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Pulmon

The Journal of Respiratory Sciences

Constrictive bronchiolitis: jargons and clinician's dilemma

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Constrictive bronchiolitis (CB) is a disease characterised by irreversible fibrosis of small airways triggered by a variety of causes. As the name indicates, there is constriction of membranous bronchioles by concentric fibrosis in the submucosal region. Terminal respiratory bronchioles and alveoli are not affected. As the disease progresses, bronchiolar lumen gradually gets narrowed due to intramural fibrosis and in later stages lumen gets completely obliterated. The counterpart of constrictive bronchiolitis is inflammatory bronchiolitis where the main pathology is cellular inflammation (granulation tissue) affecting the respiratory bronchioles with minimal or no fibrosis. Unlike CB, lesions in this type of bronchiolitis are predominantly intraluminal and extend to terminal respiratory bronchioles. Polypoidal granulation tissue occlude the lumen of bronchioles and hence designated as proliferative bronchiolitis (PB). Almost similar inflammatory reaction is seen in bronchiolitis obliterans with organising pneumonia (BOOP), where inflammatory buds are seen filling the alveoli. BOOP is now renamed as Organising pneumonia (OP). PB and OP are two different disease entities, the former an exclusive airway disease and the latter alveolar disease.[1]

It is to be noted that in CB, the bronchioles ultimately lose their architecture by concentric fibrosis and not discernible in advanced stages, where as in PB the architecture is well maintained, has minimal fibrosis and can potentially revert to original status with treatment. Although the causal triggers are often observed to have a common platform, the two entities are mediated entirely by different cellular and cytokine pathways and have entirely different pathologic features. In both conditions, lesions are patchy in distribution and a pathological diagnosis can be very well be missed by transbronchial biopsy. The exact pathogenic pathways of the fibrotic and proliferative bronchiolitis are not yet clearly delineated.[1]

Related terminologies and underlying causes

Bronchiolitis is generic term used for describing a wide spectrum of diseases involving respiratory bronchioles of less than 2 mm size. It includes acute and chronic

diseases of diverse aetiology. Currently there is lot of confusion on terminologies related with bronchiolitis often used interchangeably by different authors. This is probably because of the overlap of clinical, radiological and histopathological features of different diseases involving the bronchioles. There are no standalone diagnostic criteria for any of these diseases except perhaps for OP.[1] The course and prognosis of bronchiolitis vary widely despite having same exposure or having same predisposing factors. For example, viral and mycoplasma infections or toxic fume exposure can result in bronchiolitis. In a fraction of these subjects, uneventful recovery can occur within a short time, whereas in others it might turn out to be an indolent or progressive disease culminating in severe respiratory disability and respiratory failure. Brief description of confusing clinical entities of respiratory bronchiolitis is provided below.

Acute bronchiolitis can be due to infective agents (e.g. adenovirus, respiratory syncitial virus, mycoplasma) or can occur in association with any chronic bronchial diseases like asthma, chronic bronchitis and bronchiectasis. The lesions are multifocal, seen as centrilobular opacities in high resolution imaging and may include tree-in-bud appearance, mosaic perfusion pattern and air trapping depending on the severity and chronicity of the disease. Majority of these lesions are reversible, but potentially can turn chronic.[2,3]

Diffuse bronchiolitis can occur in chronic aspiration pneumonitis, hypersensitivity pneumonitis, diffuse panbronchiolitis (a specific disease of unknown aetiology), in chronic smokers and in respiratory bronchiolitis associated interstitial lung disease (RB ILD). The radiological and pathological features of these lesions are specific to the underlying aetiology.

Constrictive versus proliferative bronchiolitis: Although the pathology and pathogenesis of constrictive and proliferative bronchiolitis are entirely different, the causal factors of these two diseases overlap to a significant extent. Both conditions can occur as idiopathic variety or associated with connective tissue diseases, reaction to toxic fumes, drug related reactions, post infectious or in allograft recipients of bone marrow and heart lung transplants. However, it is observed that scleroderma, pencillamine drug reaction, toxic fume exposure to ammonia and sulphur dioxide exclusively predispose to CB, whereas in lupus erythematosus, mixed connective tissue diseases, amiodarone reaction and exposure to nitrogen dioxide the predominant involvement is proliferative bronchiolitis. Likewise, both CB and PB can be manifested in allograph transplant recipients of lung, bone marrow and stem cell. In early literature the term bronchiolitis obliterans (BO) was used to designate both constrictive and proliferative bronchiolitis. Now, with

better understanding of the pathological process the recommendation is to avoid using this term.[4]

Organising pneumonia (OP)

OP and PB have many similarities in terms of aetiology, pathology and response to treatment, but it is to be noted that they are two entirely different disease entities and OP is not a progressive stage of PB.[5] PB is a bronchiolar disease, whereas OP is primarily an alveolar disease categorised as interstitial lung disease (ILD). To avoid confusion, the recommended new terminology of BOOP is (cryptogenic) organising pneumonia (OP). In OP, inflammatory buds fill the alveoli (pathognomonic feature of OP) and the same type of reaction can be seen extending to respiratory bronchioles. In contrast to CB, both PB and OP runs an acute course with a potential of complete anatomic and physiologic recovery.

Bronchiolitis obliterans syndrome (BOS)

Bronchiolitis is very common in recipients of allograft transplant (heart-lung, bone marrow and stem cell) and can occur at variables phases after transplantation. However, the term bronchiolitis obliterans syndrome (BOS) is used specifically to designate bronchiolitis associated with delayed allograft rejection in transplant patients and should necessarily be preceded by graft-versus-host disease (GVHD). Around 50% of lung transplant patients surviving five years develop BOS. It is the leading cause of death for lung transplant recipients one year after transplant. BOS can manifest either as proliferative or constrictive type. Syndromic nomenclature is conferred because a pathological diagnosis may not be feasible for diagnosing the disease. Since the lesions are patchy, it can easily be missed by transbronchial sampling and diagnosis can be delayed for want of histopathology evidence. Delayed diagnosis can culminate in complete rejection of tissue and death of the patient. To facilitate early diagnosis, International Society for Heart and Lung Transplantation (ISHLT)/American Thoracic Society (ATS)/European Respiratory Society (ERS) has issued guidelines for early clinical diagnosis of BOS without depending on histopathology. The guideline emphases the importance of evaluating patients with unexplained dyspnoea in whom chest x-ray and spirometry may be normal as delay in intervention can meet with drastic outcomes.[6,7,8]

Constrictive bronchiolitis (CB)

Bronchiolitis obliterans (BO) and obliterative bronchiolitis (OB) are terminologies used interchangeably for CB by various authors creating confusion

among clinicians. However, CB is a better terminology as it rightly describes the underlying pathology, hence more specific and less confusing.

CB is an extremely rare disease with diverse aetiology. It may occur as primary lung disease or it may manifest in underlying lung or systemic diseases. Idiopathic CB is extremely rare. It can occur as post infectious sequelae or as a part of autoimmune systemic reactions occurring from connective tissue diseases, drug reactions or tissue transplants. Most of the initial reports were focusing on inhalational injury from chemical toxins and fumes probably because of the dramatic course that follows cloud exposure. The occupational association escaped notice for many years because of the indolent nature of the disease, latency in developing clinical symptoms and similarity in clinical, radiological and physiological features with other common respiratory diseases. Hence most cases of CB are misclassified as chronic bronchitis, asthma, bronchiectasis or ILD.

The first authentic evidence on association between occupational exposure and CB was based on publication of case series of workers employed in microwave popcorn plant in 2002. Diacetyl is considered as a safe food additive (used as butter flavouring for popcorn) and its possible role as an inhalational toxic agent escaped notice because of the silent and indolent course of CB.[9] The subjects were closely followed up over a period of eight years bringing to light the clinical course and physiological, radiological and pathological features of diacetyl associated CB.[10] Almost during the same period, follow up data of US soldiers deployed in Iraq and Afghanistan (exposed to sulphur mine fire in 2003) and Iranian soldiers exposed to sulphur mustard during Iran-Iraq war of 1984-88 were published.[4,11]

CB is now conceptualised to have a variable course and is best described using a "three-phase" model. Immediately after massive exposure to toxic fumes there is a stage of few hours of latency manifested only as eye and skin reaction. This is followed few hours later by features of severe lung injury mounting to acute respiratory distress syndrome (ARDS) in situations where the exposure is massive. Those who survive the acute event progress to the third phase of developing classical constrictive bronchiolitis. This phase has an indolent and progressive course ranging from days to years, that is irreversible and non-responsive to treatment culminating in severe respiratory morbidity and death over a variable period.[7] Clinicians must be on guard that many patients fail to recall toxic fume exposure when the first two phases of the disease were mild or went

unnoticed. Thus, diagnosis of the disease and its trigger may remain elusive leading to delayed diagnosis and continued exposure to noxious agents.

In occupational setting like popcorn plant, exposure to noxious fumes is less massive, but workers are exposed to the fumes daily. As the symptoms are absent or mild and limited to eyes and skin, respiratory involvement is overlooked. There is significant latency before respiratory symptoms are manifested. It is possible that many subjects would have left the occupation for reasons that may or may not be related with the occupation. Classical symptom is exertional breathlessness in a subject do not have a background of smoking history and breathlessness is disproportionate to clinical, radiological and physiological findings. Disease manifestation starts after the small airways are significantly involved. High index of suspicion is warranted in patients with exposure history even if spirometry and chest x-ray are normal. Features of small airway obstruction demonstrable by spirometry and HRCT (sensitive indicators) will be absent in the early stages of the disease.[4,11] In CB, the lesions are patchy and focal and hence lesions can be easily missed in small biopsies. In advanced disease, affected areas are completely replaced by scar tissue and bronchioles cannot be identified. Hence pathological diagnosis is almost impossible unless reviewed in the context of clinical and radiological features.[1] An in-depth and exhaustive occupational and environmental exposure history is required for clinching the clinical dilemma. High index of suspicion and public awareness will be advantageous in curtailing further exposures by means of personal and institutional protective strategies.

In conclusion, CB is an extremely rare disease. It is possible that majority of CB due to occupational exposure are undiagnosed because of its indolent course and lack of awareness. Most patients are misclassified as asthma, COPD, bronchiectasis or ILD. Breathlessness disproportionate to clinical, radiological and physiological observations should alert clinicians for considering constrictive or proliferative bronchiolitis and take effort to explore environmental or occupational exposures especially if the patients are non-smokers. The burden of occupational constrictive bronchiolitis may be huge and published reports could be just the tip of iceberg. It is heartening to note that recently clinicians are taking keen interest in unravelling the occupational background of chronic respiratory disease among non-smokers. The article on bronchiolitis and coffee processing in this issue needs special mention as the authors have clearly exposed yet another occupational health hazard of constrictive bronchiolitis.

References

1. D.W. Visscher, J.L. Myers, Bronchiolitis: the pathologist's perspective, Proc.Am. Thorac. Soc. 3 (1) (2006) 41–47.
2. Murata K, Itoh H, Todo G et al. Centrilobular lesions of the lung: demonstration by high resolution CT and pathologic correlation. Radiology 1986;161:641-5.
3. Essadki O, Grenier P. Bronchiolitis: computed tomographic findings. J Radiol. 1999 Jan;80(1):17-24.
4. Kathleen Kreiss. Occupational causes of constrictive bronchiolitis. CurrOpin Allergy Clin Immunol. 2013 April; 13(2): 167–172.
5. Gary R. Epler. Constrictive Bronchiolitis Obliterans: The Fibrotic Airway Disorder. Expert Rev Resp Med. 2007;1(1):139-147.
6. Meyer KC, Raghu G, Verleden GM, Corris PA, et.al., ISHLT/ATS/ERS BOS Task ForceCommittee; ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. Eur Respir J. 2014 Dec;44(6):1479-503.
7. Gary R Epler. Diagnosis and treatment of constrictive bronchiolitis. F1000 Medicine Reports 2010 2:32.
8. Kerger BD, Fedoruk MJ. Pathology, toxicology, and latency of irritant gases known to cause bronchiolitis obliterans disease: Does diacetyl fit the pattern? Toxicol Rep. 2015 Nov 2;2:1463-1472.
9. KreissK., Gomaa A, Kullman G, Fedan K. et al. Clinical bronchiolitis in bronchiolitis obliterans in workers at microwave-popcorn plant. N Engl J Med. 2002 Aug 1;347(5):330-8.
10. Akpinar-Elc M, Travis WD, Lynch DA, Kreiss K. Bronchiolitis obliterans syndrome in popcorn production plant workers. Eur Respir J 2004; 24: 298–302
11. King MS, Eisenberg R, Newman JH, Tolle JJ, et.al. Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan. N Engl J Med. 2011 Jul 21;365(3):222-30.

Pulmon is now Indexed

We are happy to inform you all that Pulmon is now indexed in Index Copernicus. On this occasion we thank the past editors, the past and current office bearers and governing council members of APCCM, those enriched the journal with articles, members and well wishers of APCCM whose relentless efforts made this remarkable achievement possible. Saluting the founder editor Late Dr.R.C.Babu for his far sighted vision even during the infancy period of the journal. We request all to continue your patronage and support.

Editorial team Pulmon

Palliative and end of life care in COPD

Sujeet Rajan

Abstract:

The word 'palliative' itself often evokes a strong response from my professional colleagues. These range from positive to negative and often indifferent too. No branch has been more underutilised in modern clinical medicine than palliative care medicine.

Modern day medicine has brought with it an amazing assortment of newer technology, drugs and devices that have completely changed our understanding and management of patients today – degree of comfort, and prolongation of life span of a level never seen or imagined before. Yet many of our patients with advanced COPD remain miserable at the end of their lives - so much that it is difficult to fathom where we have gone wrong at times.

Multiple reasons can be attributed to this. Every patient trusts a 'family' doctor – and this person could range from a general practitioner to a non-allopath, to any specialist. If this trusted doctor cannot sense the direction of care his patient needs, the patient is likely to receive care directed at potential cure or prolongation of life, the former being largely impossible in progressive end-stage COPD, and the latter coming at the cost of quality of life. It is we as a physician community that need to strive to change that.

Introduction:

Despite the significant mushrooming of palliative care services across India, the focus of palliation continues to remain largely on pain management and terminal cancer care. Since its origins in the city of Mumbai are from a cancer centre itself, it is not surprising that it has taken time for the branch to develop its roots into non-malignant conditions. Just take a round of a Hospital in any city and you will find more elderly patients than children by far.

The average age of an in-patient in a Hospital is increasing by the day. When put into 5 year bands, the single largest group of patients in a study in the UK comprised the 65 – 69 year group[1]. I would believe that this would not be far off the mark in India.

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And these are most certainly not all cancer patients. A large group of these patients comprise patients with progressive diseases of either the heart, lungs, kidney, liver or neurological systems, and often combinations of various organ diseases. Some of the challenges we face are as follows:

Challenges in implementing end of life and palliative care in COPD:

1) Teaching in medical colleges:

Despite the mushrooming of medical colleges in India, the specialty of palliative care remains underrepresented. Medical students are ever eager (and not surprisingly) to learn about new drugs and technology. That just caring for and communicating with a patient and his/her family with COPD can go a long way in relieving suffering is the beginning of palliative care. New drugs are not always the solution. Studies have shown that multiple hospital admissions *themselves* occur due to drug-induced side effects[2], and invasive ventilation is often used in patients with progressive lung disease, despite extreme unlikelihood of any significant improvement in quality of life – in contrast, marked deterioration in the same. A multi-centric European study has shown that COPD is a strong predictor of withdrawing or withholding therapies [3,4].

2) The business model of private hospitals

Let's face it - A private hospital has a business to run, just like many other businesses. And we can't blame the hospital CEO – he has a mandate from his board of trustees. Invariably that mandate includes improving and (if possible) maximising bed occupancy. The domino effect of that mandate is obvious, for most Hospital insiders to see. In-hospital occupancy takes priority over out-patient preventive care. The patient is 'looked after' well medically – one needs to question whether that implies improved 'health' care. In a private Hospital, shared decision-making is far from being the norm, despite numerous studies suggesting that it results in improved patient outcomes[5,6].

3) Lack of awareness among hospital physicians

"What is palliative care?" – I have forgotten how many times colleagues at the Hospitals I work and primary care physicians have asked me this question. An Indian study just a few years ago suggests that 85% of doctors felt that cancer was the commonest reason for palliative care services to be involved, and that pain control was the major objective of a palliative care physician[7]. In our experience it takes just one non-cancer palliative care physician and a few committed respiratory physicians to galvanise this branch in a Hospital. The message spreads like wild-fire across every echelon of a Hospital set-up. From the ward boy who sees the patient more comfortable and less 'complaining', to the nurse who observes the caring conversations and comfort that they so long to give the patient

as well, to the resident doctor who sees a satisfied patient with a different perspective - Everyone in the Hospital is sensitised. The effect is unbelievable, yet true in every respect.

4) Patient and doctor perception that the palliative specialist has 'Given Up'

No physician should give up caring for his patient. The palliative care specialist doesn't give up even after death – the family and care-givers need care at this stage too. A common question from my physician colleagues - "Is there no new drug, device or intervention that will help our patient?" My answer is often a simple 'no', but there is a lot that can be achieved with a good conversation with patient and family, and of course judicious use of morphine. Giving up something by choice is what we often do in life, and wouldn't we all like to do that, given a choice of a miserable, versus comfortable and pleasant life ahead?

5) Lack of communication skills in general

An interesting conversation with medical students (often lacking training in good communication skills), reveals that they are increasingly being taught what to say, but not how to say it[8]. Communication has never been a subject of the medical curriculum, yet all clinicians do every day is talk to new people. Just like in any other profession, communication skills complement competency, and are essential for inspiring confidence in a patient, and garnering trust. Even the most competent (and extremely well-read) physician can fail miserably in clinical practice due to poor communication skills. Palliative care communication is challenging and demanding, but can be very enjoyable in the right circumstances. It all depends how one has been trained to do it, and how we have witnessed our seniors doing it. Role play can be an amazing teaching technique here, something that can be highlighted in pre conference workshops.

