribute to obesity, diabetes, and depression. Song Y et al[12] have shown that chronic airway inflammation in asthma may be involved in the pathogenesis of diabetes.

In our study, prior history of pulmonary tuberculosis was present in 1.19% of the controlled asthma population and 9.52% of uncontrolled asthma patients (odds ratio-8.7;95% CI:1.06-71.4). Rajasekaran et al[13] have found that post-tuberculosis bronchial asthma patients, with a moderate or far advanced residual lesion, had more persistent symptoms needing continued corticosteroids therapy. Gastroesophageal symptoms were present in 17(20.24%) of controlled asthma patients and 44(52.3%) of uncontrolled asthma patients (odds ratio of 4.3;p-value <0.001). Liou A et al[14], Simpson WG et al[15]and Boulet LP et al[16]have also found symptomatic GERD is an independent

Table3-Factors associated with depression in asthma

	Multivariate analysis				Bivariate analysis			
Risk factors	**OR**	**95%CI**		**P value**	**OR**	**95%CI**		**P value**
Female sex	6	1.8	21.8	0.001	7.8	1.06	58.4	0.04
Gastro oesophageal reflux disease symptoms	6.2	3	12.6	<0.001	4.4	1.8	10.6	<0.001
Use of oral steroid	10.5	3.9	28.3	<0.001	2.3	0.2	22.9	0.4
High dose ICS	4.4	2.1	9.03	<0.001	1.3	0.4	3.8	0.5
ICU admission	4.6	1.6	13.2	0.002	2.2	0.5	8.4	0.2
Previous exacerbation	12.5	4.2	36.9	<0.001	2.5	0.2	26	0.4
Hypothyroid	3.7	1.4	9.9	0.004	1.9	0.5	7.3	0.3
Duration>10 years	2.3	1	5.2	0.04	0.7	0.2	2.3	0.6
Dislipidemia	3.1	1.02	9.5	0.003	1.56	0.39	6.2	0.5
Firewood smoke exposure	6	2	15	<0.001	0.8	0.1	3.7	0.7
Passive smoke exposure	2.6	1.3	5.1	0.005	2	0.8	5.3	0.1
Poor asthma control	8.1	3.7	17.8	<0.001	1.2	0.3	4.7	0.7

ICS-inhaled corticosteroid, ICU-intensive care unit, OR-odds ratio, CI-confidence interval

factor most strongly associated with severe and uncontrolled asthma. The relationship between rhinosinusitis and poor asthma control has been widely studied. The temporal sequence of disease and parallel inflammatory pathways involved suggest that they may be progressive manifestations of a common disease process. In our study rhinosinusitis, symptoms were reported by 12(14.29%) of controlled asthmatics and 25(29.76%) of uncontrolled asthmatics (odds ratio-6.6;p-value-0.004).

Poor compliance with medication was observed in 25(29.76%) of controlled asthmatics and 54(64.29%) of uncontrolled asthmatics (odds ratio-14.8;p-value <0.001). Araujo et al[17] in 2007, in Brazil, has observed non-compliance to treatment in 68% of difficult to control asthmatics. Approximately 50% of adults and children on long-term therapy for asthma fail to take medications as directed at least part of the time[18]. Most patients (around 70–80%) are unable to use their inhalers correctly[18]. Using an inhaler is a skill that must be learned and maintained for the medication to be delivered effectively. In our study wrong inhaler technique was demonstrated in 28(33.3%) of controlled asthmatics and 67.8% of uncontrolled asthmatics (p value<0.001).

Based on various previous studies[5-6,19]proportion of depression among the controlled asthma population ranges from 12% to 34% and among the uncontrolled asthma population, it ranges from 30% to 60%. P Demoly et al had noticed depression in 18% of controlled asthmatics and 31% of uncontrolled asthmatics, whileDi Marco et al,found that 18% of controlled asthmatics and 49% of uncontrolled asthmatics experienced depression. Coban and Aydemir et al have also noted depression in 34% of controlled asthmatics and 60% of uncontrolled asthmatics. In this study depressive symptoms were present in 11% of controlled asthma patients and 52% of the uncontrolled asthma patients. These results are on par with the previous study results. After doing a bivariate analysis with a patient health questionnaire-9 score cut-off value of 9, a statistically significant association was found between depression and asthma control, with an odds ratio of 8.14(95% CI:3.7-17.8) and p value<0.001. Multivariate analysis also showed a strong association between depression and asthma control with an odds ratio

of 11.2(95% CI:3.2 to 39) and p value< 0.001.

In our study after bivariate analysis, factors significantly associated with poor control of asthma included depression, poor compliance with medication, low socioeconomic status, age more than 40 years, female sex, firewood smoke exposure, passive smoke exposure, wrong inhaler technique, rhinosinusitis, GERD, diabetes mellitus, dyslipidemia, and previous pulmonary tuberculosis. All these variables were included in the logistic regression analysis. After the logistic regression analysis the odds were significant only for depression, poor compliance with medication, rhinosinusitis, low socioeconomic status, and FeV1<60%.

Factors associated with depression in the study population were also analyzed, taking "asthmatics without depression" as controls and "asthmatics with depression" as cases. After doing bivariate analysis, factors that were significantly associated with depression included female sex, associated GERD, use of frequent oral corticosteroids, use of high dose inhaled steroids, previous ICU admission, previous year exacerbations, hypothyroidism, duration of illness more than 10 years, dyslipidemia, firewood smoke, and passive smoke exposure. Apart from these, poor asthma control itself was significantly associated with depression(OR=8.1;95% CI:3.7-17.8). But after multivariate analysis, the odds were significant only for associated GERD and female sex.

Mangold R et al[20]have reported that asthma subjects with depressive symptoms had significantly lower quality of life scores and less knowledge about their disease than subjects with no depression. Woledesenbet MA et al[21]has listed, cardiac illness and poor asthma control as factors contributing to depression in asthma. According to Al-Dubai SA et al[22], factors associated with depression in asthmatics were the patient's age, race, monthly household income, and employment status.

Based on our study GERD symptoms and female sex were contributing to depression in the study population. Further studies are needed to find out various factors contributing to depression in the asthma population. By addressing those factors and thereby controlling depressive symptoms in asthmatics; good adherence to treatment and better control of asthma can be attained. It is also not known whether poor asthma control is causing depression, or depression is contributing to poor asthma control. To determine the causality further prospective trials may be needed.

Conclusions

Depression is associated with poor control of asthma. Various other factors associated with poor asthma control were also determined.

Limitations of the Study

The temporal association between asthma and depression could not be determined since this was not a prospective study.

Financial support and sponsorship

There was no financial support needed for this study.

Conflicts of interest

There were no conflicts of interest.

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

A 54-year-old lady presented with history of cough with expectoration and occasional hemoptysis for the last 7 years. She did not give any history of tuberculosis, pneumonia or atopy in the past. On examination, she was tall and underweight and had digital clubbing. Respiratory examination revealed bilateral crepitations.
Her X-ray and HRCT thorax pictures are given below.