6) Gross lack of communication skills in end of life care

End of life care communication in COPD is even more challenging than regular and basic communication between the patient and doctor.

"Where is the time to do it? The patient is anyway dying."

"Why talk about the harmful effects of a ventilator which could take a few minutes, when we could use this wonderful new machine just purchased by our Hospital and buy more time for the patient instead?"

"Why discuss the possibility of a patient dying, when the patient is alive? Will be perceived as so negative by the family".

"Why talk about the likelihood of the patient dying when the family has complete hope in you to do 'something' for the patient"?

Conversations and care in advanced COPD

often seem 'inadequate' in a sense – something that good training in end of life care communication can transform[9].

7) Poor accessibility to morphine

Despite the tremendous benefit of morphine in advanced non-malignant lung conditions, its use is far from what it should be. Kerala state has progressed here, with far easier access to this drug[10], and a mushrooming of palliative care clinics across the state - far more than the rest of the country combined. Multiple licence requirements by chemists, fear of side effects, and the lack of awareness amongst physicians about its effectiveness in palliating breathlessness are just some of the reasons that contribute to the underuse of this wonderful drug in palliative care medicine.

8) "No time for it!"

Too many patients, or too less time is a frequent complaint of Indian physicians. We often argue that our biggest challenge in practice is time. Managing time is crucial in clinical practice. This is another facet of medicine not taught in medical colleges in India. Managing time is critical to life itself, forget medicine. Just listening to a harrowed patient with advanced COPD can do a whole lot of good to alleviating suffering. The patient feels he has been heard at least. In the limited time we have with the patient, focusing on what is important to the patient, and what can make a significant difference to his quality of life is what will matter most, finally.

Triggers in COPD to commence / Discuss end of life and palliative care:

1) Patient or a family member indicates that they wish to discuss advance care planning/ directives

2) Very severe COPD - FEV1 < 30%

3) Severe refractory dyspnoea (even on supplemental oxygen)

4) 1 or more than 1 hospitalisation in the last year

5) Advancing age with increasing dependence on others

6) Oxygen dependency or commencement

7) Use of Home NIV

8) Frailty and weight loss– undernourished patients with a BMI < 21 have a much worse prognosis in COPD.

So what do we need to do ?

*(*Note that much of this can be done by the pulmonologist in the absence of a trained palliative care specialist*)*

a) Identify a palliative care physician in your locality/hospital and mention to the patient that he is part of your team someone whose job it is to focus on the patient's symptoms and quality of life. If there is no such physician, try and at least identify a nurse, psychologist or social worker to be part of your team for this aspect of your service. If you are unable to identify a per-

son, you will need to do the palliative care yourself ; something you will have to factor a little time for, but well worth it for your patients. Patients value a doctor's time even more these days – see the difference when you listen more and talk less.

b) Stress to the patient that involving the palliative care consultant/specialist is not going to stop you and the patient from looking at newer advances in the treatment of COPD, and keep discussing the pros and cons of those as one goes along.

c) Ask the patient what he/she feels about meeting the palliative care doctor/nurse. Give them time to decide if they appear reluctant, but keep subtly mentioning it as you see progressive deterioration in the quality of the patient's life.

d) Explain to them the meaning of palliative care in a language and manner that the patient can understand. Ask the patient if what you said was understood.

e) Ask the patient about their objectives and goals in life – especially if you don't have a specialist to start this conversation. Ask about any unfinished business and tasks to do in life.

f) Ask the patient what bothers them the most with their COPD – often you will get surprise answers like 'fear of dying' rather than breathlessness. This, you would realise, cannot be addressed by a bronchodilator or steroid inhaler.

g) Involve the patient in pulmonary rehabilitation if you have this service at your hospital. If not, just get your trusted physiotherapist to keep the patient more mobile. Simple continued mobility every day goes a long way in improving patient well-being, both mental and physical.

h) Identify depression early – here weight loss can be an ominous sign, and one of the commonest presentations of depression in the elderly. Involve a geriatric psychiatrist early on, or (if not available) at least a psychologist – consider starting a slow-release serotonin uptake inhibitor (SSRI) if no psychiatric consultation possible. Escitalopram at 5 mg/day for starters is a good choice. Be careful with drug-induced hyponatremia, especially in elderly patients.

i) Ask them (especially if they have been admitted to hospital before), about their experience and what they would feel if the need arises again – the patient will usually give you all the answers you need to hear – just listen. This will often lead to the next point.

j) Ask them if they have any advance directives like negative consents for intubation, ICU care, dialysis, tube feeding etc. – should the need ever arise in the future.

k) Talk to them and prescribe morphine early especially if they are breathless despite oxygen – start with about 2.5 mg twice daily and slowly escalate if required to 4 times a day – remem-

ber this can be used in even hypercapnic patients – monitor drowsiness and pCO_2 levels periodically – if the hypercapnic patient is stable (and not drowsy), then 3 monthly blood gases should be fine. Remember that evidence suggests that low dose, short-acting morphine has no tolerance effect even after years of use, unlike the benzodiazepines.

l) Sometimes discussions may need to be had on what needs to be done if the COPD patient gets breathless despite morphine at a maximum dose of 30 mg/day – at this juncture parenteral morphine or 'terminal sedation' may need to be instituted – this can be done at home or in the hospital – this is often best discussed in advance. Sometimes these discussions can be very difficult, but move your conversation with the flow from the patient (and if the patient is not competent) from the most proximal family member. For good advance directives or living wills to be in place, it is extremely important to have these conversations early on. You wouldn't want to learn to swim when your ship is sinking, right? Rather when well on a sunny 'good' day.

m) Finally, encourage your hospital to have a negative consent form for withholding and withdrawing futile unnecessary treatments in end-stage COPD. Some Hospitals have called these 'comfort care' forms which sounds more positive. These forms need to be discussed with the patient (if competent) and all family members (who are direct caregivers), before signatures are obtained. Family meetings go a long way in ensuring these forms are signed in an appropriate way. Never force a signature. Listen to the patient, and the family members. If differences in opinion exist between children of the patient, tell them to consult a doctor whom they all trust, and leave the decision to that doctor – that doctor (usually a GP or specialist the patient has been with for the longest time) will in all likelihood take decisions in the best interests of the patient.

Conclusions:

The challenges we face can all be overcome. None are insurmountable. It takes a will to change a paradigm in medicine. And this change is the need of the hour.

It is only through more palliative care specialists that pulmonary medicine will move from a drug and technology driven branch to a more humane one, albeit with the technology still there – but judiciously used.

Medicine and Hospitals have never before faced these challenges – and what a more appropriate time to overcome them – a time when Hospitals and physicians are often facing accusations of being mercenary and uncaring. In my experience it takes just one committed palliative care physician and a few understanding pulmonologists to take this branch to another

level – one that inspires not just confidence in the patient that all can be done, but also trust in patients that all *does not* always need to be done.

References:

1) NHS Digital. November 9 2016
2) Caranosos GJ et al. Drug-induced illness leading to hospitalisation. JAMA 1974; 228(6):713-717
3) Sprung CL et al. End-of-life practices in European in tensive care units. The Ethicus study. JAMA 2003;290:790-797
4) Carlucci A et al. Palliative care in COPD: Is it only an end-of-life issue? EurResp Rev 2012; 21 :126, 347-354
5) Elwyn G et al. Shared Decision Making: A Model for Clinical Practice. J Gen Intern Med 2012 Octo ber; 27(10): 1361 – 1367
6) Wilson SR et al. Shared Decision Treatment Decis ion Making Improves Adherence and Outcomes In Poorly Controlled Asthma. Am J RespirCrit Care Med Mar 15;181(6):566-77. doi: 10.1164/ rccm.200906-0907OC. Epub 2009 Dec 17.
7) Bhadra K. et al. Awareness of palliative care among doctors of various departments in all 4 teaching medi cal colleges in a metropolitan city in Eastern India: A survey. J Educ Health Promot. 2015; 4: 20
8) Ruddock A. AIIMS teaches its doctors what to ask a patient, It must also teach them how. 2018 Scroll.in
9) Galushko M et al. Challenges in end-of-life com munication. CurrOpin Support Palliat Care. 2007 September ; 6(3) 355-364
10) Rajgopal MR et al. Oral Morphine Use In South India: A Population-Based Study. J Glob Oncol ,

Articles Invited

The Pulmon, official publication of Academy of Pulmonary and Critical Care Medicine (APCCM) which is indexed in Index Copernicus invites articles in the form of original research papers, review articles, case reports, radiology pearls and letters to the editor. The articles which are original and plagiarism free should be prepared in MS Word with double column in single spaced typed pages.The same should be submitted to the editor electronically as an attachment on E mail ID *editorpulmon2019@gmail.com.* All articles will be subjected to plagiarism check and standard review process.

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Editor in Chief Pulmon

COVID-19 pandemic: let's gear up for the heavy battle !

Ajith Kumar A.K[1] **, Justin Aryabhat Gopaldas** [2]

In February 2020, the World Health Organization (WHO) coined the term " COVID-19 " for the disease caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). Noticing it's relentless spread to almost 114 countries with further signs of progression, the WHO has declared COVID-19 spread as a pandemic on 11th of March, 2020. This was done to gear up the entire globe for an intense battle in the coming weeks and months to contain and manage as best as we could. At the time of writing this article, confirmed cases of COVID-19 world over have crossed 465,000 with more than 21,000 deaths. About one third of the infected are documented to have recovered. India has 606 confirmed cases,10 deaths, and 43 persons have recovered as per records

Complete genome sequencing of SARS-CoV-2 with phylogenic analysis shows that these enveloped RNA viruses are beta-corona viruses coming under same subgenus of SARS virus. Phylogenetic analysis of 103 strains from China has identified 2 different sub-types of SARS-CoV-2 i.e. L types (70 %) and S types (30 %) [1]. Similar to SARS corona virus the COVID-19 virus binds to the target cells via ACE2 receptors expressed by epithelial cells of the lung, intestine, kidney, and blood vessels.

Phases of a pandemic spread of an infection is well defined by WHO from experiences of other respiratory illnesses like the one caused by H1N1 Influenza (2009). In the case of COVID-19, epidemiological investigations in Wuhan, China zeroed on to a seafood market where live animals were sold as the initial source of infection. Since then they continued to move from Phase 1 to 3 over a course of 8-12 weeks and required large scale state lockdown and other preventative measures other than just caring for the ill. The same above course has been replicated in Italy with much more devastating effects on population. Lessons from these countries allow us to understand the rapidity and infectivity of the spread. Incubation period with COVID-19 infection could be up to 14 days with most of the infections occurring within 4-5 days of exposure making the identification and containment extremely difficult. [2,3,4] India is now at the verge of phase 3 transition. Flattening the surge curve is being addressed with various community measures as well as constant test for community transmission.

Spread is both in droplet form and through contact of infected surfaces. The predominant spread is thought to be droplet

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infection which occurs whenever an infected person coughs/speaks or sneezes resulting in dispersion of infected respiratory secretions to the contacts who in turn gets infected when the droplet particles settles on their mucous membranes. Since droplets are larger (> 5 microns) particles, the spread is usually limited up to a distance of 2 meters. The droplets being larger particles will not get suspended in the air for a longer time, unlike the smaller airborne particles. The modes of transmission have impact on measures devised to control the spread and in view of uncertainties regarding the transmission mechanisms, few countries have opted for airborne precautions in all areas of infection control whereas others have opted for air borne precautions only in certain high risk aerosol generating circumstances.

Transmission of SARS-CoV-2 from asymptomatic carriers (including those within the incubation period) have been reported and it is also believed that infectivity may continue for weeks even after clinical recovery from an infection. Faeco route of transmission is believed to be non-significant though the virus has been detected and cultured in stool specimens [5]. Intrauterine vertical transmission has not been documented in initial studies, though neonatal infections have been reported [6]. An Indian Council of Medical Research (ICMR) statement dated 17th March 2020 mentions that India is still in stage 2 of the COVID-19 outbreak where the dominant method of spread is local transmission.

The clinical spectrum ranges from mild infections requiring only self quarantining, moderate infections requiring hospital admission, to severe life threatening infections requiring intensive care management. Pneumonia is the most frequent serious manifestation presenting with fever, cough with or without sputum production, breathlessness and bilateral lung findings. Fatigue, sore throat, head ache, myalgia rhinorrhea, or diarrhoea may be present. Some authors have described patients not developing respiratory distress even with profound hypoxemia. Chinese Centre for Disease Control and Prevention reported the following features in about 44,500 confirmed infections [7].Mild infections constituted 81 % of the patients with absent or mild pneumonia,14 % developed severe disease with dyspnea, hypoxemia or pneumonia with more than half of the lung involvement on imaging, occurring within 1-2 days .Only 5 % had developed critical disease in the form of severe respiratory failure, shock or multi organ dysfunction. The overall case fatality was 2.3% with deaths reported only in critically ill patient.

Majority of the life threatening manifestation resulted from severe ARDS with or without associated multi organ failure. Acute cardiac injuries and arrhythmias were also reported in a good number of patients. Cytokine storm and secondary haemophagocytic lympho histiocytic syndromes are also well documented. Majority of the fatal cases occurred in patients with advanced age or underlying co-morbidities including cardiovascular disease, chronic pulmonary disease, diabetes, hypertension and malignancies[7,8].

The common laboratory findings include lymphocytopenia (most common), though

leucocytosis or leucopenia have also been reported. Thrombocytopenia (usually not less than 100,000 /mm^3),and elevated aminotransferase levels have been documented. Elevated lactate dehydrogenase and ferritin levels are common. Normal procalcitonin levels were found in many pneumonias at admission though a 2020 meta analysis of 4 studies suggested that high Procalcitonin values are associated with a nearly 5-fold risk of severe SARS-CoV-2 infection (OR, 4.76; 95% CI, 2.74–8.29) [9].High D-dimer levels and more severe lymphopenia have been associated with high mortality.

Chest radiograph is an insensitive tool in mild or early disease where it could be often interpreted as normal. CT scan thorax has much more sensitivity, and the features include bilateral ground glass opacities with consolidative pattern in a more peripheral distribution, vascular thickening and predominant involvement of lower lobes. Atypical features include mediastinal lymphadenopathy, pleural effusions and nodular patterns. USG findings include B-lines, consolidations, irregular and thickened pleural lines and appearance of A-profile in the recovery phase.

The revised Indian COVID-19 testing strategy dated on 16th March 2020 and endorsed by ICMR and Ministry of Health and Family Welfare (MHFW) recommends quarantining of patients who are in physical contact with laboratory confirmed cases, or persons who have travelled to high risk COVID-19 affected countries in the past 14 days. If they get symptoms within the 14 days during quarantine, they need to undergo throat and nasal swab tests (Reverse Transcription Polymerase Chain Reaction (RT-PCR)) with the samples collected in a single tube in a viral transport medium in cold chain. ICMR in a further notification on 20-03-2020(version 3) also included all symptomatic health care workers and all hospitalized patients with Severe Acute Respiratory Illness(fever AND cough and/or shortness of breath) within the purview of testing strategy. Viral culture should not be attempted due to safety reasons.

Preparation for the pandemic includes hospital/ICU readiness for the surge in numbers as well as challenges to the infection control processes that are there in any specific institution. In view of the surge, it is advised that each individual physician, ICU and hospital adapt or develop a policy to prepare themselves with understanding of the available resources as well as how and when to use them. Safety of the health care workers (HCWs) is of paramount importance noting the experience of Italy where loss of the caring medical or nursing team members are noted and is extremely unfortunate. This leads us in India to prepare with adequate training of donning and doffing of the personal protective equipment (PPE) in each hospital that are due to receive cases of COVID-19 infections. Specific protocols in relation to triage, admission, communication process, transport of these patients to and from ICU,and specific medical care are evolving by the day with arrival of experience/research data from China, Europe and USA.

The management of proved COVID-19 in patients with minimal infection or who are asymptomatic relies on self quarantining in a

facility where further exposure to the community is nullified. However they do need close monitoring of progress of their clinical condition. In moderate to severe clinical disease the patients need to be referred to a hospital not only with isolation facility but also with facilities for respiratory/other organ supports.

Patients developing ARDS and/or multi organ failure needs organ support measures in intensive care settings. Though reports of successful management of COVID19 patients on Non Invasive Ventilation/High Flow Nasal Cannulas are available, there are still ongoing concerns regarding the risk of increased transmission to care givers in view of high aerosol generation in such settings. Intubated patient require lung protective ventilatory strategies including commencement prone position ventilation, whenever indicated. Restrictive fluid strategy will be appropriate in ARDS settings. Renal replacement therapies are initiated in the appropriate patients. ECMO could be a rescue modality in severe refractory hypoxemia.

Data regarding safety and efficacy of various pharmacological agents are currently scanty. In the current pandemic setting, since the number of patients included in individual trials are low, we must go on using them in bigger numbers in research settings to power our studies and generate appropriate messages. The pharmacological agents which are tried currently include lopinavir/ ritonavir combination,chloroquine or hydroxychloroquine, remdesivir, toclizumab (interleukin 6 inhibitor), interferon beta-1 and convalescent serum. Various combination therapies are instituted in many countries at this stage. Other investigational agents include umifenovir/darunavir,combination, rintatolimod, azvudine,danoprevir,favipiravir, and sarilumab (interleukin 6 inhibitor). CDC and WHO recommends against the use of glucocorticoids unless there are other indications like underlying COPD acute infective exacerbation or septic shock [10,11].

There has also been ongoing debate regarding the use of ACE Inhibitors andAngiotensin Receptor Blockers (ARBs) in view of their potential for increased expression of ACE2 receptors in diabetic and hypertensive patients making them increasingly predisposed to COVID-19. However many international societies including European College of Hypertension, Canadian Cardiovascular Society and American College Physicians recommend all such patients to take ACE inhibitors/ARBs uninterruptedly at this juncture. The WHO has recommended to avoid Ibuprofen (and prefer Paracetamol) for COVID19 symptoms in view of it's potential for increased ACE2 expression, at this stage.