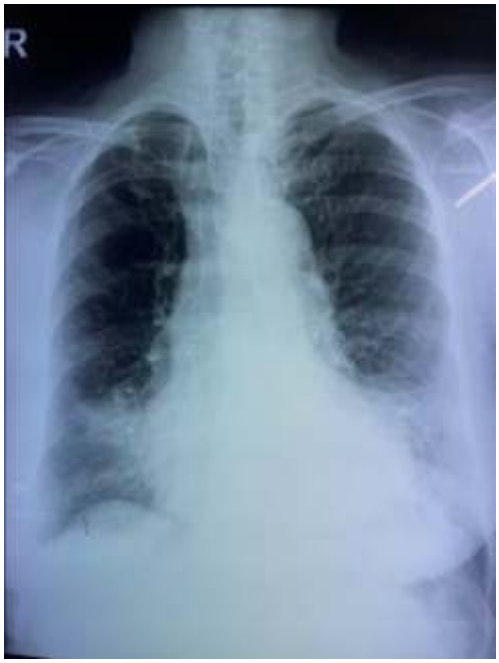

Fig 1: X-ray chest PA view

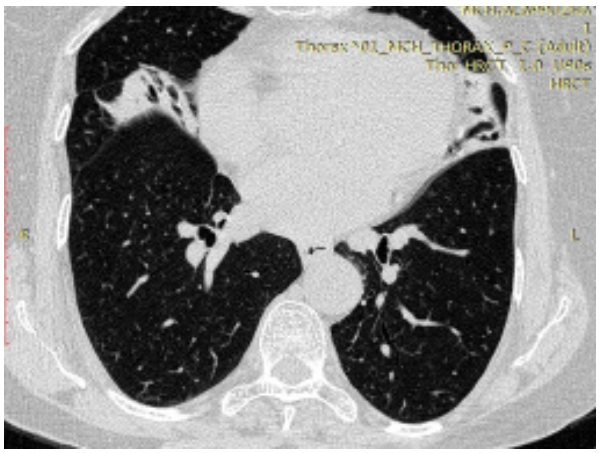

Fig 2: HRCT Thorax

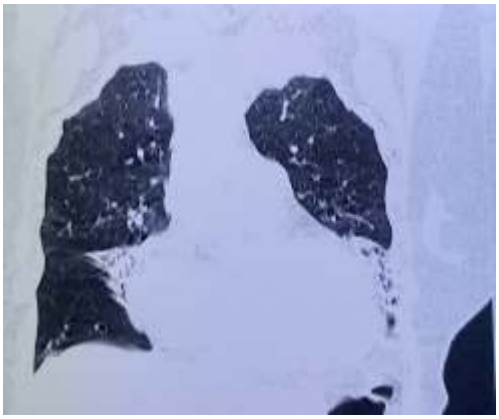

Fig 3: Coronal section CT

What is the diagnosis?
What is the likely organism to be isolated from microbiological examination of sputum or bronchoalveolar lavage of this patient?

Answer:

Lady Windermere syndrome (LWS)
Mycobacterium avium complex (MAC)

The X-ray Chest and HRCT thorax of this patient shows atelectasis and bronchiectatic changes limited to the middle lobe and lingua. Such a radiological picture in a middle-aged lady is consistent with a diagnosis of LWS and requires prompt investigation to rule out MAC.

Discussion

Lady Windermere Syndrome (LWS) was first reported by Reich and Johnson in 1992 among elderly or middle-aged immunocompetent nonsmoker females with no prior lung disease. The bronchiectasis was limited to the right middle lobe or lingual or both.[1] The syndrome is named after a character in one of Oscar Wilde's play, "Lady Windermere's Fan".

It is believed to occur secondary to habitual voluntary cough suppression leading to poor clearance of secretions (especially from the middle lobe and lingula), which can result in formation a chronic nidus for inflammation favoring infection by Mycobacterium avium complex (MAC).

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Middle lobe and lingula are anatomically predisposed to non-specific inflammation because of their structure (long and narrow bronchi with acute angulation) and absence of collateral ventilation.[2] LWS is usually seen in thin elderly women who may also have chest wall and thoracic spine abnormalities (including pectus excavatum, mild scoliosis and straight back)[3]. Diminished cough reflex due to the abnormal bony cage may predispose the middle lobe and lingula to chronic infection and inflammation.[4] LWS can be diagnosed by Chest X-ray or CT scan with evidence of right middle lobe (or left lingula) lung infection and a sputum or bronchoalveolar lavage culture showing MAC.[5]

MAC which is ubiquitous in soil and water and is believed to have no human-to-human transmission, causes a slowly progressive disease, taking months to years to manifest. In immunocompromised states, MAC can follow an aggressive course, become a disseminated disease and are frequently cavitary. However, in LWS, cylindrical bronchiectasis involving the right middle lobe and lingula is seen. Other radiological findings include subsegmental atelectasis with mucosal impaction, reticulonodular infiltrates, small nodules, tree in bud shadows and occasional ground glassing.

Risk factors for MAC infection include multitude of host anatomic, immune, and genetic factors, and environmental factors. Anatomic factors that predispose to MAC infection are skeletal abnormalities, low BMI, and mitral valve prolapse. Skeletal abnormalities especially scoliosis and pectus excavatum, are seen in up to 51% of patients with pulmonary NTM.

Women with LWS have a low-normal BMI and a slender body habitus with decreased subcutaneous fat which has been associated with an increased adiponectin/leptin ratio which inhibit the Th-1 response, an important adaptive immune response to M. avium infection.

Low estrogen levels in slender, post-menopausal women may increase susceptibility to MAC disease. Malnutrition has been associated with increased risk of tuberculosis and with poorer outcomes in NTM infections and may also contribute to the development of LWS.

LWS is treated just like any bronchiectasis. Making a diagnosis of MAC disease does not mandate therapy, which is a decision based on weighing the risks and benefits of instituting drugs with potentially severe toxicities in frail patients. If progressive, MAC may be treated with three-drug regimen of clarithromycin (or azithromycin), rifampicin and ethambutol for at least one year after sputum conversion. Selected patients may benefit from surgical intervention like thoracoscopic pulmonary resection.[2]

Acknowledgement:

Dr Suma Job, Professor of Radiodiagnosis, Government TD Medical College, Alappuzha

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A less common cause of cavitation

Divya R[1], Melcy Cleetus[1], Dr Paul Joy[2], Sreekutty S[3], Jolsana Augustine[1], Rajesh V[4]

Case Summary

A 70 year old lady, known case of type 2 diabetes mellitus for 12 years, presented with cough, fever, right sided pleuritic chest pain and shortness of breath for 10 days. She denied any loss of weight or loss of appetite. Her past history was unremarkable except for the long standing diabetes mellitus. A chest radiograph done in an outside hospital 7 days back revealed right lower zone consolidation with small effusion for which she was given broad spectrum antibiotics. Despite this, she worsened clinically and radiologically.

Chest Xray- posteroanterior projection (Fig 1) as well as representative images of contrast enhanced CT chest – mediastinal window and lung window (Fig 2 – a, b and c) are shown below.

What is the diagnosis?

Diagnosis

Acute pulmonary embolism involving right lower lobe pulmonary artery with cavitating lung infarction

Discussion

Chest radiograph (Fig 1) reveals right lower zone alveolar infiltrates with right minimal costophrenic angle blunting. Representative images of contrast enhanced CT chest – pulmonary embolism protocol (mediastinal window – fig 2 a and b) reveal a filling defect within the right lower lobe pulmonary artery and lack of opacification of the entire posterior segmental branch of right lower lobe of pulmonary artery. Small right pleural effusion is noticeable. The lung window (fig 2c) reveals a peripheral area of consolidation in the posterior basal segment of the right lower lobe measuring 3.4 x 2.5 x 2.5 cm with internal air lucencies, consistent with cavitation. The overall appearance is consistent with acute pulmonary embolism involving right lower lobe pulmonary artery and a cavitating lung infarction involving the posterior basal segment of the right lower lobe.

Pulmonary infarction is rare in pulmonary embolism due to the dual blood supply of the lungs. However, pulmonary infarction is reported to occur in 10% cases of pulmonary thromboembolism[1]. 4-7% of pulmonary infarcts are known to cavitate[2]. Cavitation can occur due

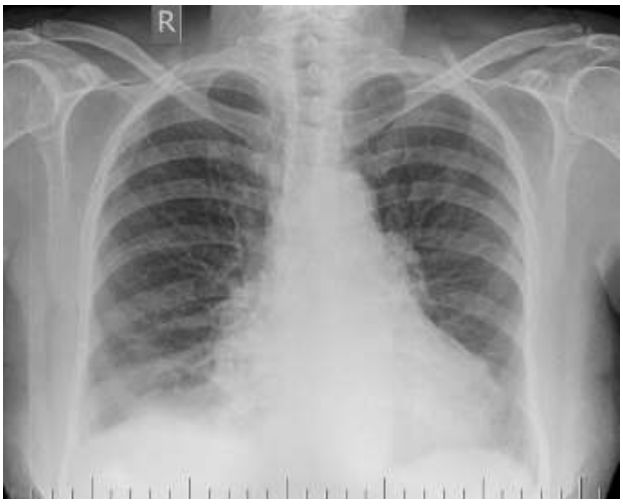

Figure 1 – Chest radiograph – posteroanterior view at presentation

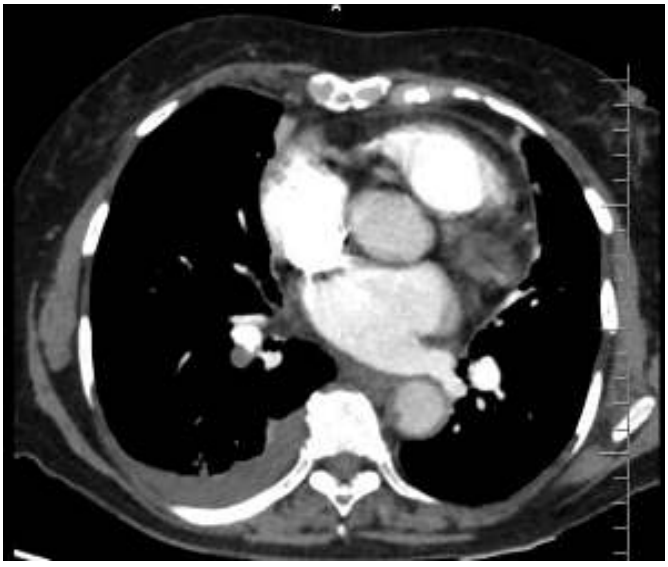

Figure 2 a – Contrast enhanced CT chest – representative mediastinal window image

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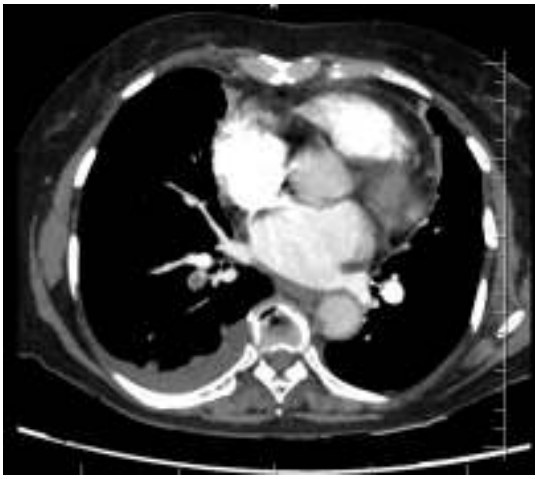

Figure 2 b – Contrast enhanced CT chest – representative mediastinal window image

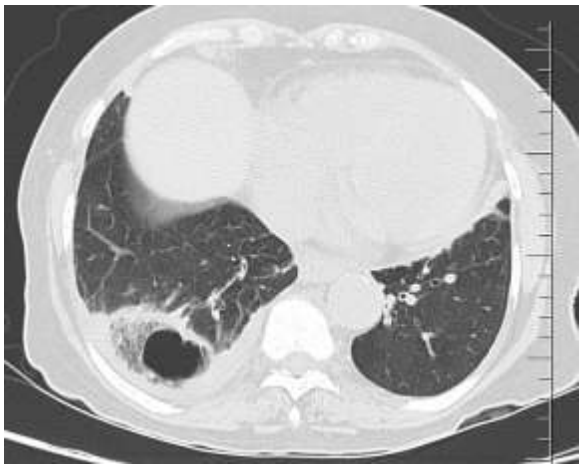

Figure 2 c – Contrast enhanced CT chest – representative lung window image

to aseptic necrosis of the infarcted lung or secondary infection. Infarct size larger than 4 cm is a major risk factor for aseptic necrosis and cavitation[3]. Secondary infection and pulmonary cavitation is usually caused by gram negative bacteria and may lead to abscess formation in a small number of patients. Pulmonary infarction and cavitation occurs mostly in elderly patients who have comorbid conditions like congestive heart failure and chronic lung disease[4]. The mean time to cavitation for an infected pulmonary infarction is 18 days[5]. Infected pulmonary infarctions lead to cavitation faster than bland infarctions with aseptic necrosis[6]. In our case, the cavitation was evident within 10 days of symptom onset.

The differential diagnosis of cavitating pulmonary lesions include infections, (both acute and chronic), malignancies (primary lung carcinoma or metastatic malignancies), systemic diseases (granulomatosis with polyangitis, rheumatoid nodules), pulmonary infarct etc. Lung infections that can cavitate include bacterial (Staphylococcal, gram negative bacillary, anaerobic etc), mycobacterial and fungal infections. Pin pointing the etiology of cavitating lesion as secondary to infarct may be challenging. The presence of acute thromboembolism in the pulmonary artery branch leading to the segment harbouring the cavity may give a clue. The peripheral location of the consolidation and cavitation may be supportive. Secondary infection may have to be ruled out by appropriate microbial tests.

Our patient was treated with anticoagulation (low molecular weight heparin) as he was hemodynamically stable and had no right ventricular dysfunction. Bronchoscopy and BAL was sterile for microbial agents. Glycemic status was optimally controlled. She responded well in the five days with defervescence of fever, improvement in dyspnoea and correction of hypoxia. Chest radiograph on the seventh day (fig 3) revealed clearance of the right lower zone opacities and she was sent home in a stable fashion.

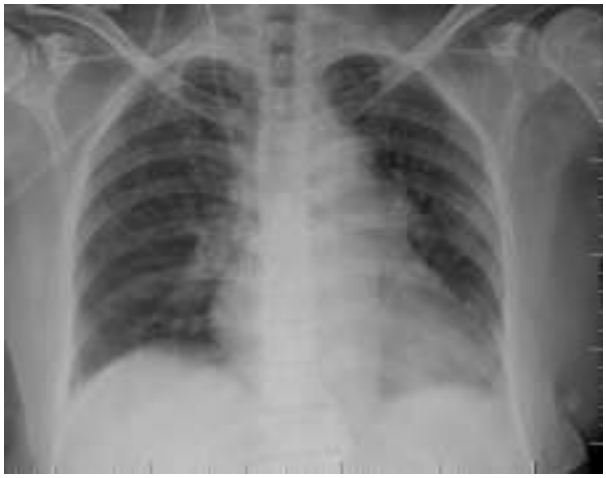

Figure 3 – Chest radiograph at fifth day of admission showing clearance of right lower zone opacities

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Etanercept induced pleuro-pericardial effusion – a rare adverse effect.

Shriram S[1] , Sachin D[2] , Padmasundaram[3] .

Abstract :
Many of the pharmacological agents used in clinical practice can potentially cause some adverse reaction in any part of the pulmonary system. As more drugs are being discovered, the list of pulmonary toxicities also is getting longer. We present a case of a 25 year old man, known case of Ankylosing spondylitis, who presented with orthopnea and was found to have pleuro-pericardial effusion. Investigations revealed exudative eosinophilic fluid with low adenosine deaminase levels. Thoracoscopic pleural biopsy showed dense eosinophilic infiltration of the pleura. Infection and malignancy were ruled out by relevant tests. A diagnosis of drug induced pleuro-pericardial effusion was made by exclusion of other causes..Etanercept was witheld and patient was started on steroids after which he showed significant improvement on follow up. We suggest Etanercept be considered in the growing list of drugs causing pleuro-pericardial effusion. To our knowledge, a case of pleuro-pericardial effusion with eosinophilic pleural infiltration due to Etanercept specifically has not been previously described.
Key words : Etanercept , pleural effusion, adverse reaction, eosinophilic pleural inftration

Introduction :
Drug-induced pleural disease is uncommon as compared to parenchymal lung disease. Pleural reactions from drugs manifest as pleuritic chest pain, eosinophilic pleural effusions (EPE), pleural thickening and may occur in the absence of parenchymal infiltrates.[1] Routinely used anti Tumour necrosis factor alpha (TNF) inhibitors are- monoclonal antibodies such as infliximab, Adalimumab, Certolizumab, Golimumab and a receptor fusion protein such as Etanercept. Thalidomide and its derivatives lenalidomide and pomalidomide have shown some anti TNF activity.[2]Etanercept is a soluble receptor that binds both TNF-alpha and TNF-beta to inhibit the inflammatory response in joints and skin. It is used by rheumatologists as a mono therapy or taken with other immunosuppressants, such as methotrexate.[3] As per FDA information on Etanercept, it is produced by recombinant DNA in Chinese hamster ovary (CHO) mammalian cell system. It consists of about 900 amino acids and has molecular weight of approximately 150 kilo Daltons.[4]A number of infectious (Tuberculosis, Histoplasmosis , etc.) and non- infectious complications such as drug induced Lupus, non- specific pulmonary granulomatous inflammation etc. arising as an adverse effect of anti- TNF therapy have been described.[5,6,7.]

To our knowledge, a case of pleuro-pericardial effusion due to Etanercept specifically has not been previously described.

Case presentation:

We present a case of a 25 year old gentleman, known case of Ankylosing Spondylitis (HLAB27 positive) diagnosed since one year , on Etanercept 50mg subcutaneously once weekly since 4 months. There were no other comorbidities. He presented with intractable orthopnea and bilateral pedal edema since 7 days. Routine blood investigations were unremarkable except that the erythrocyte sedimentation rate was 35 mm/hr. 2DEcho revealed massive 25mm pericardial effusion with few fibrinous strands.