The WHO, CDC, Indian Council of Medical Research and Ministry of Health and Family Welfare/Directorate General of Health Services (Government of India) are constantly reviewing, revising and issuing updated information regarding preventive as well as treatment strategies against COVID-19 .The need of the hour is to re ensure that the entirehealth care professionals are working in strong unison with the government and general public to succesfully tackle the killer pandemic pandemicin the coming weaks and months.

References:

1. Tang X, Wu C, Li X, et AL On the origin and continuing evolution of SARS-CoV- National Science Review. 2020;
2. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Li M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z,Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JTK, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020;
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS, China Medical Treatment Expert Group for Covid-19 Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;
4. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, K, Yuen KY A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10223):514. Epub 2020 Jan 24.
5. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID- www.who.int/docs/default source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf (Accessed on March 04, 2020).
6. Huijun C, Guo J, Wang C, Luo F, Yu X, Zhang W, Li J, Zhao D, Xu D, Gong Q, Liao J,Yang H, Hou W, Zhang Y. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. The Lancet. Published online February 12,2020. https://doi.org/10.1016/S0140-6736(20)30360-3
7. Wu Z, McGoogan JM Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Out break in China: Summary of a Report of 72/314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020;
8. Zu F, Yu T, Du R, at al Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study Lancet. 2020;
9. Guiseppe Lippi, Mario Plebani.Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis (letter to editor). Clinica Chimica Acta 505(2020) 190-191
10. Centers for Disease Control and Prevention. Interim Clinical Guidance for Management of Patients with Confirmed 2019 Novel Coronavirus (2019-nCoV) Infection, Updated February 12, 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html (Accessed on February 14, 2020).
11. World Health Organization. Novel Coronavirus (2019-nCoV) technical guidance: Patientmanagement. https://www.who.int/emergenciesdiseases/novel-coronavirus-2019/technical-guidance/patient-management (Accessed on February 02, 2020).

APCCM annual conference Pulmocon 2020 postponed

14-03-2020

Dear Colleague,

We were eagerly waiting to meet you all with an academic feast at Kannur from 17th to 19th April- PULMOCON- the 22nd Annual National Conference of Academy of Pulmonary and Critical Care Medicine (APCCM), when the COVID-19 pandemic spread the havoc.

The country is unlikely to be Corona free in the next one or two months. As a responsible scientific national body of Pulmonologists we cannot move ahead with this program when the authorities have asked to cancel all seminars, workshops and gatherings, which is likely to spread the disease out of proportions.

We have been conducting discussions with seniors and authorities all the while, discussed and weighed the merits and demerits of going ahead with the conference. We are aware of the huge commitment and hard work put in by the team Kannur Chest Society for a memorable Pulmocon. All the faculty for CME and workshops were finalised, and individual intimations sent. Venue arrangements were going on in full swing. We have to keep safety ahead of glory, when the country is under threat of the pandemic. Furthermore, we cannot spare three days in a conference when we are supposed to serve the needy.

Complying with the majority sentiments and the law of the land we are forced to postpone the PULMOCON 2020 with a heavy heart, in the best interest of health and safety. Our priority is the safety and wellbeing of delegates and therefore, we will be monitoring the situation closely to ensure that it remains a safe and appropriate time to hold the event.

The conference will be conducted at a later date at the same venue in Kannur. The new dates of the conference will be communicated to you all at the earliest. The registrations already made will be carried over to the new dates. The APCCM elections 2020 will take place during the conference as announced earlier. The scientific program will remain the same and all abstracts stand accepted for presentation during the new dates. Kindly visit www.apccm.in for updates.

In the meantime, our thoughts and wishes remain with patients and healthcare professionals affected across the world

The inconvenience caused to you all is regretted. Hope to see you all at Kannur soon.

Warm regards and thanking you for your understanding,

Dr. T.P. Rajagopal
President, APCCM

Dr. B. Jayaprakash
Secretary, APCCM

Dr. Manoj DK
Organizing Chairman,
Pulmocon 2020

Dr. Sanjeev Kumar
Organizing Secretary.
Pulmocon 2020

Bronchiolitis obliterans in workers of coffee processing unit among a cohort of patients treated as COPD - A prospective observational study

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Abstract

Bronchiolitis obliterans due to diacetyl is seen among workers of coffee processing unit as this gas is a natural byproduct during coffee processing. Aim of this study is to identify cases of bronchiolitis obliterans among a cohort of COPD and to study its relationship with coffee processing in Wayanad. Study setting is a tertiary care facility in Wayanad for a period of 6 months from 1.1.2018 to 30.6.2018. 6 cases of bronchiolitis obliterans is identified from a cohort of 200 COPD patients admitted for COPD exacerbation. Study concluded that there are cases of bronchiolitis obliterans among coffee processing workers of Wayanad and are being mistakenly treated as COPD.

Keywords: Bronchiolitis obliterans, Popcorn Lung, Diacetyl

Introduction

Bronchiolitis obliterans is a type of obstructive lung disease affecting the small airways[1]. It is a rare condition characterized by fibrosis of terminal and distal bronchioles and spirometry showing predominant small airway dysfunction. It usually leads to progressive decline in lung function and has variable outcomes. Etiology includes lung transplant and hematopoietic stem cell transplantation, exposure to inhaled toxins and gases including mustard gas, nitrogen oxides, diacetyl and fiberglass. Bronchiolitis obliterans is also associated with autoimmune disorders. This study is to find out cases of bronchiolitis obliterans due to diacetyl among workers of coffee processing units in Wayanad.

Objectives

1) To identify cases of obliterative bronchiolitis among a cohort of patients treated as COPD

2) To create awareness that occupational exposure to coffee processing may cause bronchiolitis obliterans which is different from COPD.

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Study Methodology

This is an observational study among hospitalized COPD patients in a tertiary care hospital in Northern Kerala. All cases of COPD admitted in the hospital for a period of 6 months from 1st Jan 2018 to 30th June 2018 were included in the study after obtaining informed consent.

They were all treated as COPD acute exacerbation as per GOLD guidelines. A detailed occupational history of all these patients was taken. Those who give a history of working in a coffee processing unit for more than 2 years at any point of time in their life are further evaluated by reviewing their spirometry and X-Ray Chest. HRCT Thorax is taken for those patients having significant small airway dysfunction (FEF25-75 <50% Predicted) by spirometry and bilateral reticular shadowing in the X ray. A diagnosis of bronchiolitis obliterans is made if the HRCT shows bilateral reticulation, bronchiolar wall thickening, mosaic attenuation, tree in bud shadows and cyst formation.

Institutional ethics committee approval was obtained before the initiation of the study.

Results:

200 patients were admitted with COPD exacerbation during the study period. There were 168 males (84%) and 32 females (16%) in the cohort. This group included 151 smokers (75.5%) and 49 nonsmokers (24.5%). 19 patients gave history of working in a coffee processing unit. The period of employment ranged from 2 years to 20 years. There were 15 males and 4 females in this group. Of these 19 patients 11 had significant small airway dysfunction in spirometry. Even though most patients of COPD showed small airway dysfunction apart from typical obstructive function of COPD, these patients showed predominant small airway dysfunction (Fig-1). Hence 5.5% of patients in the COPD cohort showed involvement of small airways. Among workers of coffee processing units 58% had small airway dysfunction. Of these 19 patients 6 patients had X-Ray and HRCT features to suggest bronchiolitis obliterans. These 6 patients include 4 males and 2 females. The age range varied from 49 years to 63 years. All the male patients were smokers. Thus 3% of study cohorts and 32 % of those working in coffee processing units showed clinical and radiological features of bronchiolitis obliterans (Fig-2, Fig-3). These finding are not a feature of COPD and suggest involvement of bronchioles.

Discussion

Bronchiolitis generically refers to inflammation and/or fibrosis involving (a) airways smaller than 2 mm in diameter, which often lack a cartilaginous wall, and/or (b) the alveolar ducts. Bronchiolitis often exhibits nonspecific clinical manifestations that range from an insidious onset of cough and shortness of breath to an acute fulminant illness. Inflammatory bronchiolitis is due to infection with viral or atypical organism, exposure to organic antigens or noxious particles and aspiration. Constrictive bronchiolitis is seen in transplant recipients.

Bronchiolitis obliterans secondary to noxious particles resembled that of "Popcorn Lung" reported in workers of a microwave popcorn plant in Missouri in 2002[2]. This was caused by a flavoring agent termed diacetyl (2,3-butanedione) which is used to give the popcorn a buttery taste[3]. Later, it was reported that this flavoring agent is extensively used in e-ciga-

Table-1: Showing the details of study subjects including gender distribution and smoking status

Study subjects	Total number	Male	Female	Smokers	Nosmokers
Hospitalized COPD	200	168 (84%)	32 (16%)	151 (75.5%)	49 (24.5%)
Employed in coffee processing units	19 (9.5%)	15 (78.9%)	4 (21.1%)	15 (78.9%)	4 (21.1%)
Reduced small airway function	11 (57.8%)	9 (81.8%)	2 (18.2%)	9 (81.8%)	2 (18.2%)
Radiological abnormality	6 (31.5%)	4 (66.6%)	2 (33.4%)	4 (66.6%)	2 (33.4%)

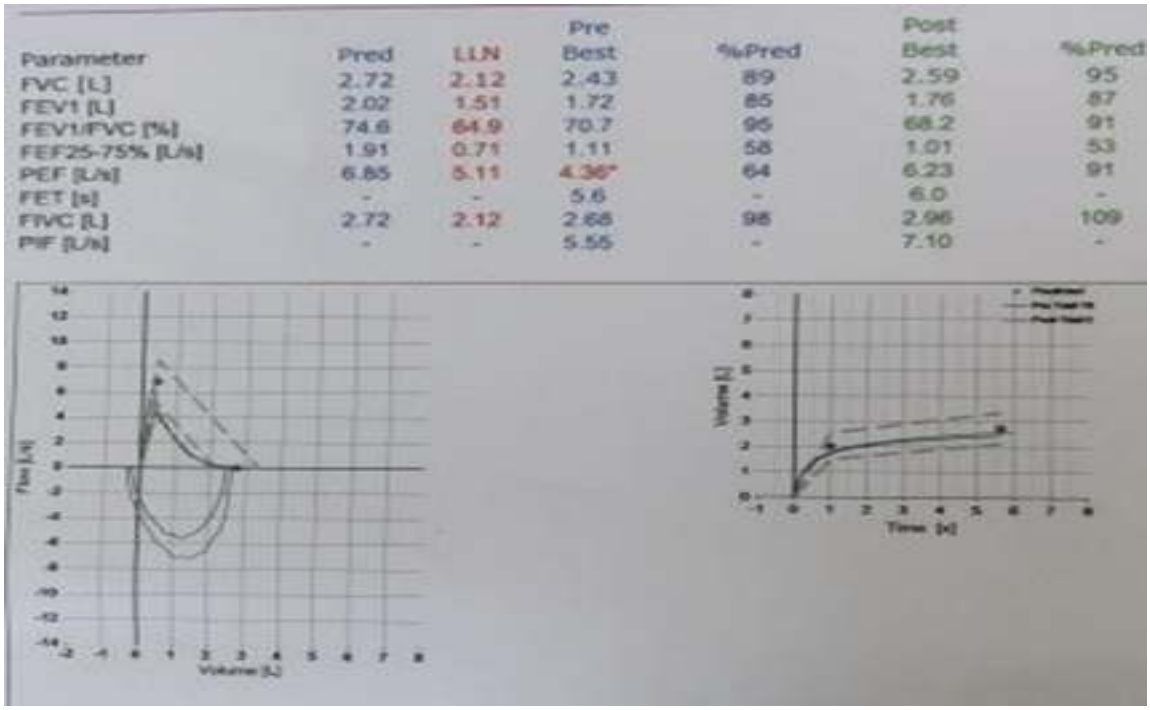

Fig-1: Spirometry of 53-year-old non-smoking female patient showing reduced small airway function with normal FEV1/FVC ratio.

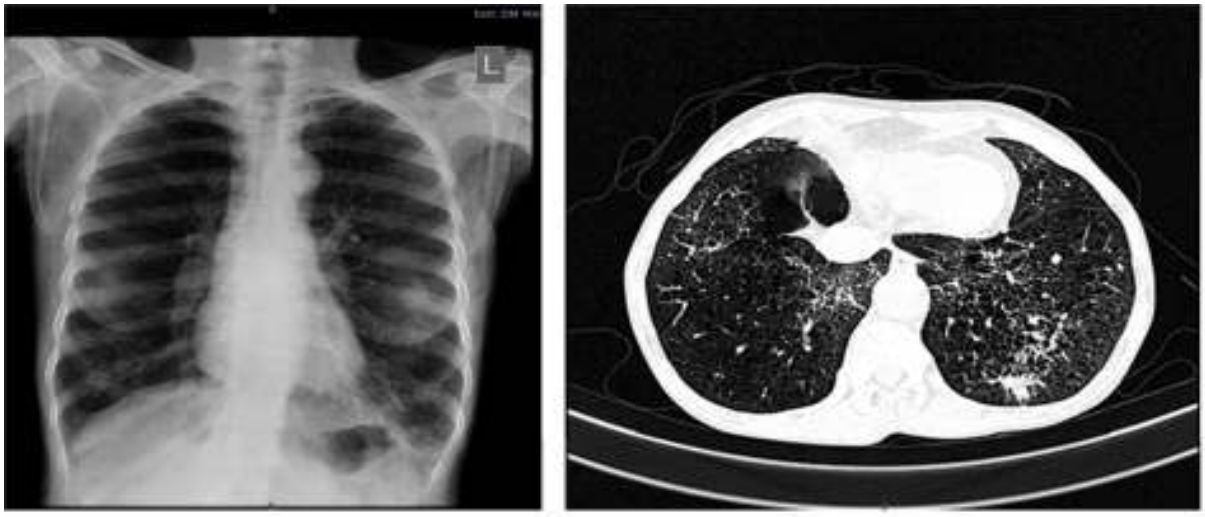

Fig-2:X-Ray Chest and HRCT Thorax of a 53-year-old non smoking female. X-Ray shows hyperinflation along with diffuse reticular shadows as a marker of bronchiolar wall thickening. HRCT sections from lower lobe showing reticular shadows, few nodular shadows and air trapping. Tree in bud lesions are also seen.

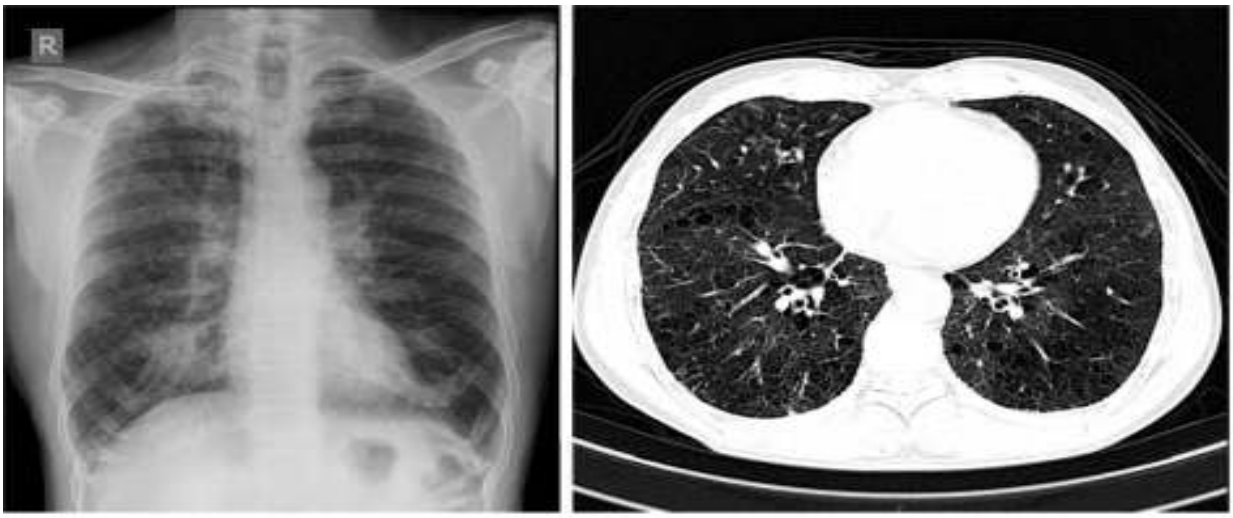

Fig-3:X Ray Chest and HRCT Thorax of a 51-year-old male smoker who was treated as COPD for the last 10 years. He worked in coffee pounding mill for 20 years and stopped that work when he started developing symptoms. X-Ray shows hyperinflation, reticular shadows throughout with coalescence in the right lower zone. HRCT section from the lower lobes shows extensive reticulation, architectural destruction and cyst formation.

rettes, favoring the development of this condition among those who use e-cigarettes. Further, it is proved that this chemical is a natural byproduct in coffee-roasting and coffee-grinding processes[4,5]. Hence, unacceptable levels of diacetyl in these units may cause popcorn lung. In their report, the Centers for Disease Control and Prevention (CDC) confirmed that occupational exposure to diacetyl and a related compound, 2,3-pentanedione, can cause bronchiolitis obliterans and loss of lung function. The CDC also reported that these potentially harmful chemicals were found at higher-than-expected levels at some coffee-processing facilities[6].

Wayanad district in Kerala is predominantly a tea and coffee growing farmland at a moderate high altitude. Hence there are lot of small and large scale coffee processing units. It is highly possible that workers in these processing units (Roasting or grinding) may be exposed to diacetyl leading to development of bronchiolitis obliterans. These patients due to their nonspecific symptoms and poor awareness of this entity are treated as COPD[7].