Contrast Computed Tomography of Chest [Fig. 1.] showed bilateral (left more than right) pleural effusion with multiple septations and pericardial effusion with no significant mediastinal nodes, lung parenchyma was normal . Pleural and pericardial fluid was exudative (as per

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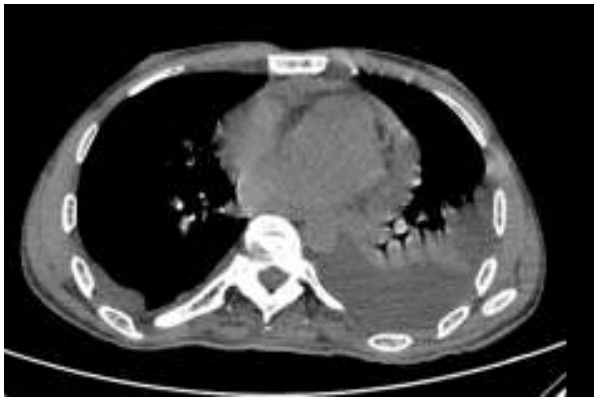
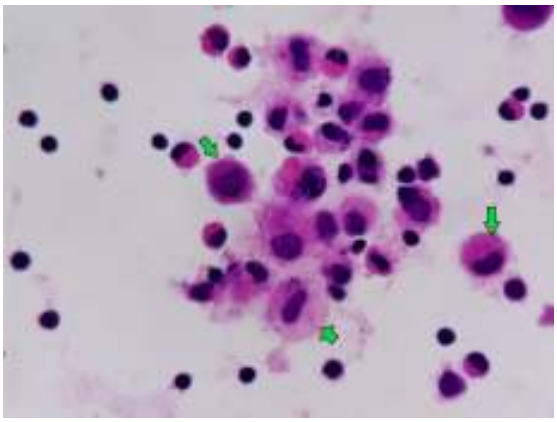
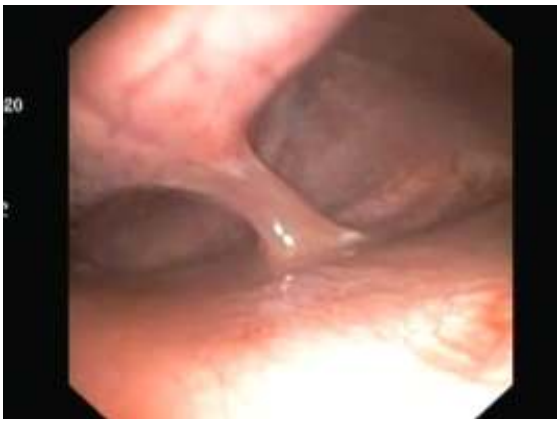


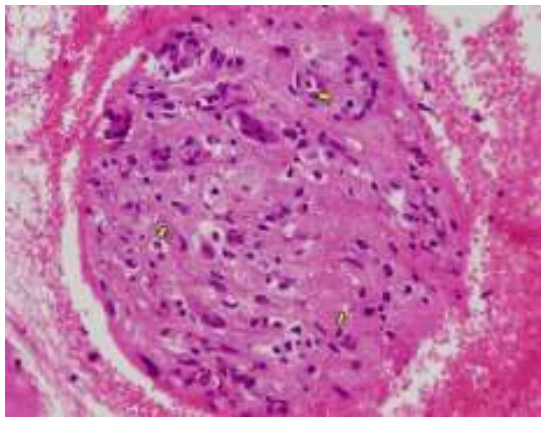
[Fig. 1: Computed tomography showing pleuropericardial effusions with normal parenchyma.]



[Fig. 3: Eosinophils seen on pleural fluid cytology (green arrows)].



[Fig. 2: Thoracoscopic images of septae



[Fig. 4: Dense eosinophilic infiltration of pleura (yellow arrows)].

Light's criteria)[8] with low Adenosine deaminase (ADA), Ziehl–Neelsen (ZN) stain and Gene Xpert Tb was negative. He underwent a medical thoracoscopy which showed straw coloured pleural fluid and multiple thin septations. Visible pleural surfaces otherwise appeared healthy. [Fig. 2.] However, fluid cytology revealed multiple eosinophils and no malignant cells. **[Fig. 3].**

Histopathology showed eosinophilic infiltration of pleura and absence of granulomas or atypical cells .[Fig. 4].

As per rheumatologist's advice, patient's Antinuclear antibody (ANA) profile was sent which showed: 1:1280 (positive) homogeneous pattern; anti dsDNA positive. Thus, a diagnosis of drug induced pleuro-pericardial effusion was made by exclusion . Patient was treated with oral corticosteroids and showed significant clinic-radiological improvement 2 weeks follow up in OPD.

Dicsussion :

Drug-induced respiratory disease (DIRD) is a disease of exclusion, as most of the drugs responsible cannot be pin-pointed by any one specific test. An important aspect of DIRD is the pulmonary end-organ effects, some of which are specific such as Ergot drugs and the pleura, anorectic drugs and the pulmonary circulation, etc. .Some drugs, in contrast, can cause distinct interstitial patterns of respiratory involvement like amiodarone, bleomycin and many others.[9] As more agents get clinically approved, newer patterns of involvement are still being described.[10,11] Commonly implicated drugs in pleural effusion are Phenytoine,Amiodarone, Nitrofurantoin, , Penicillamine and Cyclophosphamide to name a few.[12]

Pathogenesis of drug induced pleural effusion may be due to oxidant-induced mesothelial cell injury or hypersensitivity reaction in the pleura. A direct dose re-

lated toxic effect or a chemical-induced inflammation may also cause pleural inflammation. Although a general knowledge of the mechanisms exists, the exact process remains unclear.[13]

Ankylosing spondylitis (AS) is a rheumatic disease with chronic inflammatory changes in vertebrae and with an underestimated prevalence.[14]Previously, AS has been treated mainly with non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy. Now, treatment with the tumor necrosis factor alpha (TNF-a) receptor antagonists such as Etanercept, has shown benefit in patients with active disease in randomized controlled trials.[15]

Anti TNF-alpha agents such as Infliximab, etanercept, and adalimumab are indicated in autoimmune inflammatory diseases. Several adverse effects such as congestive heart failure, skin rashes and malignancy have been reported during treatment.[16]Although the role of TNF in response to infection is well known, the pathway underlying non-infectious complications arising due to TNF-targeted therapy are not well known.[17] Anti-TNF-á agents are known to induce either anti-dsDNA antibodies or new onset Anti-nuclear antibodies (ANA) positivity in previously ANA-negative patients and increase ANA titers in previously positive patients. Several other autoimmune disorders have been implicated with use of anti-TNF agents, including vasculitis, sarcoidosis, psoriasis and granulomatous nephritis.[18] They can also result in a reactivation of Tuberculosis(TB).[19]Serial pulmonary function tests has been used to to evaluate patients for pulmonary toxicities, but has proved largely unsatisfactory.[20] The laboratory findings commonly include an elevated ESR and a positive ANA. Most frequently, the ANA staining pattern is homogeneous and is caused by antibodies to histones.[21]Soh et al. reported large pericardial effusion and cardiac tamponade in two Rheumatoid arthritis patients who were treated with Adalimumab.[22]

We diagnosed drug induced pleuro-pericardial effusion after ruling out other causes of pleural effusion and further corroborating the diagnosis with evidence of eosinophilic pleural effusion and dense eosinophilic infiltration of pleura. This presentation due to Etanercept is indeed rare. Symptoms subside with withdrawal of offending drug and prompt steroid therapy after active infection is ruled out. In our case too, withdrawal of Etanercept and treatment with steroids resulted in remarkable improvement.

Conclusion:

Anti-TNF-alpha agents are an important addition to therapy for many autoimmune disorders. Unfortunately, these agents can cause a host of untoward infectious and noninfectious complications that make discontinuation of theapy unavoidable. In pleuropericardial effusion due to these agents, it is a knee jerk reaction to think of Tuberculosis in developing countries. We wish to highlight the need to be aware of drug induced serosaldisease . The possibility of re-challenge with these agents requires further research.

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A lung mass with a laryngeal lesion – which is the primary ?