Bronchiolitis obliterans often is associated with symptoms of cough and shortness of breath, similar to that seen in patients with COPD and asthma. This pathology is irreversible and progressive, and there is no definite treatment. Diagnosis is often delayed due to nonspecific clinical features and is initially treated as asthma or COPD. Lung tissue biopsy is necessary to confirm the diagnosis of bronchiolitis obliterans. Radiological feature may help in differentiating from COPD and asthma, as these patients will show subtle features of bronchiolar wall thickening and fibrosis. Chest radiographic can be normal or non-specific in early stages. Later it may show features like hyperinflation, attenuation of vascular markings or reticular/ reticulonodular markings. These fine reticulations represent bronchiolar wall inflammation. On HRCT chest, there are often sharply defined, areas of decreased lung attenuation associated with vessels of reduced caliber. These changes represent a combination of air trapping and oligemia (mosaic attenuation pattern). Other features include centrilobular micronodules (often seen as tree-in-bud opacities), bronchiolectasis, bronchial wall thickening and ground glass opacities. In later stage of disease dense network of reticulation with thin walled cysts due lung destruction are seen. These finding are seen also in lung disease secondary to Marijuana exposure.

Conclusion

6 cases of bronchiolitis obliterans are detected in this study from a pool of patients treated as COPD. This may be an iceberg phenomenon and more similar cases may be there in the community. The clinical significance is that workers exposed to diacetyl, which is a natural byproduct in coffee processing, develop this disease, and a clinical suspicion among coffee plant workers presenting with symptoms of obstructive airway disease will help in early diagnosis. Wayanad district of Kerala state is a moderately high-altitude farmland with coffee plantations and coffee-processing units. An epidemiological research to detect the level of these chemicals in coffee-processing units and to assess its health hazard among workers may help establish a causative relationship.

Limitation of this study:

The causal relationship is only postulated. Lung biopsy in suspected cases and an environmental assessment to detect the presence of diacetyl are ideal for establishing a definite relationship with coffee processing work.

Conflicts of interest: Nil to declare. This is not a funded study

References

1. Chambers DC. Bronchiolitis obliterans syndrome ' endotypes' in haematopoietic stem cell transplanta tion. Respirology. 2019 May;24(5):408-409. [PubMed]
2. Akpinar-Elci M, Travis WD, Lynch DA, Kreiss K. Bronchiolitis Obliterans syndrome in popcorn pro duction plant workers. EurRespir J 2004;24:298-302.
3. Schlecht PC, O'Connor PF. NIOSH Manual of Analytical Methods. 4th ed., 3rd Suppl. Cincinnati: Department of Health and Human Services , Public Health Service, C enters for Disease Con trol and Prevention, National Institute for Occupational Safety and Health (US); 2003
4. Duling MG, LeBouf RF, Cox-Ganser JM, Kreiss K, Martin SB Jr., Bailey RL. Environmental characteriza tion of a coffee processing workplace with obliterative bronchiolitis in former workers. J Occup Environ Hyg2016;13:770-81.
5. Akiyama M, Murakami K, Ohtani N, Iwatsuki K, Sotoyama K, Wada A, *et al.* Analysis of volatile compounds released during the grinding of roastedcoffee beans using solid phase micro-ex traction. J Agric Food Chem 2003;51:1961-69.
6. LeBouf RF, Martin B Jr., Mugford C, Stanton ML, Bailey RL. Evaluation of Exposures and Respira tory Health at a Coffee Roasting and Packaging Facility.Report No. 2015-0082-3287. U.S. Depart ment of Health and Human Services, Centers for Disease Control and Prevention, National Insti tute for Occupational Safety and Health; 2017.
7. Ravindran Chetambath**.** Popcorn lung – Report of a rare case and its significance in a coffee-grow ing district of Kerala. Lung India 2019; 36(4):367-68.

Original article

Prevalence of cardiovascular co morbidities among chronic obstructive pulmonary disease patients

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Abstract

Background

Chronic obstructive pulmonary disease (COPD) represents a complex respiratory disorder characterized by chronic airflow limitation and increased inflammatory response of airways. Co-morbidities in COPD have well known negative impact on patients' prognosis and health status**.** Cardiovascular disease (CVD) is the major contributor to morbidity and mortality in COPD patients. Studying the association between COPD and cardiovascular disease is deemed important because coexistence of cardiovascular disease and COPD may have implications for the management of these patients. Early detection of cardiovascular comorbidities in COPD patients and its management is crucial in preventing further cardiac events. Data regarding the prevalence of CVD are less in Indian literature.

Objectives: Primary objective: To find out the period prevalence of cardiovascular comorbidities among COPD patients

Secondary objective: To identify the pattern of distribution of individual cardiovascular comorbidities

Methodology: A cross sectional study was conducted among COPD patients in the Department of Pulmonary medicine, Government Medical College, Thiruvanathapuram.

Results: 30.9% of the COPD patients in this study had cardiovascular co-morbidities. Majority had Pulmonary Hypertension (18.2%), followed by ischemic heart disease (11.8%), heart failure (6.4%)and arrhythmia (4.5%.).

Conclusions: The period prevalence of cardiovascular co morbidities among COPD patients was 30.9%. Pulmonary hypertension was the most common comorbidity followed by ischemic heart disease, heart failure and arrhythmia.

Key words: COPD, cardiovascular co-morbidities,prevalence.

Introduction:

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious par-

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ticles or gases[1]. COPD is currently the fourth leading cause of death in the world [2],but is projected to be the 3rd leading cause of death by 2020[3]. COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis of COPD in such patients, the presence of a post-bronchodilator FEV1/FVC < 0.70 confirms the presence of persistent airflow limitation. Assessment of the presence or absence of airflow obstruction based on a single measurement of the post-bronchodilator FEV1/FVC ratio should be confirmed by repeat spirometry on a separate occasion if the value is between 0.6 and 0.8, according to the GOLD guidelines 2018[1,3]. Exacerbations of COPD are important events in the management of COPD because they negatively impact health status, rates of hospitalization readmission, and disease progression[4]. Co-morbidities often exists in COPD patients which have a direct impact on the clinical course of the disease and they are associated with an increased risk of hospitalization and death, as well as with an increased cost of care in COPD , but despite this, they are often under-diagnosed and undertreated[5]. Cardiovascular disease is the major contributor to morbidity and mortality in patients with COPD[6]**.** The prevalence was found to vary from 28 to 70% from a previous study[7].

Studying the association between COPD and cardiovascular disease is deemed important because coexistence of cardiovascular disease and COPD may have implications for the management of these patients. Early detection of cardiovascular co-morbidities in COPD patients and its management is crucial in preventing further cardiac events. Local data regarding the prevalence of cardiovascular diseases in COPD patients are limited.

This study was to find out the period prevalence of cardiovascular co-morbidities in COPD patients, and to find out the pattern of distribution of cardiovascular co-morbidities such as coronary artery disease, pulmonary artery hypertension, heart failure and arrhythmias.

Aim and Objectives of the study

Primary objective

To find out the period prevalence of cardiovascular co-morbidities among COPD patients.

Secondary objective

To identify the pattern of distribution of cardiovascular co- morbidities among COPD patients.

Materials and methods

Study design - Cross sectional study

Study period - Nov 2015 –July 2017

Study setting - Department of Pulmonary Medicine, Government Medical College, Thiruvanathapuram.

Study population- All patients who are diagnosed to have COPD as per GOLD 2015 criteria attending the d epartment of Pulmonary medicine, Government Medical College, Thiruvananthapuram

Inclusion criteria

1. Patients who are diagnosed to have COPD as per GOLD 2015 Guidelines

Exclusion criteria

1. Patients who have other chronic lung disease other than COPD.

2. Patients not willing to give consent.

3. Patients with congenital heart diseases

Data collection

After taking informed consent detailed history taken, physical examination, investigations were done.

They underwent spirometric evaluation and diagnosis of COPD was established as per GOLD 2015 guidelines.

Those patients who satisfy inclusion criteria undergo complete hemogram, routine bio chemical investigations, ECG, Chest X -ray PA view. Cardiology consultation and 2D ECHO and opinion were taken from expert cardiologist. From the above data, study subjects having any of the following 4 cardiovascular comorbidities were analysed.

1. Heart failure

2. Arrhythmias

3. Ischemic heart diseases

4. Pulmonary hypertension

As diagnosed by an expert cardiologist are identified.

Statistical analysis

The data was entered into Microsoft Excel and analysed using trial version of SPSS software. Quantitative variables were expressed as mean and standard deviation. All categorical variables were expressed in proportions. The outcome variable cardiovascular co-morbidity was expressed as proportion (Prevalence) with 95% Confidence interval. The statistical test Chi-square was done for testing the association between categorical variables and cardiovascular comorbidities among COPD patients. If any of the cells in contingency table had expected values less than 5, Fishers exact test was used, instead of Chi square test. The strength of association was expressed using odds ratio. Mann Whitney U test was done to test the association between quantitative variables and cardiovascular co-morbidities. All tests were interpreted as a significance level of 95%. Binary logistic regression was used to find out the independent predictors of the outcome. The adjusted odds ratio with its confidence interval obtained from the final regression model was taken as strength of association for final interpretation.

Results

Of the total 110 subjects, males 96 (87.3%), females14 (12.7%.) .The mean age was 64.75± 7.62.

Out of the total, 34 had any of the cardiovascular diseases. The proportion of COPD patients having cardiovascular co morbidities [total] was 30.9%.

Out of 110 COPD patients, 20 had pulmonary hypertension (18.2%), 13 had ischemic heart disease (11.8%), 7 had heart failure (6.4%) and 5 had arrhythmia (4.5%.) (21.8%) patients are in group A,18(16.4%) in group B,12(10.8%) group C and 56(50.9%) are in group D as per the COPD GOLD guidelines (Table1).Group C and group D patients were at high risk of having cardiovascular comorbidities.

Table 1: Distribution according to ABCD grouping of COPD.

Group	Frequency	Percentage
A	24	21.8
B	18	16.4
C	12	10.9
D	56	50.9
Total	110	100.0

After multivariate analysis of the factors that are independently associated with increased risk of CVDs are female gender,[OR (95% CI): 7.30(1.73-30.87)],occupational exposure, [OR(95% CI) :5.18(1.65-16.25)] ,Group C & D patients [OR(95%CI) :4.74(1.006-22.33)],low FEV1 value [OR(95% CI) :4.78(1.005-22.75)](Table2).

Lung Health Study, the 5-year mortality in 5,887 patients aged 35 to 46 years with COPD and mild to moderate airways obstruction was 2.5%, of which 25% died of a cardiovascular events[8]. The TORCH study, a randomized, double-blind, placebo controlled trial including 6184 COPD patients and a three year follow-up time described that 27% of all deaths in COPD patients were related to cardiovascular causes[9]. In our study 30.9% of COPD patients had cardiovascular co-morbidities. Mean age of the study population was 65±7.62.Majority are elderly above 60 yrs of age. But considering the risk of cardiovascular comorbidities there is no statistical significance when compared to the younger age group. These results are in consistent with the study done by Laura Miranda et al, in which he studied therisk factors associated with cardiovascular comorbidities in COPD patients[10].

Table 2: Determinants of cardivascular co-morbidities among COPD patients.

Variable	Adjusted Odds ratio	95%confidence interval	p value
Female gender	7.30	1.73 – 30.87	0.007
Occupational expossure	5.18	1.65 – 16.25	0.005
Group C and D patients	4.74	1.006 – 22.33	0.049
FEV1value ≤ 1L	4.78	1.005 – 22.75	0.049

Discussion

Cardiovascular disease is a leading cause of death in patients with COPD. In the

Michela Bellocchia et al in his study on Predictors of cardiovascular disease in asthma and chronic obstructive pulmonary disease con-

cluded that older age is a significant predictor of cardiovascular co morbidity among COPD [11]. In our study 87.3% were males, and 12.7%were females and female gender was found to be significantly associated with cardiovascular comorbidities and the majority of them had ischemic heart disease. In a retrospective matched cohort study from the Northern California Kaiser Permanent Medical Care Program involving 40,966 patients with COPD diagnosed between 1996 and 1999, the risk for hospitalization and cardiovascular disease was higher in patients with COPD and female patients had higher risk than older male participants [12].

Smoking is a major risk factor for both COPD and cardiovascular disease. In our study majority of males are smokers. There was no statistically difference between cardiovascular comorbidities and smoking status. 53.1% of the subjects who were having firewood exposure especially in females had cardiovascular co-morbidities. Mean BMI of the study population was 20±3.0.A study done by Jennifer L,Black-Shinn et al ,they found that higher BMI is a risk factor for cardiovascular comorbidities and the mean value of BMI was 28.97[13].Theysuggested that there is a high risk of cardiovascular disease in those with higher BMI. In our study BMI is not statistically significant in relation to the cardiovascular risk. Occupational history taken in detail and those subjects who had work related exposure to the particle that predisposes to COPD were found to have at higher risk for developing cardiovascular diseases (Odd ratio 5.18,[1,65-16.25]). Present study, those who are in exacerbation had more cardiovascular comorbidities. 43.9% who are in exacerbation had cardiovascular comorbidity with a significant p value 0.002 on bivariate analysis. But on further statistical analysis, after multivariate analysis, it is not found to be significant thus those with exacerbation may be acting as a confounding factor.

Twenty four (21.8%) patients are in group A,18(16.4%) in group B,12(10.8%) group C and 56(50.9%) are in group D as per the COPD GOLD guidelines(Table1).Group C and group D patients were at high risk of having cardiovascular comorbidities with an odds ratio 4.74 (1.006- 22.23). Majority of the patients with cardiovascular co-morbidity had FEV1 less than 1L. Low FEV1 is associated with high cardiovascular co-morbidity in majority of the studies[14]. The primary aim of this study was to find out the proportion of cardiovascular co-morbidities among COPD patients. Out of 110 COPD patients, 34 had atleast one of the cardiovascular comorbidities, accounting for 30.9%. Thus the proportion of COPD patients having unspecified cardiovascular co-morbidities at COPD is 30.9%. The results are comparable with the various other studies published[15,16,17]. Only few Indian studies are available in this aspect[18,19,20]. In this study, out of 110 patients 20 had pulmonary hypertension either alone or along with other comorbidities, which contribute to 18.2%. 13(11.8%) had coronary artery disease, of these7 patients had heart failure, Contributing 6.4%.and 5(4.5%) patients had arrhythmia(Fig 1).Three of them had atrial fibrillation and two had premature ventricular contractions. 5 of them had more than 1 cardiovascular co-morbidities. The most common cardiovascular comorbidity associated with COPD was pulmonary hypertension, which was the

commonest one found in various studies. Out of total 110 patients, 45 (40.9%) had hypertension and according to GOLD guidelines hypertension was mentioned as most frequently observed co-morbidities among COPD patients.

Statistical analysis showed that the factors that found to be associated with cardiovascular co-morbidities among COPD in our study were female gender, those with occupational exposure to the factors predisposing to COPD, low FEV1,Group C& D patients.

Conclusion:

The proportion of cardiovascular co morbidities among COPD patients was 30.9%. Pulmonary hypertension was the most commoncomorbidity(18.2%),followed by ischemic heart disease[11.8%],heart failure [6.4%], Arrhythmia(4.5%.). Results were comparable with most of the studies available in English literature.

References

1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017.http://www.goldcopd.org

2. Adeloye D, Chua S, Lee C, et al. Global and regional estimates of COPD prevalence: System atic review and meta-analysis. Journal of global health 2015; **5**(2): 020415.

3. Aaron SD, Tan WC, Bourbeau J, et al. Diagnostic Insta bility and Reversals of Chronic Obstruc tive Pulmonary Disease Diagnosis in Individu als with Mild to Moderate Airflow Obstruction. Am J RespirCrit Care Med 2017; 196(3): 306-14.

4. Burge S,Wedzicha JA.COPD Exacerbations ERJ:2003.21,46s-53s.

5. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. EurRespir J 2009; 33(5):1165-85.

6. Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. The Lancet Respiratory medicine 2015; 3(8): 631-9.

7. MüllerovaH ,Agusti A, Erqou S , Mapel DW . Systemic literature review on Cardiovascular Comorbidity in COPD, Chest. 2013; 144(4):1163–1178

8. AnthonisenNR ,Connett JE , Enright PL , Manfreda J ;Lung Health Study ResearchGroup . Hospitalizations and mortality in the Lung Health Study .Am J RespirCrit Care Med . 2002 ; 166 (3): 333 – 339

9. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775-89.

10. Laura Miranda de Oliveira Caram[1] Renata Ferrari[1] Cristiane Roberta Naves. Risk factors for cardiovascular disease in patients with COPD: mild-to-moderate COPD versus severe-to-very severe COPD.J. bras.pneumol. vol.42 no.3 São Paulo May/June 2016.

11. MichelaBellocchia, Monica Masoero, Antonio Ciuffreda, Silvia Croce, Arianna Vaudano, Roberto Torchio,MonicaBoita, and Caterina Bucca1Predictors of cardiovascular disease in asthma and chronic obstructive pulmonary disease. MultidiscipRespir Med. 2013; 8(1): 58.

12. Sidney S, Sorel M, Quesenberry CP Jr, DeLuise C, Lanes S, Eisner MD.COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program.Chest. 2005 Oct;128(4):2068-75.

13. Pilar de Lucas-Ramos,Jose Luis Izquierdo-Alonso, Jose Miguel Rodriguez-Gonzalez Moro,Jesus Fernandez Frances,et al, Chronic obstructive pulmonary disease as a cardiovas cular risk factor. Results of a case–control study (CONSISTE study).Int J Chron Obstruct Pulmon Dis. 2012; 7: 679–686.

14. Miller J, Edwards LD, Agustí A, Bakke P, Calverley PM, et al. Evaluation of COPD Longi tudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort.Respir. Med.2013; 107:1376-1384.

15. Mannino DM ,Higuchi K , Yu TC, Zhou H , Li Y,Tian H , Economic Burden of COPD in the Presence of Comorbidities. Chest.2015; 148(1): 138 – 150

16. Müllerova H , Agusti A , Erqou S , Mapel DW ,Systemic literature review on Cardiovascular Comorbidity in COPD, Chest.2013; 144(4):1163–1178.

17. Finkelstein J , Cha E , Scharf SM . Chronic obstructive pulmonary disease as an indepen dent risk factor for cardiovascular morbidity.Int J Chron Obstruct PulmonDis .2009 ; 4 :337 – 349

18. Kaushal M, Shah PS, Shah AD, Francis SAetal.Chronic obstructive pulmonary disease and cardiac comorbidities.A cross-sectional study.Lung India. 2016 Jul-Aug; 33(4):404-9.

19. Vineeth Alexander, R. Pajanivel, K. Surendra Menon, ArunPrasath.Prevalence of cardiac comorbidities and its relation to severity staging of chronic obstructive pulmonary disease.Int J Cur Res Rev.September 2015: 7 .17 .

20. Amit co-morbidities associated with patients with chronic obstructive pulmonary diseases.The Egyptian Journal of Broncology.2019, 13: 5, 591-595.

A 66 year old man with left sided chest pain.

Asmita A. Mehta[1], Wesley M Jose[2], Pavithran K[3]

Case

66-year-old man presented to the Respiratory Medicine out patient department for evaluation of low back ache and left sided chest pain of 5 months duration. He had an episode of mild blood tinged sputum last 2 months ago. He also gave history of fever, exertional dyspnea grade II, loss of weight and loss of appetite. He had been treated for sputum positive pulmonary TB and right sided empyema which was treated with intercostal drainage in 2002.

On examination, he was conscious and oriented. There was no pallor, icterus, clubbing, pedal edema or lymphadenitis. He was afebrile with 98% oxygen saturation on room air. His vitals were stable. His respiratory system as well as other system examination were normal.

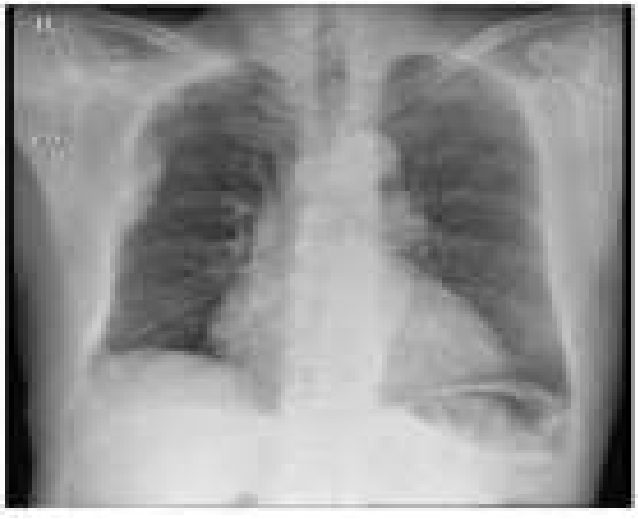

Fig: 1

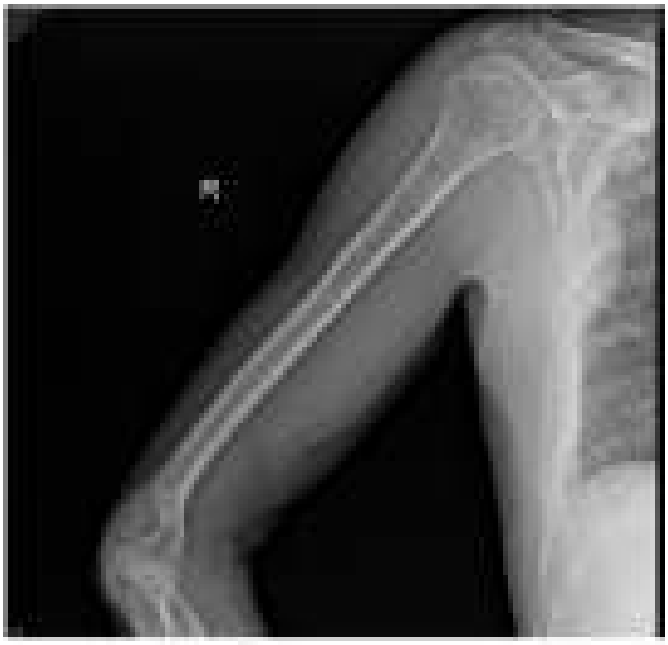

Fig: 2

Further investigated with special x rays

1.What is your diagnosis?

2.What are the classical signs seen on radiographs?

3.What will be your further line of management ?

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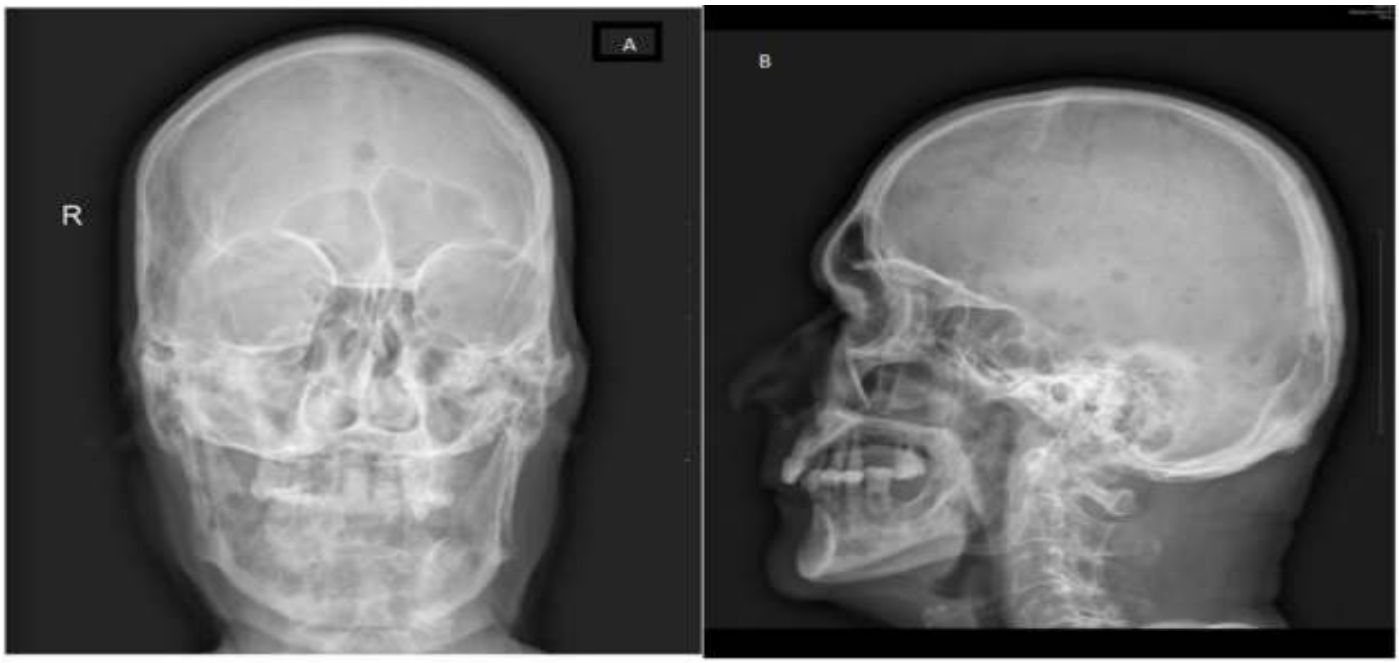

Figure 3A & B

Answer 1:

Most likely diagnosis: Multiple myeloma

Answer 2:

Figure : 1 Lytic lesions seen on right side 4th rib along with right humerous showing lytic lesions

Figure : 2 Multiple lytic lesion on right humerous

Figure: 3 A and B Punched out lytic lesions in skull

Answer: 3 : Further evaluation and management of patient. He was admitted under Respiratory Medicine with above mentioned history and complaints. His laboratory investigations were as following : Hb 9.8gm/dl, Platelets 280x 10^3/ml, total white cell counts 7900/ml with 24% eosionophils.

Peripheral smear showed normocytic normochromic anemia with eosinophilia. There was significant roleaux formation.

Liver function test showed total protein of 8.8 gm/dL with albumin of 3.9 and globulin of 4.95. Renal function test showed blood urea of 80.4 mg/dl and creatinine of 4.2 mg/dl.

Special investigations:

Immunoglobulin (Ig) levels were as following: IgA 1556 mg/dl, IgG 790 mg/dl, IgM 45 mg/dl.

Freelite (Free light) chains were sent which showed kappa 4485 mg/L and lambda of 16. 3 mg/L.

Bone marrow aspiration and biopsy done for further evaluation.

Aspiration showed hypercellular marrow with 95% plasma cells - suggestive of plasma cell myeloma. Bone marrow biopsy report showed hypercellular marrow showing diffuse sheets of plasma cells - Suggestive of plasma cell my-

eloma. Serum protein electrophoresis showed two M bands - one towards the anodal end of the gamma region and another faint band towards the cathodal end of the gamma region- M protein: 2.2g/dl (anodal end) -0.1g/dl (cathodal end).

Final diagnosis: He was diagnosed as case of IgA Kappa Myeloma.

Follow up and treatment:

After discussion he was planned on weekly chemotherapy with cyclophosphamide, bortezomib and dexamethasone. He improved symptomatically and was discharged in stable condition with an advice to followup for further chemotherapy on outpatient basis.

Learning pearls:

1.The present case highlights the importance of clinico radiological correlation in all the patients seen in routine outpatient practice. The history may be misleading as it was in the present case. The patient gave history of left sided chest pain and had lesions on the right side of chest. He also had history of right sided empyema and intercostal drainage was inserted on the right side previously. That history also could have misled the clinician to think the correlation between the two as there were no previous chest radiographs available for comparison. But if we look closely, even the chest radiograph showed multiple lytic lesions, which should not be missed Don't forget to look at extrathoracic sites also when looking at chest radiograph.

2.The patient was recently diagnosed to have acute kidney disease with out any history of Diabetes Mellitus or hypertension. There was associated elevated ESR, eosinophila and anemia. Liver function test showed A:G reversal. Peripheral smear showed roleaux formation. All these findings in association with sudden onset of kidney disease, with lytic lesions on the x ray should prompt clinician to suspect multiple myeloma.

3.The work up for multiple myeloma includes bone marrow aspiration and trephine biopsy, serum protein electrophoresis / immune electrophoresis, skeletal survey (with x-rays or MRI or PET scan), quantitative immunoglobulin and freelite assessment, FISH analysis for deleterious mutations, Albumin and beta 2 microglobilin for staging purpose. [1]

A diagnosis of multiple myeloma can be made if there is evidence of clonal bone marrow plasma cells ≥10% or biopsy proven bony or extramedullary plasmacytoma and any one or more of the following myeloma defining events:

Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

- Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance 177 micro mol/L (>2 mg/dL)
- Anaemia: haemoglobin value of >20 g/L below the lower limit of normal.
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT

Any one or more of the following biomarkers of malignancy:

- Clonal bone marrow plasma cell percentage ≥60%
- Involved : uninvolved serum free light chain ratio ≥100
- >1 focal lesions on MRI studies[1]

References

1. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538–e548. doi:10.1016/S1470-2045(14)70442-5

ECG Quiz

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Case: 25 year old female having a diagnosis of cyanotic congenital heart disease presented with acute lower respiratory tract infection. On examination she had central cyanosis, clubbing, kyphoscoliosis, dextrocardia, situs inversus, pulmonary stenosis, ventricular septal defect, double outlet right ventricle, right ventricular hypertrophy and transposition of great arteries.

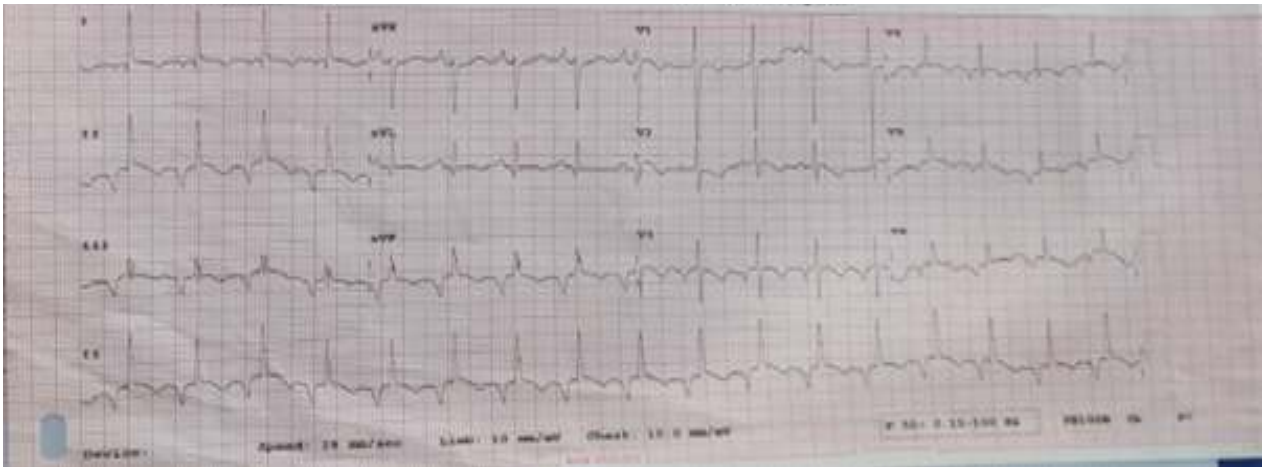

Fig-1: ECG of a 25 year old female having dextrocardia, situs inversus and congenital cyanotic heart disease.

ECG showed tachycardia (ventricular rate 100 beats/minute), inverted p wave in all leads except aVR, V1 and V2, normal PR interval, narrow QRS complex and T wave inversion in all leads. These ECG findings are in favour of accelerated junctional rhythm.

Answer: Accelerated junctional rhythm

Discussion:

Accelerated junctional rhythm (AJR) occurs when the rate of an AV junctional pacemaker exceeds that of the sinus node. This situation arises when there is increased automaticity in the AV node coupled with decreased automaticity in the sinus node. Causes of AJR are digoxin toxicity, use of beta-agonists, e.g. isoprenaline, adrenaline, Sick sinus syndrome, myocardial ischaemia, myocarditis (acute rheumatic fever, lyme disease, Diphtheria) and metabolic states with increased adrenergic tone. Certain drugs which can cause bradycardia such as beta blockers, calcium channel blockers and antiarrhythmic agents can also induce AJR.

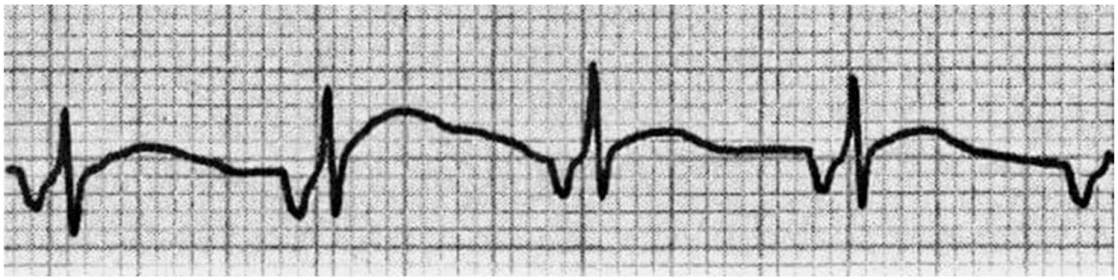

Fig-2: Example of an accelerated junctional rhythm (courtesy ECG library).

ECG features of AJR

- Narrow complex rhythm; QRS duration < 120ms (unless pre-existing bundle branch block or rate-related aberrant conduction).
- Ventricular rate usually 60 – 100 bpm.
- Retrograde P waves may be present and can appear before, during or after the QRS complex.
- Retrograde P waves are usually inverted in the inferior leads (II, III, aVF), upright in aVR + V1.
- AV dissociation may be present with the ventricular rate usually greater than the atrial rate.
- There may be associated ECG features of digoxin effect or digoxin toxicity.

Periods of junctional rhythm are not necessarily associated with an increase in mortality. If an obvious cause is present, such as complete heart block or sick sinus syndrome, then the morbidity or mortality is directly related to that and not to the junctional rhythm mechanism, which is serving as a "backup rhythm" during the periods of bradycardia. Accelerated junctional rhythms may be a sign of digitalis toxicity.

ECG features may be mistaken for that of dextrocardia as this patient is having dextrocardia and situs inversus. In dextrocardia inverted P wave is seen only in Lead-1 and upright P in aVR. Other features are right axis deviation, positive QRS complexes (with upright P and T waves) in aVR, inversion of all complexes (global negativity) in Lead I and absent R-wave progression in the chest leads.

Complications

Complications of junctional rhythm are usually limited to symptoms such as dizziness, dyspnea, or presyncope. Exacerbation of cardiac comorbidities, such as congestive heart failure and rate-related cardiac ischemia, may occur.

Resistant Pneumocystis jiroveci pneumonia in post transplant patients

Bushna Bavumon [1], K P Suraj[2], Sreelatha M[3], Anand M [4], Paulo Varghese Akkara[5]

Abstract:
Pneumocystis jiroveci pneumonia (PJP) is a common opportunistic infection encountered in kidney transplant recipients. We report two cases of post renal transplant patients, who were on triple immune suppressants and PJP prophylaxis and presented with short history of fever, cough and dyspnoea on exertion. They were tachypnoic and not maintaining saturation in room air and had bilateral basal fine end inspiratory crepitations. Chest X Ray and HRCT thorax were suggestive of PJP. We proceeded with bronchoscopy and TBLB which confirmed diagnosis of PJP. They were started on trimethoprim/ sulfamethoxazole and oral steroids. Even after 7 days of intensive therapy they did not respond and was switched over to second line drugs –clindamycin and primaquine. One among the two responded well to the treatment but the other one worsened and expired. Here, we highlight the importance of suspecting PJP resistance to trimethoprim/sulfamethoxazole combination in patients not responding to first line therapy in a week time and early switching over to second line drugs.

Keywords: Post renal transplant, Pneumocystis jirovecii, trimethoprim/sulfamethoxazole, drug resistance.