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Abstract

Patients having two or more lesions involving non contiguous anatomical locations are encountered frequently in clinical practice. When both or all lesions have clinico-radiological features of malignancy, the assumption of metastasis is made more often than considering two contiguous primary neoplasms. We share the case of an elderly gentleman who presented with a lung and laryngeal lesion simultaneously, evoking suspicion of synchronous primaries. Biopsy of laryngeal lesion revealed a squamous cell carcinoma and lung mass proved to be adeno carcinoma. PET- CT revealed both malignancies to be localised. Definitive radiotherapy to both sites led to complete remission of both lesions. He remains under clinicoradiological follow up. The case throws light on the important but relatively uncommon situation of simultaneous primary malignancies with potential for curative treatment of both

Introduction

Multiple primary malignant neoplasms (MPMN) are defined as more than one cancer in the same individual[1]. This entity was first described in 1879 by Billroth but the initial and widely accepted diagnostic criteria were laid down by Warren and Gate in 1932[2]. MPMN are categorised as synchronous or metachronous malignancies. If the interval between detection is less than or equal to 6 months it is categorized as synchronous whereas, if the interval is more than 6 months it may be grouped as metachronous according to International Agency for Research on Cancer (IACR/IARC)[1]. Overall reported frequency of multiple primary cancers varies between 2.4% and 17%[3] with synchronous occurrence much less common. With advancements and increasing use of sophisticated imaging modalities for staging, synchronous multiple tumors are more commonly detected. Assuming the second primary malignancy as metastasis will change the intent of treatment from curative to palliative and hence greater awareness among clinicians is of paramount importance. We share the case of an elderly gentleman who presented with a lung mass and a laryngeal ulcer simultaneously. Since metastasis to larynx from a lung primary is not very common and vice versa, we entertained an upfront suspicion of synchronous primaries. Biopsy of laryngeal lesion revealed a squamous cell carcinoma and lung lesion proved to be adeno carcinoma, making our diagnosis easy. He had an excellent outcome with sequential definitive radiotherapy of both lesions.

Case Report

An 81 year old gentleman, a known case of of chronic obstructive pulmonary disease, systemic hypertension and type 2 diabetes mellitus, presented with complaints of dysphagia, odynophagia and cough for 2 weeks. There was no history of breathing difficulty, chest pain, hemoptysis, fever or night sweats. He had history of loss of appetite. He however denied history of weight loss. He was a reformed smoker with a smoking history of 40 pack years. His symptoms were initially attributed to reflux disease and he was on proton pump inhibitors with minimal relief. He developed change in character of voice for which he sought an ENT specialist's opinion. After consultation by ENT surgeon chest radiograph and laryngoscopy were suggested. His basic blood investigations were normal except for elevated blood sugar levels. Video laryngoscopy was done which revealed ulcerative growth over left side of epiglottis. This was subjected to a laryngoscopy and biopsy. Chest radiograph showed a right

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lower zone mass lesion. (Fig 1) A contrast-enhanced computed tomography of thorax (CECT) revealed a 4.8 x 3.6 x 4.3 cm mass lesion in the lateral segment of the right lower lobe (Fig 2a and b) with tiny foci of calcifications; the lesion showed areas of necrosis and the solid component of the lesion showed enhancement on post contrast images. Antero- laterally the lesion was found to be abutting the oblique fissure and causing its retraction. Adjacent pleural tags and mild perilesional ground glassing was also present.

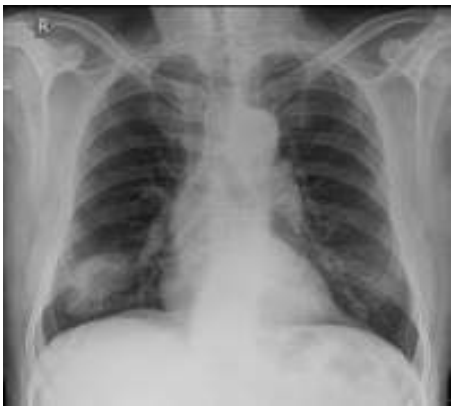

Figure 1 : CXR showing right lower zone well defined mass lesion

CT guided biopsy from the lesion was undertaken and the histopathology report was suggestive of adenocarcinoma (Fig 3 a and b). Immunohistochemistry revealed tumour cell positivity for Naspin A, TTF 1 and CK7, and negativity for CK 20 confirming primary origin from lung. Meanwhile, histopathology from epiglottic lesion showed an invasive neoplasm with keratin pearls suggestive of moderately differentiated squamous cell carcinoma (Fig 4 a and b). The confirmation of two different histological subtypes eased the diagnosis of two separate primary malignant processes in the lung and larynx.

Whole body 18F- deoxy glucose positron emission computed tomography (18F-FDG PET-CT) was done as part of metastatic work-up which showed intense 18 FDG avid mass in the lateral basal segment of the right lung lower lobe (Fig 5) with tiny foci of internal calcifications and areas of necrosis. FDG avid focal thickening of left epiglottis was also visualised. There were no FDG avid lymph nodes or any other distant lesions suggesting that both malignancies were localised to site of origin.

He was initiated on SBRT to lung mass and radical radiation therapy to epiglottic lesion. Total of 5 cycles of Stereotactic body radiation therapy was given to the right lung mass lesion, while 30 cycles of radical radiation therapy was delivered to the epiglottis. He tolerated radiotherapy well. On follow up, there was significant improvement in his dysphagia, odynophagia and cough. Repeat laryngoscopy at the completion of radiotherapy revealed resolution of ulcerative lesion of left epiglottis, while repeat chest radiograph showed regression of mass lesion of right lower lobe (Fig 6). He remains under clinical follow up.

Discussion

Simultaneous structural involvement of larynx and lung due to the same disease can occur with tuberculosis, connective tissue diseases like rheumatoid arthritis, vasculitis like granulomatosis with angiitis, amyloidosis, neoplastic lesion of one site (with metastasis to the other) etc. Distant metastasis is uncommon but can occur in up to 19% of cases of laryngeal carcinoma. The most common site of distant metastases from laryngeal cancer is the lung although lesser common sites like skeletal muscle has been described[4]. Laryngeal metastasis from carcinoma lung is reported much less frequently[5]. We considered all the afore mentioned possibilities in our case, but were convinced that dual site biopsy was necessary to rule out the possibility to synchronous primary neoplasms and arrive at a definitive diagnosis.

MPMN are divided broadly into two categories depending on the interval between tumour diagnosis. Second neoplasms occurring simultaneously or within six months after the diagnosis of first neoplasm is grouped as "Synchronous malignancies", while second neoplasms that develop after more than six months from the diagnosis of first malignancy is grouped as "metachronous malignancies"[1]. The prevalence of multiple primary malignancies ranges between 2.4% and 17%. They are more commonly seen in the upper digestive tract, respiratory system, urogenital system and head and neck region[6-10].

Detection of a second lesion in an already established case of malignancy poses a diagnostic dilemma. Whether the second lesion represents metastases, an unrelated non neoplastic entity or a second primary malignancy is difficult to ascertain. Warren and Gates criteria, dating way back to 1932 insists on the following pre-requisites[2]

(1) Each tumor should present a definite picture of malignancy

(2) Each tumor should be histologically distinct

(3) The possibility that one is a metastasis of the other must be excluded

Although the criteria provide commendable initial efforts, synchronous primary malignancies of the same

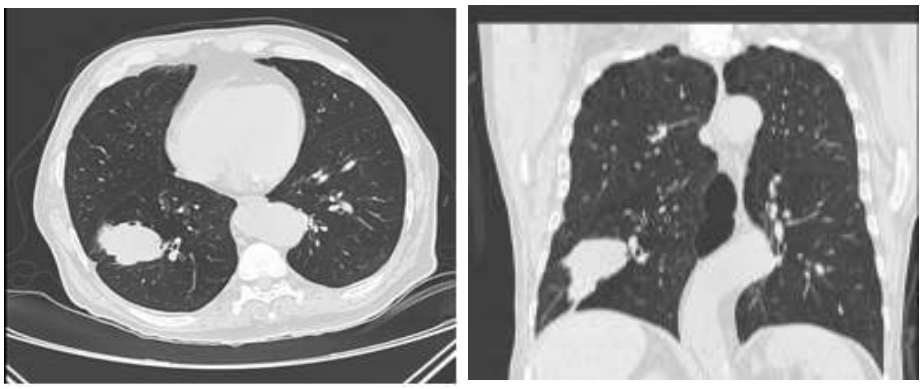

Figure 2 a and b: Computed tomography of chest showing 4.8 x 3.6 x 4.3 cm sized mass lesion in the lateral segment of the right lower lobe with foci of calcification, and necrosis