Introduction:

Post renal transplant patients are at risk of developing opportunistic infections. The risk is maximum during the initial 6 months of post transplantation period. Pneumocystis jirovecii is an important opportunistic pathogen known to cause life threatening infection in kidney transplant recipients.[1] The most typical time of onset of symptoms of PJP is 6–8 weeks following initiation of immunosuppressive therapy. The unicellular fungus is ubiquitous in the environment but has an untreated mortality of 90–100% in immunocompromised HIV-negative patients[2] and falls to 35% with treatment[3]. The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the monitoring, management, and treatment of kidney transplant recipients recommend 3-6 months of PJP prophylaxis post-renal transplantation and additional prophylaxis for 6 weeks following the treatment of acute rejection[4].The attack rate of PJP in renal transplant patient is 0.6–14 % in patients not on prophylaxis and 0.4–2.2 % on patients with prophylaxis[5]. The standard regimen of treatment for PCP is combination of sulfamethoxazole (SMX) and

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trimethoprim (TMP)[3]. However, a few studies have reported therapeutic failure of the first line treatment. Here, we report 2 cases of PJP in post renal transplant patients which did not respond to first line treatment.

Case 1:

29 year old male, after 6 months of renal transplantation, who was on triple immunosuppressants (mycophenolate mofetil, tacrolimus and oral corticosteroids) and PJP prophylaxis presented with fever, cough with scanty expectoration and dyspnoea on exertion of 2 weeks duration. On examination, he was febrile, had pallor, was tachypnoeic (RR:36/') with heart rate of 106/' and saturation was only 88% in room air. Examination of respiratory system revealed bilateral fine end inspiratory crackles in the basal areas. Other systems were clinically normal.

Lab investigation revealed haemoglobin 8.6 gm/dl, total count of 6000 cells/µl with deranged renal status (urea :120 mg/dl and creatinine of 5.2 mg/dl).Arterial blood gas analysis showed pH: 7.44, pCO2 : 26.9 mm Hg, pO2:46 mm Hg and HCO3:17.9 and A-a gradient 62 mmHg.Chest x-ray showed bilateral perihilar fluffy opacities almost sparing upper zone (fig:1). All his cultures were sterile and sputum AFB and Genexpert were negative. Serum lactate dehydrogenase (LDH) was 350 and Cytomegalo Virus PCR was <85.14 IU/ml. HRCT thorax showed diffuse geographic ground glass opacities and interlobular septal thickening resulting in crazy pavement appearance suggestive of PJP (fig:2).

In view of clinical and radiological findings of PJP, he was started on parenteral cotrimoxazole and oral prednisolone dose was hiked to 40mg BD. He underwent bronchoscopy and TBLB was taken from left lower lobe and Gomori's methenamine silver (GMS) staining was suggestive of PJP. (fig:3).Even after 7 days of therapy, patient was deteriorating and was started initially on non invasive ventillatory (NIV) support.

Suspecting PJP resistant to cotrimoxazole therapy, he was started on second line treatment with clindamycine and primaquine. After changing treatment, there was improvement in saturation and reduction in respiratory rate. He was weaned off from NIV and oxygen support and repeat chest x-ray after 3 weeks showed radiological clearance.(fig:4)

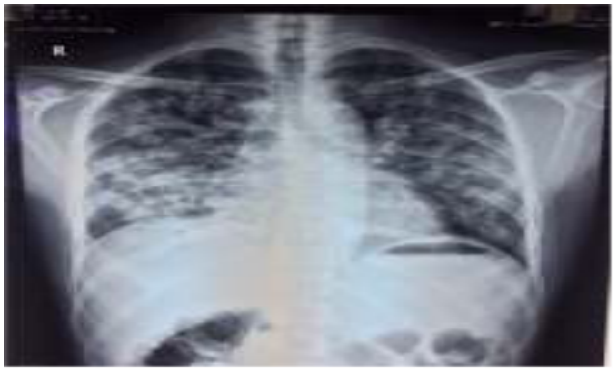

Fig 1

Case 2:

35 year old male who underwent renal transplantation 3 months ago and was on on triple immune suppression (mycophenolate mofetil, tacrolimus, oral corticosteroids) and PJP prophylaxis presented with fever, cough and dyspnoea on exertion of 1 week duration. He was tachypnoeic and resting saturation was only 82% in room air. There was bilateral basal fine end inspiratory crepitations .Other systems were within normal limits.

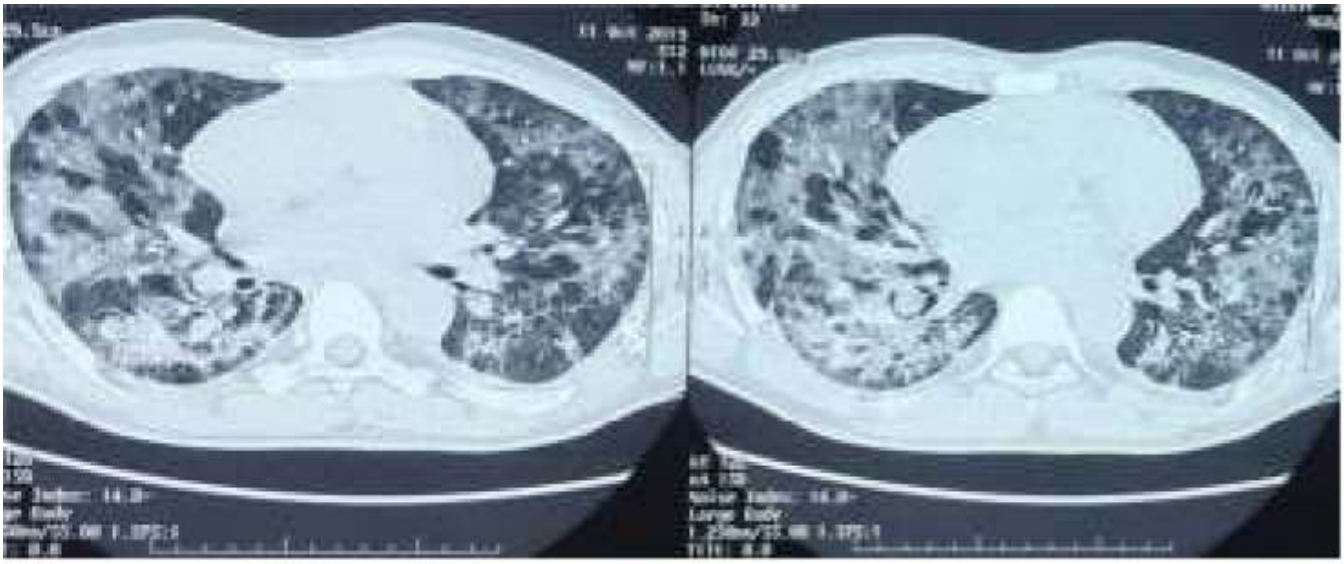

Fig:2 HRCT thorax showing geographic ground glass opacities with interstitial thickening (crazy pavement appearance)

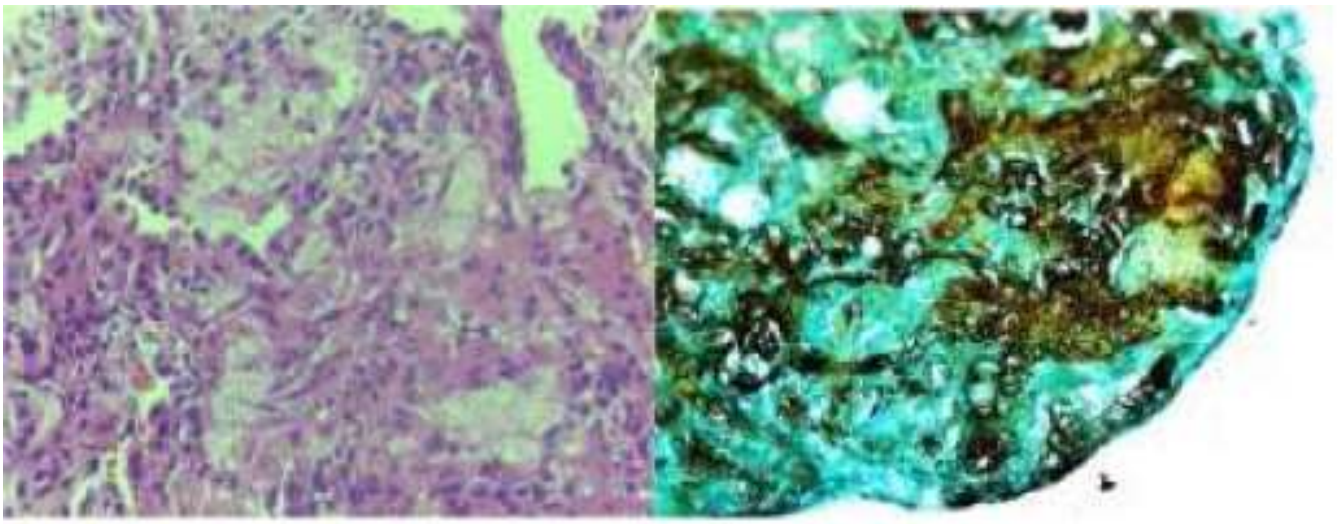

Fig: 3 Photomicrography of *Pneumocystis jirovecii* pneumonia (A) Hematoxylin and eosin staining shows foamy macrophages accompanied by mild interstitial inflammation (B) Gomori's methenamine silver (GMS) stain visualized many cystic and trophic form organisms in alveolar exudate, consistent with *Pneumocystis jirovecii* infection .

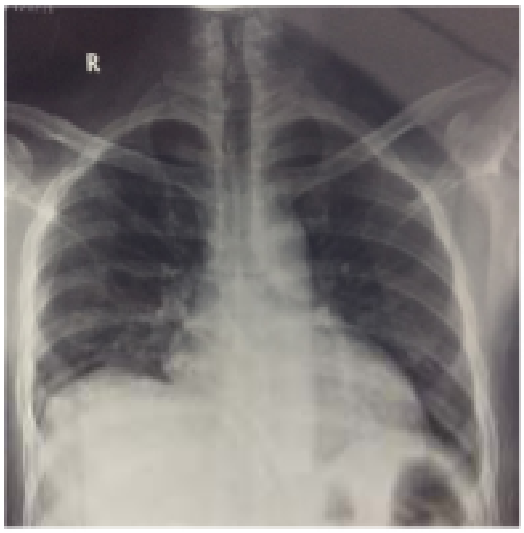

Fig 4: Repeat Chest x-ray after 3 weeks showing radiological clearance

Lab investigations showed normal blood count, renal and liver parameters. ABG showed pH: 7.42, pCO2 :32.4mm Hg, pO2:36 mm Hg and HCO3:21 and A-a gradient 80 mmHg. Chest x-ray revealed bilateral lower zone reticular shadows.

Microbiological investigations were normal. HRCT thorax showed bilateral interstitial thickening and ground glassing with few areas of consolidation (fig:5). Bronchoscopy was done, BAL and TBLB was taken from lingua. BAL cultures were sterile and gene expert was negative. TBLB GMS staining was positive for PJP. He was also not responding to intra venous cotrimoxazole and oral prednisolone.His condition was deteriorating. He was initially given NIV support and later intubated and ventilated.Considering PJP resistant to cotrimoxazole,he was started on second line therapy with clindamycin and primaquine, but he did not improve and expired.

Discussion :

Pneumocystis jiroveci is an opportunistic fungal pathogen, which causes life threatening pneumonia in immunocompromised patients including congenital immunodeficiency, organ transplantation and acquired immune deficiency syndrome. The estimated mortality is 6.6% in HIV patients and 39% in non-HIV patients[6]. Typically, PJP develops 6-8 weeks following initiation of immunosuppressive therapy. The use of trimethoprim–sulfamethoxazole prophylaxis resulted in a RR of 0.08 (95% CI 0.023–0.036) of developing PJP compared to either a placebo, control or no intervention[7].

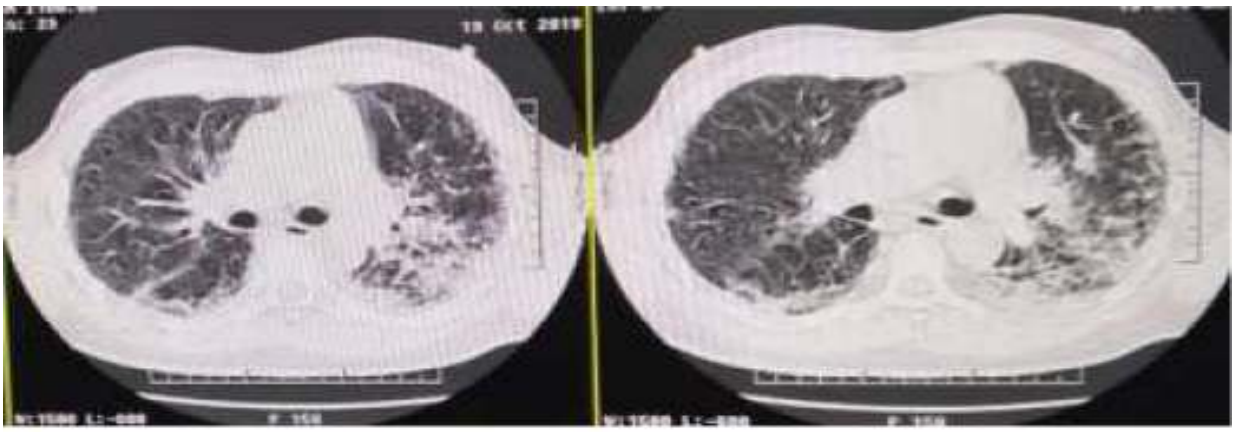

Fig 5 : HRCT thorax showing ground glassing with interstitial thickening

Pneumocystis jirovecii pneumonia (PJP) in non-HIV patients generally has poorer outcome than that of HIV patients. It is because intense host inflammatory response in non HIV patients with PJP, despite the lower number of organisms, contribute to severe lung injury. A definite diagnosis is made by demonstrating organism in lung tissue or lower respiratory tract secretions. BAL fluid neutrophilia, high D(A-a)O2, combined bacteraemia, increased BUN, and preexisting lung disease are all independent predictors of a poor prognosis in non-HIV PJP[8].Rapid progression of illness necessitate the need for early diagnosis and treatment .Early diagnosis and treatment within three days is crucial for the survival of PJP patients without HIV infection.

The standard regimen of treatment for pneumonia caused by Pneumocystis jiroveci is cotrimoxazole which contains sulfamethoxazole (SMX) and trimethoprim (TMP)[9]. TMP-SMX acts by interfering with folate metabolism Dihydrofolate Reductase (DHFR) and Dihydropteroate Synthase (DHPS) in *Pneumocystis*. It has excellent tissue penetration and is available in intravenous and oral formulations that achieve comparable serum levels. The dose of TMP-SMX for patients with normal renal function is 15 to 20 mg/kg of TMP intravenously or orally daily in three or four divided doses for 21 days. Patients should receive intravenous therapy until they are clinically stable ($PaO_2 \geq 60$ mmHg, respiratory rate < 25) and have a functioning gastrointestinal tract.

Severity of PJP patients is assessed based on oxygenation. Mild if PaO_2>70 mm Hg and alveolar-arterial O2 gradient <35 mm Hg, moderate if PaO_2>70 mm Hg and gradient between 35 -45 mm Hg and severe if $PaO_2 \leq 70$ mm Hg and gradient>45mm Hg[10]. All patients with moderate to severe PJP should be treated with adjuvant corticosteroid therapy**.** The glucocorticoid regimen is prednisone 40 mg orally twice daily for five days, followed by 40 mg orally once daily for five days, followed by 20 mg orally once daily for 11 days. KDIGO guidelines also recommend corticosteroids for Kidney transplant recipients with moderate to severe PJP[3]. Both of our patients had features of severe PJP.

Clinical failure is defined as lack of improvement or worsening of respiratory function documented by arterial blood gases after 4 days to 8 days of anti-PCP treatment[11]. Polymorphisms in the genes targeted by anti-PJP therapies are recognized as reason for resistant PJP. Mutations in DHFR and DHPS are the commonest cause for resistance to TMP/SMX[9]. Molecular investigations to identify polymorphisms include sequencing and real-time PCR assays. Presence of DHPS mutations was an independent predictor associated with an increased all-cause mortality at 3 months with a hazard ratio of 3.10[12]. Studies show association between DHPS mutations and the use of trimethoprim-sulfamethoxazole for PJP prophylaxis[13]. Both of our patients were on TMP/SMX prophylaxis and lack of response can be due to TMP/SMX resistance.

PJP resistant to TMP/SMX is treated with second line drugs which include clindamycin, primaquine, dapsone, atovaquone, and pentamidine. Our patients were treated with primaquine 30 mg orally once daily and clindamycin: 600 mg IV every eight hours.

Both of our patients were already on PJP prophylaxis and still they developed infection. Hence, we should be cautious regarding PJP in all patients on long term immunosuppressants even if they are on PJP prophylaxis. Patients on prophylaxis are also prone to get PJP resistant to TMP/SMX as seen in our case. Although both of our patients were treated with second line regimen, only one patient responded to treatment.

References:

1. Pneumocystis jiroveci (formerly Pneumocystis carinii). Am J Transplant 2004; 4 (Suppl 10): 135–141.
2. Hughes WT, Feldman S, Sanyal SK. Treatment of Pneumocystis carinii pneumonitis with trimethoprim-sulfamethoxazole. Can MedAssoc J 1975; 112: 47–50.
3. Yale SH, Limper AH. Pneumocystis carinii pneu monia in patients without acquired immunode ficiency syn drome: associated illness and prior corticosteroid therapy. Mayo Clin Proc 1996; 71: 5–13.
4. Kidney Disease: Improving Global Outcomes Trans plant Work Group. KDIGO clinical prac tice guideline for the care of kidney transplant recipients. Am J Trans plant 2009; 9 (Suppl 3): S1–S157.
5. EBPG Expert Group on Renal Transplantation. European Best Practice Guidelines for Renal Transplantation. Section IV: Long-term manage ment of the transplant recipient. IV.7.1 Late infec tions. Pneumocystis carinii pneumonia. Nephrol Dial Transplant 2002; 17 (Suppl 4): 36–39.
6 Roux, A.; Canet, E.; Valade, S.; Gangneux-Robert, F.; Hamane, S.; Lafabrie, A.; Maubon, D.;Debourgogne, A.; le Gal, S.; Dalle, F.; *et al. Pneumocystis jirovecii* pneumonia in patients with or without AIDS, France. *Emerg. Infect. Dis.* 2014, *20*, 1490–1497.
7. Stern, A.; Green, H.; Paul, M.; Vidal, L.; Leibovici, L. Prophylaxis for *Pneumocystis* pneumonia (PCP) in non- HIV immunocompromised patients. *Cochrane Database Syst. Rev.* 2014, doi:10.1002/ 14651858.
8. Martin, S.I.; Fishman, J.A. *Pneumocystis* pneumo`nia in solid organ transplantation.*Am. J. Transplant.* 2013, *13*, 272–279.
9. Wilkin A, Feinberg J. Pneumocystis carinii pneum onia: a clinical review. American family physi cian. 1999 Oct;60(6):1699-708.
10 . Huang L, Morris A, Limper AH, Beck JM. An offi cial ATS workshop summary: recent advances and future directions in Pneumocystis pneumonia (PCP). Proceed ings of the American Thoracic Society. 2006 Nov;3(8):655- 64.
11. Benson CA, Brooks JT, Holmes KK, Kaplan JE, Masur H, Pau A. Guidelines for prevention and treatment opportunistic infections in HIV-infected adults and ado lescents; recommendations from CDC, the National In stitutes of Health, and the HIV Medicine Association/ Infectious Diseases Society of America.2019
12. Helweg-Larsen J, Benfield TL, Eugen-Olsen J, Lundgren JD, Lundgren B. Effects of mutations in *Pneumocystis carinii* dihydropteroate synthase gene on outcome of AIDS-associated *P. carinii* pneumonia.*Lancet* 1999;354:1347–1351.
13. Kazanjian P, Armstrong W, Hossler PA, Burman W, Richardson J, Lee CH, Crane L, Katz J, Meshnick SR. *Pneumocystis carinii* mutations are associated with du ration of sulfa or sulfone pro phylaxis exposure in AIDS patients. *J Infect Dis* 2000;182:551–557.

A rare entity of acute exacerbation of pulmonary sarcoidosis following mediastinoscopy and biopsy

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Abstract

Exacerbation of interstitial lung disease (ILD) particularly following lung biopsy has been classically reported with Idiopathic pulmonary fibrosis (IPF). Acute exacerbations have been described in sarcoidosis, especially pulmonary sarcoidosis (Acute exacerbation of pulmonary sarcoidosis – AEPS) but not much information is available regarding exacerbation of sarcoidosis following an interventional or surgical procedure. Herein we report a case of a 53 year old lady with mediastinal adenopathy who underwent mediastinoscopy and biopsy and subsequently developed a clinical picture akin to acute exacerbation of interstitial lung disease immediately following the procedure and was proven to have sarcoidosis by subsequent investigations. She had a dramatic recovery following administration of systemic corticosteroids.

Key words:

Acute exacerbation, Sarcoidosis, Mediastinoscopy

Introduction:

Sarcoidosis is a multisystem disease which was initially described in 1899 by a Dermatologist named Caesar Black. Since then a lot of research and advances happened in sarcoidosis. Acute exacerbations are extremely uncommon in the natural history of the disease and have rarely been reported following reduction in dose or withdrawal of corticosteroids. But, acute exacerbation of sarcoidosis following an interventional procedure is an entity which is not described in literature, till date unlike what is encountered in Idiopathic pulmonary fibrosis.

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Exacerbation of interstitial lung disease (ILD) particularly following lung biopsy has been classically reported with Idiopathic pulmonary fibrosis (IPF). Acute exacerbations have been described in sarcoidosis, especially pulmonary sarcoidosis but not much information is available regarding exacerbation of sarcoidosis following an interventional or surgical procedure. Here we report a case of a 53 year old lady who underwent mediastinoscopy and biopsy suspecting sarcoidosis and who developed a clinical picture like exacerbation of interstitial lung disease immediately following the procedure and was proven to have sarcoidosis with biopsy.

Case report:

A 53 year old female who is a house wife, with no prior comorbidities and no previous history of any respiratory or cardiac illness presented to our hospital with complaints of cough with mucoid expectoration, exertional dyspnoea and loss of weight of 6 months duration. She did not have any fever, loss of appetite, allergic symptoms, wheeze, palpitation, chest pain or pedal edema. She did not have any symptoms of connective tissue disease, and no history of any chemical or organic exposures or radiation or any prolonged drug intake. Clinical examination revealed her vital signs to be normal. Examination of the respiratory system revealed fine end inspiratory crepitations at the lung bases, while examination of other systems was unremarkable. Her complete blood count, liver and renal function tests were normal. Her Chest X Ray PA view showed bilateral hilar prominence with reticulonodular shadows in the lower zones. Contrast enhanced CT scan of the chest showed bilateral septal thickening with honeycombing, traction bronchiectasis (Figure 1) and bilateral paratracheal, subcarinal and bilateral hilar lymphadenopathy (Figure 2).

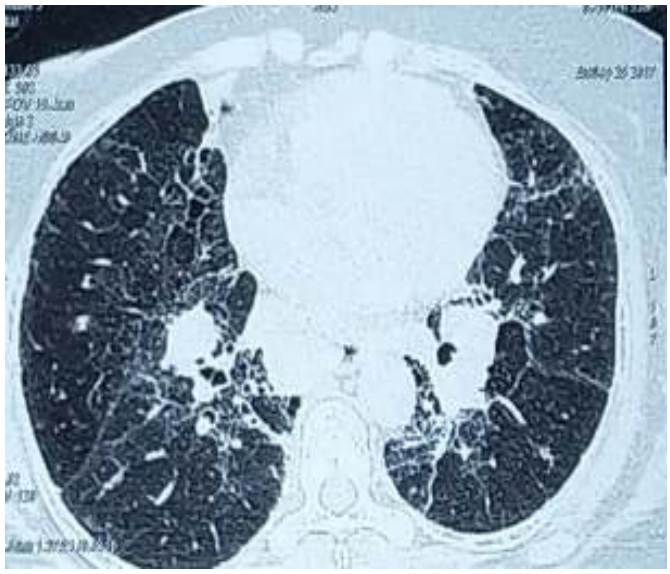

Figure 1: Axial section of High resolution CT scan of Thorax, lung window showing bilateral septal thickening and few areas of honeycombing

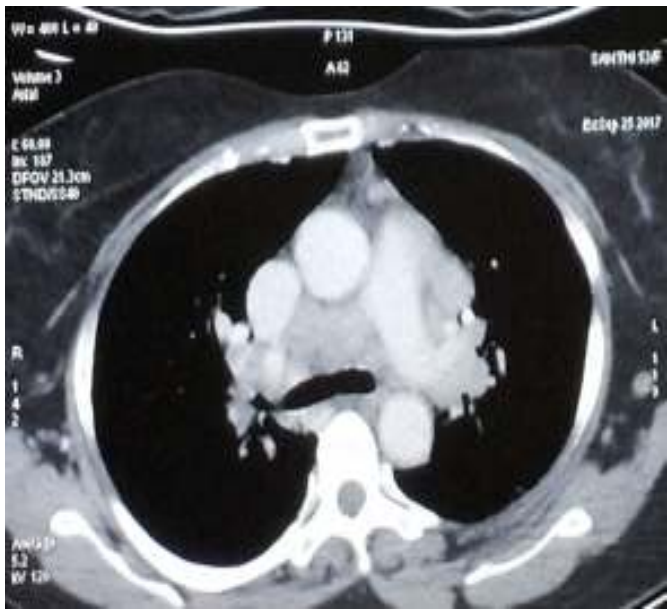

Figure 2: Axial section of Contrast enhanced CT Thorax, mediastinal window showing bilateral subcarinal and hilar lymphadenopathy

Serum angiotensin converting enzyme (ACE) levels were elevated 86.6 U/L (normal 8-52 U/L), Her serum calcium was 9.2 mg /dl (normal 8.6 to 10.2 mg/dl) and 24 hour urinary calcium was 83.8mg/dl (normal 50 to 150 mg/dl). Her connective tissue work up was negative. Sputum smear examination for acid fast bacilli as well as CBNAAT (cartridge based nucleic acid amplification test) were negative. A tuberculin test done with 2 TU did not show any induration after 48 hours. Her electrocardiogram was normal and echocardiogram showed good biventricular function and there was no evidence of pulmonary hypertension. Since sarcoidosis was of prime consideration and other common causes of mediastinal adenopathy in our country (tuberculosis and lymphoma) had to be excluded, it was decided to proceed with mediastinoscopy and biopsy of the lymph node.

She underwent the surgical procedure and in the immediate post procedure period developed desaturation and respiratory distress and had to be intubated and mechanically ventilated. Chest X Ray showed extensive alveolar infiltrates bilaterally involving all zones (Figure. 3).

An arterial blood gas analysis was suggestive of Type I respiratory failure with pH of 7.41, PO_2 of 51 mmHg and PCO_2 of 36 mmHg. A high resolution CT scan of the thorax revealed new onset ground glass lesions bilaterally superimposed on the pre existing lesions (Figure.4).

The differential diagnosis considered at this point of time were infection, pulmonary

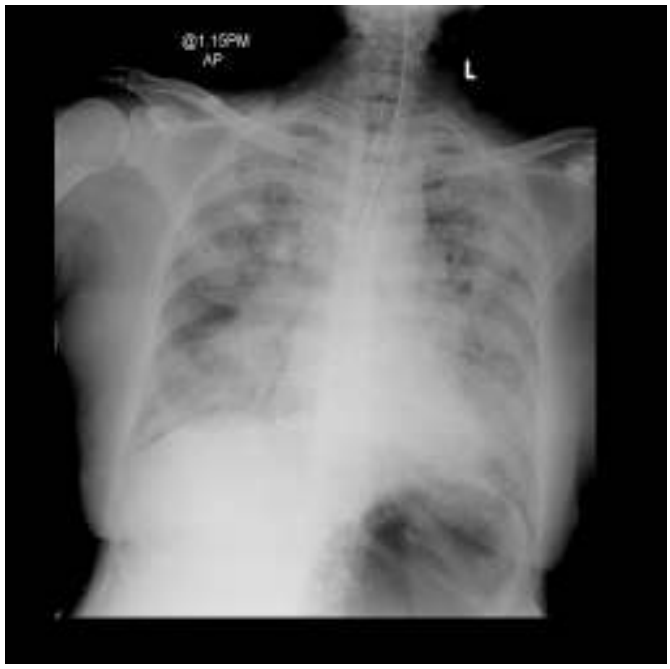

Figure 3: Chest X Ray AP view Post mediastinoscopy showing extensive alveolar infiltrates bilaterally involving all zones

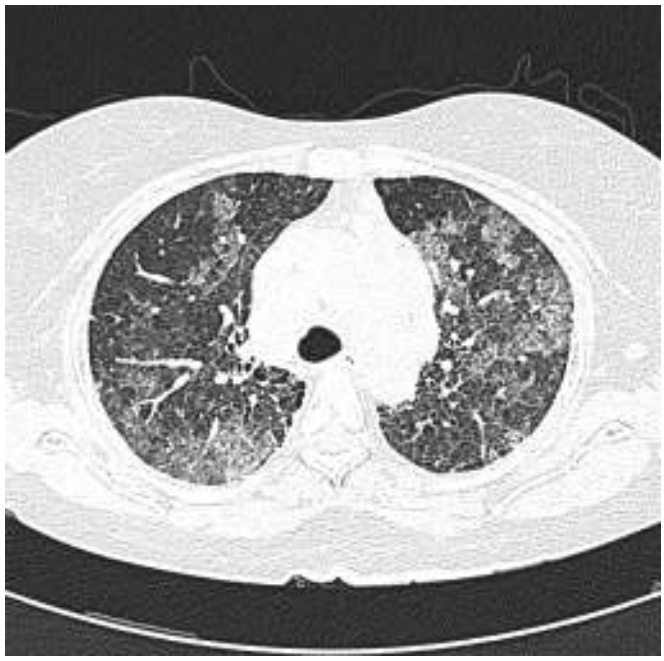

Figure 4: Axial section of High resolution CT scan of Thorax showing new onset ground glassing in post operative period

She did not have any fever or leucocytosis. The complete blood counts were normal (total count 8100). Her C reactive protein level was 8 mg/L (0-5 mg/L). Sputum gram stain and culture showed only normal oropharyngeal flora. Sputum smear examination for acid fast bacilli and CBNAAT were repeated, which were negative.

D-dimer was negative, 240ng/ ml (208-318ng/ml). A flexible bronchoscopy and lavage was done and specimen was sent for Gram stain, bacterial culture, CBNAAT, Nocardia stain, staining for Pneumocystis jiroveci, fungal stain and culture, all of which were reported as negative. An echocardiogram was done which showed good left ventricular function, so pulmonary edema was ruled out. Considering the possibility of an exacerbation of ILD, she was started on pulsed dose of steroids – methyl prednisolone 1 gram per day for 3 days. She had a dramatic improvement, was extubated and thereafter was de escalated to oral prednisolone 30mg/day. She remarkably improved after steroids, was gradually weaned off oxygen and was discharged after a week. Meanwhile the histopathology report of the biopsy became available, which showed discrete epitheloid cell granulomas, almost completely replacing the lymph nodal architecture, which stained negative for acid fast bacilli and fungus (Figure 5). There was condensation of reticulin around the granulomas with permeation of reticulin fibres into few of the granulomas. Thus a diagnosis of sarcoidosis was confirmed and she was continued on treatment with oral steroids. On follow up imaging with Chest X ray PA view after two weeks, (Figure. 6), there was good clearance of the lesions and the patient continued to symptomatically improve. She was further followed up for a year, by which time, the steroids were tapered and stopped and she continued to do well.

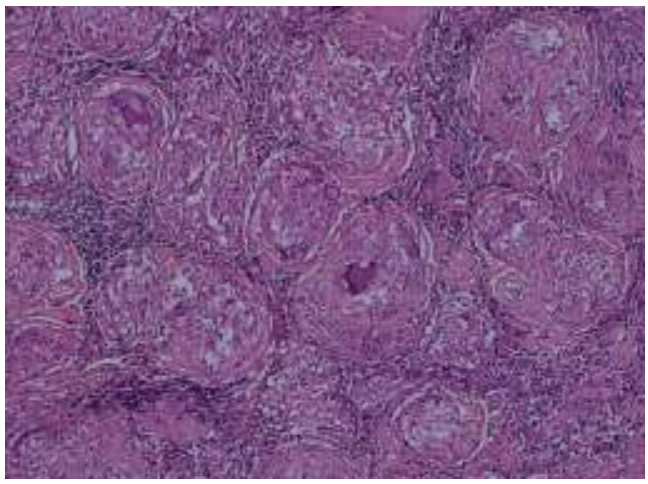

Figure 5: Histopathology from mediastinal node showing the lymph node to be almost completely replaced by multiple discrete epitheloid granulomas with scanty necrosis. (H&E, 200x)

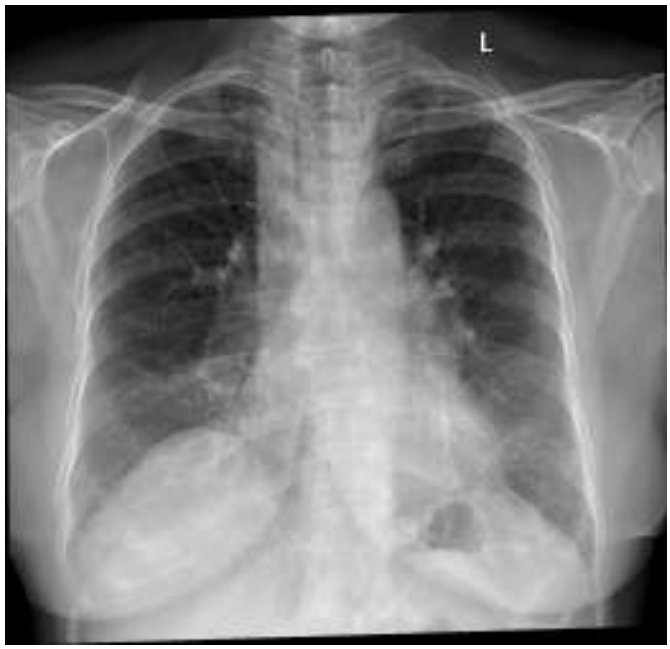

Figure 6: Follow up Chest X Ray PA view after two weeks of initiating steroid shows good clearance of lesions.

Discussion:

Acute pulmonary exacerbation of sarcoidosis (APES) has been described in patients treated previously for pulmonary sarcoidosis after reduction or discontinuation of corticosteroid therapy.[1,2] However there is no consensus definition and there is lack of information regarding definition, pathogenesis and treatment of this entity.[3] APES has been defined using different combinations of the following criteria by different researchers: (1) a decline in pulmonary function, (2) worsening pulmonary symptoms, (3) increases in biomarkers of disease activity, (4) the need to initiate or restart corticosteroid therapy, and (5) exclusion of alternative causes of pulmonary symptoms and pulmonary dysfunction.[1,2,4-6] The risk factors proposed were black race, longer duration of the disease, treatment with corticosteroids, worsening pulmonary symptoms, fibrocystic type of pulmonary sarcoidosis, treatment with interferon – alpha and HAART therapy. [3]

A chest radiograph should be performed routinely in the evaluation of APES to exclude alternative pulmonary diagnoses, although it is often inadequate to confirm the diagnosis of APES.[3] Chest CT scans may be useful to detect APES in a patient with a normal or equivocal chest radiograph. Bronchoscopy and BAL have not been recommended as first line investigations in AEPS.[3] Empiric corticosteroid therapy is considered the treatment of choice for AEPS.