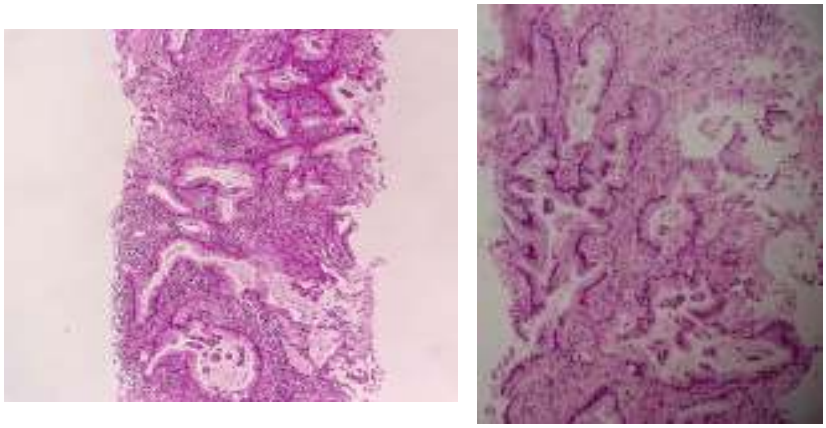

Figure 3 a and b: Histopathology slide from lung lesion - H&E, 10X & 40X showing an Infiltrating neoplasm composed of cells arranged in glandular pattern (white arrow) with papillaroid tufts. Tumor cells are tall columnar with enlarged hyperchromatic nucleus and show cytplasmic mucin suggestive of Adenocarcinoma

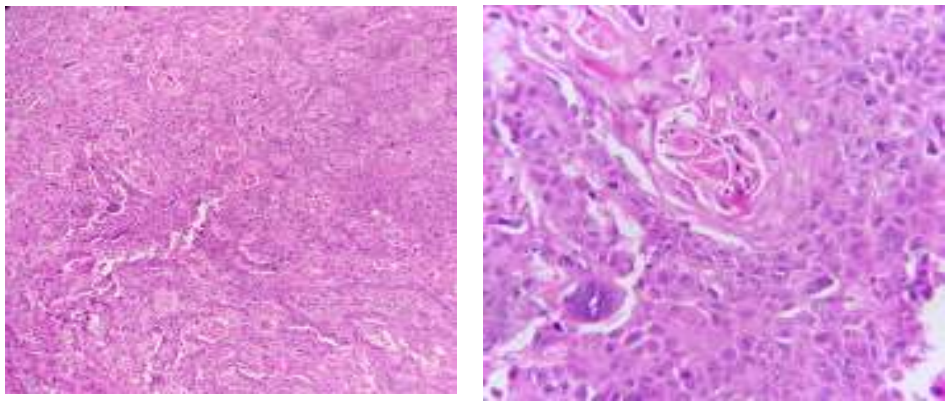

Figure 4 a and b: Histopathology slide – H&E, 10X & 40X from epiglottic lesion showing Infiltrating neoplasm composed of polygonal cells arranged in sheets and nests. Keratin pearls (white arrow) are present suggestive of Moderately differentiated squamous cell carcinoma

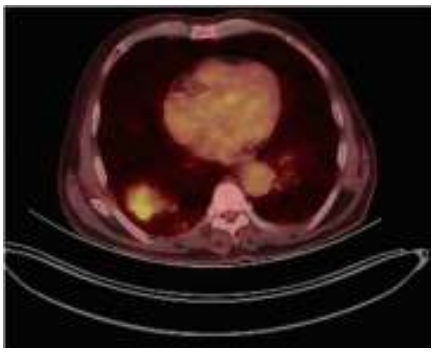

Figure 5 – PET CT image showing high uptake in lung mass

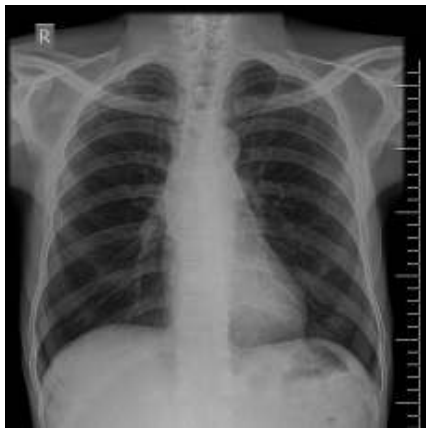

Figure 6 – Chest Xray after treatment showing complete response of right lung mass

histological subtype can occur which is not accounted for by this criteria.

Incidence of multiple primary malignant neoplasms has been steadily increasing[6], possibly due to advances in diagnostic modalities like PET scan and increased surveillance screening programs. Possible underlying causes for multiple primary cancers may include host and lifestyle-related factors, environmental carcinogens, genetic factors, immune deficiencies, and treatment related factors (long-term complication of remote chemotherapy or radiotherapy)[7].

The incidence of head and neck cancer with synchronous or metachronous primary lung cancers has also followed an increasing trend[11]. The incidence ranges from 4.5% to 14%[9].The most common secondary primary cancer following a first primary head and neck cancer is lung cancer[10]. This may be possibly due to common etiological factors like smoking, inhaled carcinogenic agents, environmental exposures etc[9,10].

A Chinese study[12] looked at 161 patients with MPMNs and showed that 78 (48.4%) patients had synchronous tumors and 83 (51.6%) patients had metachronous tumors. Most patients with MPMTs were men and older patients (>50 years old), and adenocarcinoma was the most frequent pathology type. The most frequent location of all MPMTs was the digestive system. The leading tumor association was both tumours developing from digestive system. However, patients with synchronous tumors and MPMTs of the digestive system showed a shorter survival time. In the metachronous cancer group, the median interval time was 60 months, and a short interval time (< 60 months) was associated with a shorter survival time. In addition, survival time was increased in the younger age group (<50 years old) and in patients who accepted surgery-based comprehensive therapy.

Chang et al[13] looked at 92 cases of multiple primary lung neoplasms which were surgically operated. The five year survival for these cases were 35.5% and the occurrence of lymph node metastasis was the only prognostic factor noted on multivariate regression analysis. The survival rate at 5 years fell sharply to 15% in the presence of nodal spread. The study concluded that an aggressive surgical approach was safe and justified in the absence of lymph node metastasis even if there are concurrent multiple primary lung malignancies.

The optimal therapeutic strategy in MPN is vague as most trials on surgery or medical therapy of a malignancy tend to exclude patients with a second active or previous neoplasm. Review articles[14] tend to acknowledge this fact and suggest individualised management strategies. In localised disease, the strategy may be surgery or radiation / chemoradiation therapy covering both malignancies[15, 16]. However, in the situation of advanced disease, the antitumour therapy selection is often difficult and mostly not based on evidence from the literature and clinical trials. In patients where both tumours are likely to respond to the same antitumour regimen as may be the case in patients with synchronous squamous cell carcinoma of the head and a second head and neck or squamous non-small cell lung cancer, the therapeutic decision will involve a systemic therapy, which is likely to be active in for example, a platinum-based chemotherapy.

Meticulous approaches and effort should be taken to differentiate MPM from metastatic disease in patients who have multiple non contiguous lesions, because of the better prognosis associated with MPM. In our case, different histological types led us to easy inference. More sophisticated molecular studies may be needed in confusing cases where the histology is also similar.

The treatment options considered in our patient were concomitant definitive radiotherapy to both sites versus surgical resection of both lesions, since PET-CT revealed both neoplasms to be localised. However, advanced age, multiple comorbidities (systemic hypertension, type 2 diabetes, COPD) and poor pulmonary reserve (a post bronchodilator FEV1 of 46% predicted) made the tumour board team prefer the first option to which the family concurred. The lung function would not have been an absolute contraindication to a lobectomy, but considering the advanced age and comorbidities a decision to opt out from surgery was made. It would have been interesting to decide on the treatment plan if the patient had metastatic disease in the PET scan. Although not formally discussed in the tumour board, this would have possibly prompted a decision of instituting palliative radiotherapy for the laryngeal lesion and systemic therapy (after tumor mutation analysis) for the adenocarcinoma lung. Our patient had an excellent clinical outcome with definitive radiotherapy administered to the lung as well as laryngeal tumour. We could not find an identical case with an elderly gentleman (> 80 years) with laryngeal and lung malignancy managed by definitive radiotherapy of both sites or subjected to resective surgery for head-to-head comparision of surgery versus chemotherapy. However extrapolation of our understanding from solitary lung cancers tend to suggest that surgery with systematic lymph node dissection provides superior outcomes.

The case underscores the importance of considering MPMN which can be addressed as two separate therapeutic entities rather than labelling as metastatic lesions which is associated with a much more dismal prognosis.

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Solitary fibrous tumour of the pleura presenting as a giant intrathoracic mass

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Abstract

Solitary fibrous tumours of pleura (SFTP) are uncommon tumours that usually arise from visceral pleura and remain asymptomatic till they reach huge sizes or are incidentally detected. SFTP are usually benign but can be malignant and have paraneoplastic syndromes associated. Tru-Cut biopsy is required in view of heterogeneity in large lesions. Complete resection with clear margins is the recommended treatment.

Key words:

Solitary fibrous tumours, Pleural solitary fibrous tumours, Pierre Marie-Bamberger syndrome, Doege-Potter syndrome, Hypoglycaemia, Hypertrophic pulmonary osteoarthropathy,

Introduction

Pleural solitary fibrous tumours are uncommon tumours that arise from visceral pleura. These tumours are usually detected incidentally or when tumours have grown large enough to cause symptoms. These tumours can be malignant and can have varied radiological appearance ranging from single to multiple lesions as well as pedunculated to sessile lesions. Pedunculated tumours are mobile and can be demonstrated by changing patient position. Large lesions may show geographic pattern and have necrosis. Complete surgical resection with clear margin is recommended. We here by describe a case of pleura SFT in an elderly patient with minimal symptoms.

Case Report

A 70-year elderly man with history of cigarette abuse and smoking index less than 300, presented with progressive dyspnea on exertion and dull aching chest pain left side for the last 3 months. He had no history of weight loss, loss of appetite, fever, or cough with expectoration. On examination he was a moderately built and nourished man with no abnormalities in general examination. Respiratory system examination showed decreased movements and breath sounds on the right side, with a dull note on percussion on the entire left side.

Chest X ray showed a relatively homogenous opacity filling the left mid and lower zones obscuring left heart border and left dome of diaphragm. Mediastinum shows minimal shift to right. (Figure 1) and subsequent CT scan of chest showed heterogenous enhancing lesion filling the mid and lower part of left hemithorax.(Figure 2)

Bronchoscopy showed mucosal swelling and congestion with external compression of the left main bronchus. Bronchoscope could not be negotiated further on the left side. Right bronchial tree was normal. Tru-Cut biopsy was done, and microscopy showed neoplastic cells arranged in short bundles and fascicles. Cells showed moderate cytoplasm, ovoid to spindly nucleus granular chromatin. Mitosis was sparse. IHC showed BCL2 and CDC34 positive with CK negative. Histopathology report was suggestive of solitary fibrous tumours. (Figure3,4). Patient has undergone surgery and has not had any recurrence till last follow up.

Discussion

SFT are uncommon slow growing tumours of mesenchymal origin which can be benign or malignant and can occur anywhere in the body with 30% arising in thoracic cavity, 30% in abdominal cavity and 20% are in head and neck.

Pleural SFT comprise only about 5 % of all pleural tumours. SFTPs are the most common non-mesothelial primary pleural neoplasms, and these tumours have an unpredictable course. They originate from the visceral

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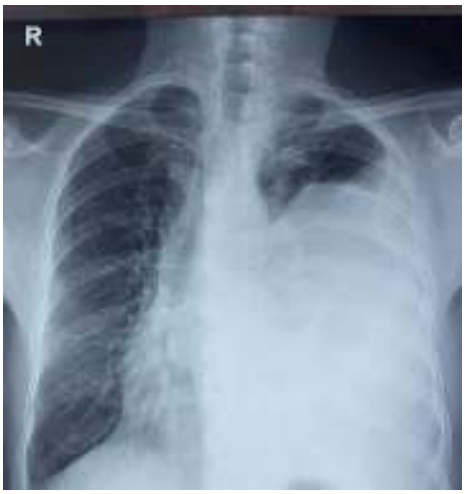

Figure 1 - Chest X ray showed a relatively homogenous opacity filling the left mid and lower zones

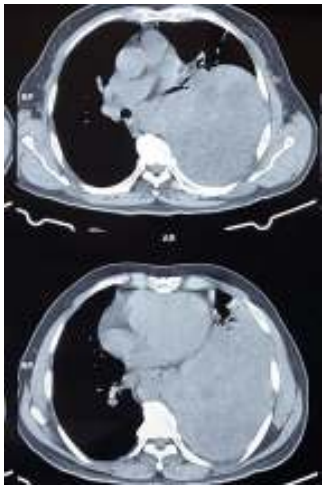

Figure 2 - Heterogenous enhancing lesion filling the mid and lower part of left hemithorax

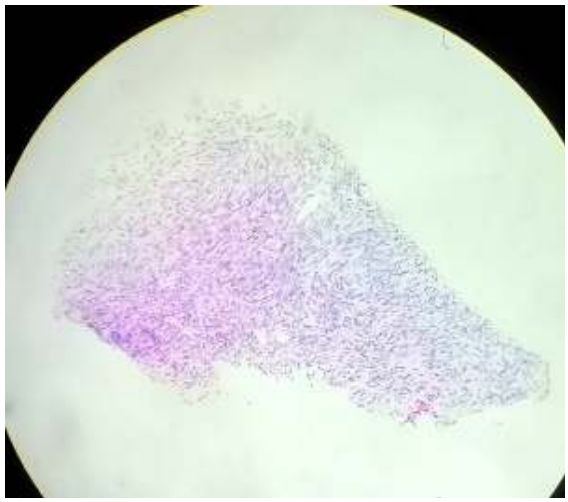

Figure 3 - Microscopy showing neoplastic cells arranged in short bundles and fascicles. Cells show moderate cytoplasm, ovoid to spindly nucleus granular chromatin.

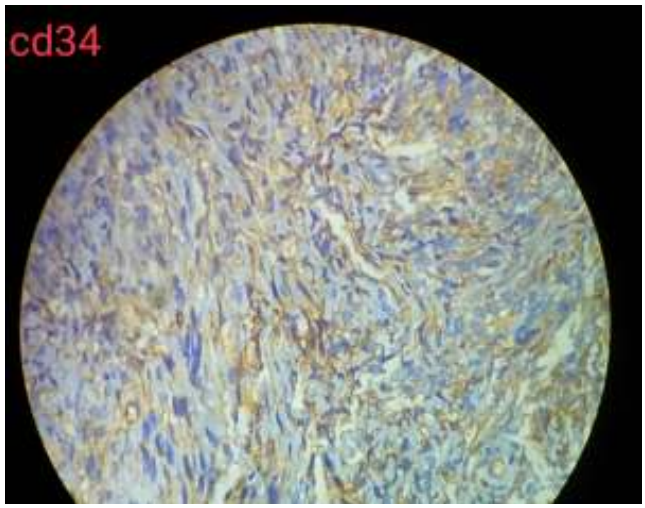

Figure 4 - IHC BCL 2 Staining

pleura in around 70% and usually have a benign course. However, in a small percentage of cases (10–15%) their behaviour is malignant.[1,2]

SFTP have peak incidence between the fifth and seventh decades of life and affect both sexes equally. There are no known aetiological risk factors. There is no association with cigarette smoking or asbestos exposure.[3]

SFT usually remain asymptomatic till tumour reaches massive size. Common symptoms seen are chest pain, shortness of breath, obstructive symptoms. Chest pain occurs more commonly in the patient whose tumor arises from the parietal pleura.[4]

Paraneoplastic syndromes may be seen especially in patients with large tumours.

Pierre Marie-Bamberger syndrome: characterised by clubbing and HPOA, seen in around 20%. Hypertrophic pulmonary osteoarthropathy (HPO) is the most common paraneoplastic syndrome in SFTP. These patients present with bilateral arthritic-like symptoms, including stiffness or swelling of the joints, edema of the ankles, arthralgias, and pain along the long bones, especially in the tibias from periosteal elevation. Symptoms may disappear rapidly within hours to days of tumour resection. These symptoms reappear in case of a recurrence.[4,5]

Doege-Potter syndrome: Tumor-producing non suppressible insulin-like active substances and insulin-like growth

factors can result in hypoglycaemia and are seen in only around 3-4%. Galactorrhoea and gynaecomastia have also been described.[5,6]

Radiology

These tumours are usually detected incidentally and appear as solid sharply marginated, well-circumscribed lesion (usually solitary) originating from the periphery of the chest or from a lung fissure. It may grow to occupy the entire hemithorax. It is virtually impossible, to distinguish them from other masses of the lung by means of a plain chest X-ray. Tumours can be pedunculated with a fibrovascular stalk. A pathognomonic radiological feature of pedunculated forms of SFTP originating from the visceral pleura is a change in shape and location of the mass during breathing or repositioning of the patient.

CT scans usually depicts a single lesion with well-defined margins arising from the chest wall (parietal pleura) or within a lung fissure (visceral pleura).

The lesion usually forms right or acute angles with a smooth tapering margin with the chest-wall. A pathognomonic finding in pedunculated lesions is the mobility of the tumour with changes in patient position. However, this is dependent on size of the tumour and usually disappear as tumour grows larger.

Tumours located in the interlobar fissures appears to grow into the lung parenchyma and are hence called "inverted" tumor.

Small lesions appear as sharp marginated masses with smooth margins, forming right or obtuse angles with the chest wall. Attenuation is homogeneous and similar to the adjacent musculature. This can help differentiate SFTPs from fatty lesions or saccular fluid collections.

In large lesions heterogeneous contrast enhancement is seen with areas of necrosis and depiction of serpiginous vessels described by "geographic" pattern. [2,4,7] MRI is superior to CT in studying the morphology and its relationship with the mediastinum, large vessels, and diaphragm.

PET scan may help differentiate clinically aggressive behaviour of SFTP identifying areas of malignant histology within benign SFTP which appear as areas of focal increase of FDG uptake (SUV max e" 3.0) within a large, otherwise benign appearing SFTP.[5]

FNA is usually inadequate for confirmation of diagnosis. True-cut biopsy is usually required.

Usually solitary but may also be multiple. Cystic, haemorrhagic, necrotic, and calcified areas can be within the lesion.

Microscopy

Microscopy shows 'pattern less' appearance of spindle cells within a collagenous matrix, found to be positive for CD34 and is considered diagnostic. Positive staining for vimentin and bcl-2, and absence of staining for cytokeratin helps differentiation from other pleural tumours. Necrosis is infrequent but associated with poorer prognosis when seen.[8,9]

Treatment[1,5,8,10]

A complete surgical resection is the mainstay of the treatment of both benign and malignant SFTPs, the absence of neoplastic residual (R0) being the main prognostic factor and hence require a 1-2 cm margin of healthy tissue making wedge resection preferred in many. However, lobectomy or pneumonectomy may be required for patients with lesions that are broad based and sessile or in cases of inverted tumour. Frozen sections are preferred to ensure adequate resection as recurrence of benign SFTP can result in a more aggressive tumour.

When the tumour originates from the parietal pleura and adheres or invades the chest wall an extrapleural dissection and a chest wall resection is usually required.

Recurrent benign or malignant tumours should undergo repeat surgical resection followed by adjuvant therapy particularly sessile, malignant tumours.

Postoperative radiotherapy has been used in patients with incomplete resection of the tumor. Chemotherapy with Ifosfamide and Adriamycin has been described for patients with inoperable tumours however data remains sparse.

Overall survival of patients affected by a benign pedunculated SFTP is close to 100%, about 92% in case of benign sessile tumour and lower in case of malignant pedunculated (85%) and malignant sessile tumour (37%).

Though most recurrences occur within 24 months of surgery, long-term follow-up, more than 15 years is recommended.[10]

Conclusion:

SFTPs are large tumours and are usually incidentally detected and are mostly benign. Symptoms when present are usually secondary to size of lesions. Surgical resection with clear margins is advocated in view of risk of malignant potential and recurrences which are exceedingly difficult to manage.

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Obituary

Remembrance - Dr. K.P. Govindan

Fourteenth July 2021 - It was with great regret and agony that we heard the demise of a Doyen of Pulmonary Medicine, Prof (Dr) K.P. Govindan Sir

He was an alumnus of Calicut Medical College. Later did his post graduation in MD (General Medicine) from GB Pant hospital and acquired Pulmonology Diploma from prestigious Vallabhbhai Patel Chest Institute, Delhi.

He was an excellent teacher, clinician and above all a good human being, who always tried to keep his fellow beings happy. It is indeed an undefiable fact that none of us has seen Sir without a smile on his face, be it in a busy OP or at the leisurely banquets lit up with his jokes which many of us cherished listening to.

Prof.K.P.Govindan, fondly known as "KPG" amongst his large gamut of students has always been known for his fatherly affection and approachability he had for them, which made their student life a pleasant experience.His positive vibes towards life inspired many in tackling toughest situations in life in much better ways than otherwise one would have dealt with. His friend's circle within the fraternity had no borders and a good number of them belonged to the National and even International circles.

He proved his mettle as an extra ordinary organizer by taking initiative to organize the first and earliest NAPCON at Calicut. His relentless efforts were behind the success in shifting the Department of TB & Chest Diseaes from General Hospital,Beach to the current coveted status of a separate Chest Institute at the Govt.Medical College, Kozhikode. He was the Professor and HOD of Pulmonary Medicine and Superintendent of Institute of Chest Diseases for several years. He was the President of Indian Chest Society and President of APCCM and has adorned various academic positions.

His interactions and behavior won him a lot of followers and through their memories, our beloved KPG, a teacher par excellence, a true philosopher, a guide and mentor to many and above all wonderful human being will live forever.

We all APCCM members and all his friends take this opportunity to share the grief of the family and sincerely pray to God Almighty.

"Let the soul of our beloved Govindan sir Rest in Peace"

T.P. Rajagopal
President, APCCM

Dr. K.P. Govindan left the mark in our lives that needs no embellishment. Most of us keep looking for him at the ever so many meetings we attend. I know it is absurd, but I expect any minute to take a call from him. Or to see his face pop around the corner. Is this what we call the spirit? If so, then the spirit is still with us and we hope it never leaves.

Dr. Karumathil Puthiyaveettil Govindan was born in Kozhikode to the late E. K. Nair and the late K. P. Ammukutty Amma. He was the youngest of the three siblings, the late K P Lakshmi and the former Union Minister K. P. Unni Krishnan. He had his schooling in Koyilandy, a remote village then in Calicut District. He did his MBBS from Calicut Medical College (1970) followed by MD General Medicine from Maulana Azad Medical College and G.B. Pant Hospital in Delhi (1974) and took the specialty in Chest Medicine (DTCD) from Vallabhai Patel Chest Institute Delhi (1975). He pursued further training as a WHO fellow in RIT, Tokyo, and Habikino Hospital, Osaka, Japan in 1989. He then joined Calicut Medical College and served as Superintendent and retired as Professor and HOD of TB and Respiratory disease. During this period, his services were sought by the Ministry of Health, Chest Diseases Hospital, Taif in Saudi Arabia for four years. Subsequently he headed the Department of Pulmonology in Yenepoya Medical College, Mangalore, Kannur Medical College and Malabar Medical College Kerala. To his legion of students in MD, DNB and PhD, he was a philosopher, friend and guide. He was a compassionate examiner for the same courses. He served as Chairman Board

of Examinations, Calicut University and was Consultant in Occupational Diseases to ESI Corporation of India. His presence in the scientific world is exemplified by the numerous papers he has to his name in various International and National Journals.

Procrastination is the thief of time. His timely referrals of patients for surgery alleviated the suffering and saved many a life.

The heart of the man beat for his profession and his soul enriched not just his patients, but all our lives. His wit and humor will always be remembered as it was consistent with the manner in how he worked and lived. He always wanted to bring people together and celebrate atomic occasions. Cricket and Football were his weaknesses. His warmth and hospitality and penchant for aqua vitae were well admired. In short, Dr Govindan lived life to the fullest.

He was the 9th President of Academy of Pulmonary and Critical Care Medicine (APCCM) in 2004 – 2005. His Crowning glory was when he was elected as the 19th President of the Indian Chest Society at the turn of the millennium (2000).

He leaves behind his wife Dr. Radha, daughter of the former Chief Minister of Kerala the late Achutha Menon. She retired as Professor and HOD Pediatrics, Calicut Medical College. He is also survived by two daughters, Dr. Anupama (PhD) w/o Sajan Babu (IT) and Dr. Aparna (Pathologist) w/o Dr. Byju (Cardiologist) along with four grand children.

Say not in grief: He is no more but in thankfulness that he was.

Dr K. P. Govindan lived respected, died regretted.

Nasser Yusuf
Senior Cardiothoracic Surgeon
Sunrise Hospital Kochi &
Chest Hospital Kozhikode

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