Our patient had an acute deterioration following mediastinoscopy. She had a fibrocystic type of disease, which is an exacerbation prone phenotype of sarcoidosis.[3] There were new onset ground glass lesions on chest imaging and she was hypoxemic and in distress, so much so that she needed mechanical ventilation. In such a scenario, it was not possible to have a spirometry done, which is a criteria mentioned to make a diagnosis of AEPS.[3] Considering that infections and cardiac causes were ruled out in this patient, and she improved with steroids this could be the entity of acute exacerbation of sarcoidosis following a surgical procedure, something akin to what is described in interstitial lung diseases like Idiopathic Pulmonary Fibrosis.

What we encountered in our patient was perhaps a very fulminant type of exacerbation leading to respiratory failure, hitherto not described in literature previously. A thorough literature search did not yield any case report nor any mention of acute exacerbation of sarcoidosis following a surgical procedure like mediastinoscopy. Hence this could well be the first description of this possible new etiology as a cause of acute exacerbation of pulmonary sarcoidosis. The uniqueness of this case is that a patient suspecting sarcoidosis underwent mediastinoscopy and following the procedure developed new respiratory symptoms and infiltrates in chest x-ray which improved following steroid therapy. This case is being reported to highlight the fact the exacerbation of ILD following surgical procedures, like in IPF, can occur in sarcoidosis also and should be considered as one of the differential diagnosis when a patient with sarcoidosis develops new respiratory symptoms or signs with increase in lesions on radiology imaging post operatively after an interventional or surgical procedure.

References

1. Mana J, Montero A, Vidal M , Marcoval J , Pujol R . Recurrent sarcoidosis: a study of 17 patients with 24 episodes of recurrence. Sarcoidosis Vasc Dif fuse Lung Dis. 2003; 20 (3): 212-21.
2. Rizzato G , Montemurro L , Colombo P . The late followup of chronic sarcoid patients previously treated with corticosteroids. Sarcoidosis Vasc Diffuse Lung Dis 1998 ; 15 (1):52-58.
3. Panselinas E , Judson M A. Acute pulmonary ex acerbation of sarcoidosis. Chest 2012; 142(4):827–836.
4. Hunninghake GW , Gilbert S , Pueringer R , et al . Out come of the treatment for sarcoidosis . Am J Respir Crit Care Med.1994; 149 (4 Pt 1): 893 - 898
5. McKinzie BP , Bullington WM , Mazur JE , Judson MA . Efficacy of short-course, low-dose corticos teroid therapy for acute pulmonary sarcoidosis exacerbations. A m J Med Sci. 2010; 339 (1): 1 - 4.
6. Judson MA , Gilbert GE , Rodgers JK , Greer CF, Schabel SI . The utility of the chest radiograph in diagnosing exacerbations of pulmonary sarcoi dosis. Respirology. 2008; 13(1): 97-102

Pruritus as a paraneoplastic syndrome of lung cancer

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Abstract

A 71 year old gentleman presented with progressive, persistent, generalized itching for the past one year. He was diagnosed as having chronic pruritus and was being treated symptomatically. During evaluation for pruritus, a chest X Ray PA view was taken, which revealed the presence of a right sided pleural effusion. He was referred to the chest clinic for further evaluation. Closed pleural biopsy revealed the aetiology of pleural effusion to be adenocarcinoma and it was confirmed to be of pulmonary origin by immunohistochemistry. His pruritus started to resolve when chemotherapy was initiated, thereby confirming it to be a dermatological Paraneoplastic Syndrome.

Key words

Lung cancer, Pruritus, Paraneoplastic syndrome

Inrtroduction

The term " Para neoplastic syndrome " refers to tumor-related symptoms and/or findings that are independent of the direct or local extent or physical effects of metastasis of the tumor[1]. Para neoplastic syndromes occur as a response to the effects of hormones and cytokines released from cancer cells or the immunological response of cancer cells. Dermatologic paraneoplastic syndromes are generally seen before patients are diagnosed with malignancy. Generalised pruritus could be a presenting symptom of underlying internal malignancy. Paraneoplastic pruritus of lymphoma has been described and can precede other clinical signs, but is extremely rare in bronchogenic carcinoma. Paraneoplastic urticaria, also called Urticarial paraneoplastic syndrome has also been described with solid tumors including lung cancer[2].

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A 71-year old gentleman who was apparently well a year back, started developing itching over arms and ventral thigh, more during night time. It progressed to generalized, intractable pruritus. He was evaluated in the dermatology department of an outside hospital, and was diagnosed as having chronic pruritus. He received treatment with multiple courses of oral antihistamines, leukotriene antagonists and topical applications but the itching remained intractable for the preceding six months prior to presentation to our hospital. He was first evaluated in the dermatology outpatient department of our hospital. Clinical examination of skin revealed no visible lesions. As part of the work up for pruritus, a chest X Ray was taken since the patient complained of some chest discomfort. In view of some radiological abnormality, he was referred to the Pulmonology department for further workup.

On interrogation, the patient was found to have cough with mucoid expectoration since the past two weeks without any prodromal symptoms or fever. There was no history of hemoptysis, breathlessness or chest pain. He was a non smoker. He had no comorbid illness. On general survey, his general condition was good. He had no pallor, icterus, clubbing, cyanosis or pedal edema. His pulse rate was 92/ min, blood pressure was 112/ 70 mm Hg. There were no palpable lymph nodes. Examination of respiratory system revealed the presence of a stony dull percussion note and diminished intensity of breath sounds in the right lower interscapular & infrascapular areas. Other systemic examinations were within normal limits. His blood investigations were as follows - Hemoglobin-12.5 gm%, total leukocyte count - 8000/mm^3 with differential count of neutrophil-73%, lymphocyte-25%, eosinophil-01%, monocyte-01%. Blood sugar, serum urea, creatinine, thyroid function and liver function tests were all within normal limits. Chest X-ray revealed right sided pleural effusion with two nodular lesions in the right mid zone, suspicious of malignancy (Fig 1).

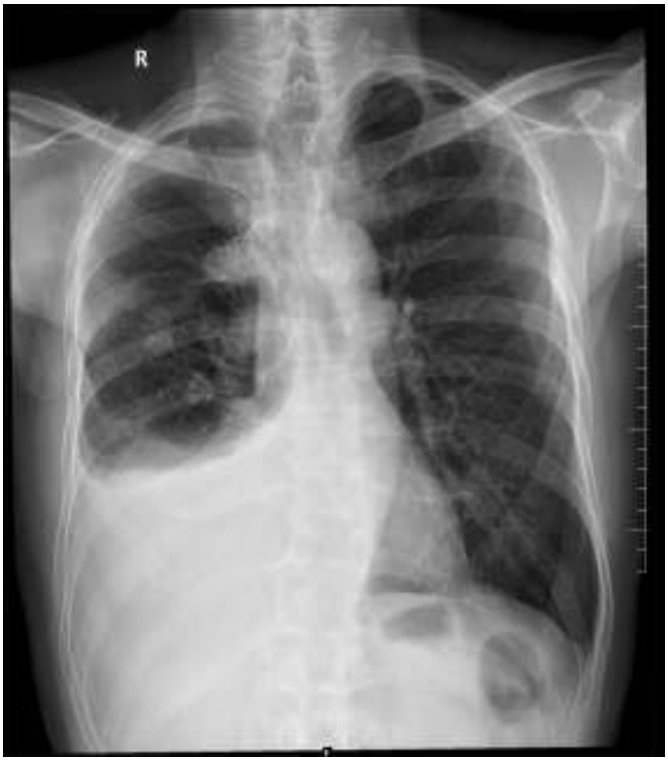

Fig 1 - Chest X ray PA view showing right side pleural effusion with nodular lesions in right mid zone.

CT thorax revealed right sided moderate pleural effusion with a spiculated heterogeneously enhancing SOL in the anterior segment of right upper lobe infiltrating the medi-

astinal pleura and into the prevascular space (Fig 2).

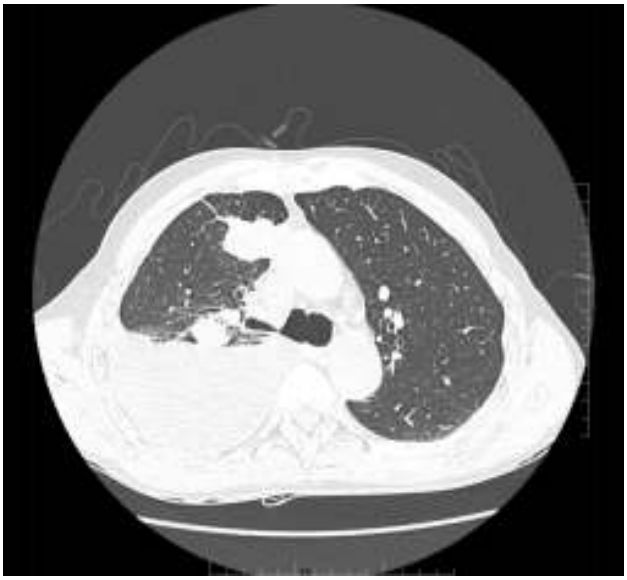

Fig 2 – C T of chest showing right sided pleural effusion with a spiculated heterogeneously enhancing lesion in the anterior segment of right upper lobe, infiltrating the mediastinal pleura.

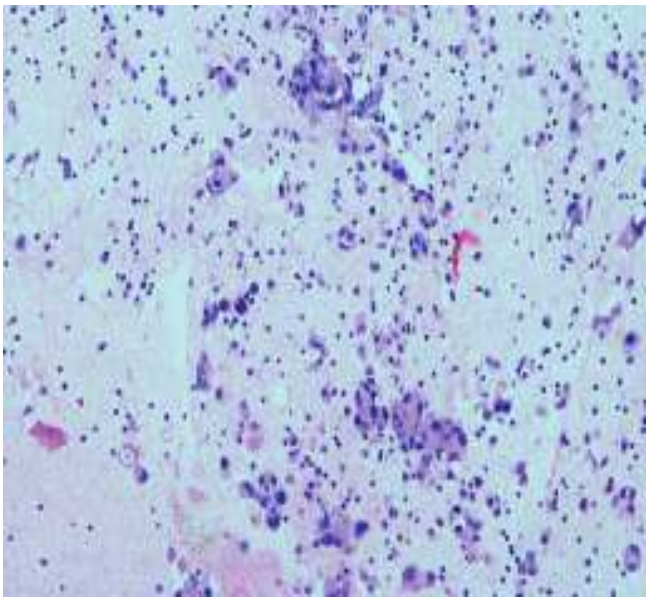

Fig 3 – Pleural biopsy specimen showing pleomorphic cells with hyperchromatic nuclei and irregular nuclear margin, arranged in clusters, scattered singly & occasional vague adeno pattern. (H & E x400)

Diagnostic pleural fluid aspiration was done and hemorrhagic fluid was aspirated. On analysis, it was found to be a lymphocyte predominant exudative effusion. Closed pleural biopsy was done using Cope's needle and histopathological examination was consistent with adenocarcinoama .

Immunohistochemistry results confirmed it as metastasis from Pulmonary adenocarcinoma (TTF1, Napsin, Calretinin positive). He was referred to the oncologist for further management. When chemotherapy was initiated, his pruritus started to reduce in intensity. However, he succumbed to the illness shortly after completion of the first cycle of chemotherapy.

Discussion

Chronic pruritus is defined as itching lasting for more than 6 weeks. Urticarial paraneoplastic syndrome is defined as: (i) urticaria that occurs during the natural process or even preceding the clinical evidence of the malignancy, (ii) it is not caused by the neoplasm invasion or compression and (iii) subsides after tumor removal[2].

Urticaria can be a paraneoplastic symptom in solid tumors of the lung, colon, brain, gastric& breast tumors, prostate and larynx[3]. Paraneoplastic syndrome in lung cancer can be endocrine, neurologic, dermatologic, rheumatologic,nephrological or haematological. Due to the high incidence of lung cancer and the increased occurrence of paraneoplastic syndromes in SCLC cases, lung cancer related paraneoplastic syndromes are more common than other cancers. Dermatologic paraneoplastic syndromes are generally seen in

patients much before they are diagnosed with malignancy[4]. The common cutaneous paraneoplastic syndromes associated with lung cancer include simple pruritus, urticaria, acanthosis nigricans, pachydermatoglyphia (tripe palms), erythema gyratum repens, acrokeratosis paraneoplastica (Bazex syndrome), acquired hypertrichosis lanuginose, necrolytic migratory erythema (NME) and dermatomyositis[5].

Chronic urticaria is a very rare paraneoplastic manifestation of lung cancer, while generalised pruritus as a paraneoplastic syndrome is even rarer. It has been mainly described in adenocarcinomas and small cell carcinomas[6]. As in our case, it could be a presenting sign of underlying malignancy. Recognition of the presence of para neoplastic syndromes is a vital clue for the early diagnosis of occult malignancy, and allows timely treatment. These conditions can be used as a marker of cancer activity and also as prognosis predictors. In our patient, his clinical presentation was intractable pruritus, but the new onset cough and presence of pleural effusion led to detection of underlying carcinoma lung.

This case is being reported to highlight a uniquely rare cutaneous manifestation of lung cancer. One should always keep in mind the possibility of an underlying malignancy while evaluating any patient who has intractable pruritus, particularly so, in the elderly age group.

References

1. Tas D. Paraneoplastic Syndromes in Lung Cancer. In: Torres AFC, editor. Lung Cancer - Strategies for Diagnosis and Treatment [Internet]. InTech; 2018 [cited 2019 Nov 29]. Available from: http://www.intechopen.com/books/lung-cancer-strategies-for-diagnosis-and-treatment/paraneoplastic-syndromes-in-lung-cancer
2. Yosipovitch G. Chronic pruritus: a paraneoplastic sign. Dermatol Ther. 2010 Dec;23(6):590–6.
3. Tarikci N, Kocatürk E, Güngör Þ, Oðuz Topal I, Ülkümen Can P, Singer R. Pruritus in Systemic Diseases: A Review of Etiological Factors and New Treatment Modalities. Sci World J. 2015;2015:1–8.
4. Lomholt H, Thestrup-Pedersen K. Paraneoplastic skin manifestations of lung cancer. Acta Derm Venereol. 2000 May;80(3):200–2.
5. Silva JA, Mesquita Kde C, Igreja AC et al. Paraneoplastic cutaneous manifestations: concepts and updates. An Bras Dermatol. 2013 Jan-Feb;88(1):9-22
6. De P, Abbasi R, Senadhira T, Orr P, Ullah A. Urticaria and large cell undifferentiated carcinoma of lung. Dermatol Online J. 2005 Dec 1; 11 (3):45

An unusual variant of adenocarcinoma lung

Soofia Mohammed[1], Rohit S [2] Ponnuthurai Bala [3], Cherian Thampi [4]

Abstract

Background: The presence of ROS1 rearrangements defines a small subgroup of lung adenocarcinomas with peculiar clinico pathological characteristics. The frequency of ROS1 rearrangement in NSCLC has been reported to range from 1.6% to 2.3%. Herein we report a rare case of lung adenocarcinoma with ROS1 mutation in a 16 year old female.

Case presentation: A 16 year old nonsmoker female presented with cough and shortness of breath of one month duration. Clinical examination revealed a hard right supraclavicular lymph node of 2x2 cm. CECT of neck, chest and abdomen revealed multiple necrotising cervical and mediastinal lymph nodes. HPR and IHC of excision biopsy of right supraclavicular lymph node confirmed lung adenocarcinoma. Further mutation studies were done and it came as positive for ROS1 mutation. Hence she was started on crizotinib therapy.

Discussion: ROS1 (ROS1 protooncogene receptor tyrosine kinase) is activated by chromosomal rearrangement in a variety of human cancers, including NSCLC, cholangiocarcinoma, gastric cancer, ovarian cancer, and glioblastoma multiforme. Crizotinib has shown to be an effective drug for improving the prognosis of NSCLC patients with ROS1 rearrangement.

Key words: Carcinoma lung, ROS1

Introduction

Lung cancer is the most commonly occurring cancer worldwide and nearly 80% to 85% of all cases accounts for non–small-cell lung cancer (NSCLC).Targeted molecular therapy is efficient for patients with advanced NSCLC with related gene mutations. The genetic landscape of NSCLC has profoundly changed in the last decade with the identification of several molecular subtypes with specific clinico pathological features and different therapeutic approaches.

The presence of ROS1 rearrangements defines a small subgroup of lung adenocarcinomas with peculiar clinico pathological characteristics : never smokers, young age, and adenocarcinoma histology.The frequency of ROS1 rearrangement

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in NSCLC has been reported to range from 1.6% to 2.3% [2].

The ROS1 oncogene encodes an orphan receptor tyrosine kinase related to anaplastic lymphoma kinase (ALK), along with members of the insulin receptor family[3].Various modalities such as immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), RTPCR, and NGS have been used in the diagnosis of these mutation. ROS1-rearranged NSCLCs present high response rate with crizotinib therapy and seem to respond well also to pemetrexed-based chemotherapy. Herein we report a rare case of lung adenocarcinoma with ROS1 mutation in a 16 year old female.

Case presentation

A 16 year old nonsmoker female presented with cough and shortness of breath of one month duration. There was associated wheeze and mucoid expectoration. She had significant loss of weight also. She denied history of fever, recent tuberculosis contact, or previous wheezing episodes. Her mother had breast cancer and expired 1 year back. Clinical examination revealed a hard right supraclavicular lymph node of 2 x 2 cm. On auscultation, there was bilateral wheeze.

Her routine lab parameters were normal except for mild anemia. CXR (fig 1) showed a nodular non homogenous opacity in the right lower zone. Smear AFB and CBNAAT were negative.

CECT of neck, chest (fig 2) and abdomen revealed multiple necrotising cervical and mediastinal lymph nodes that compress trachea,

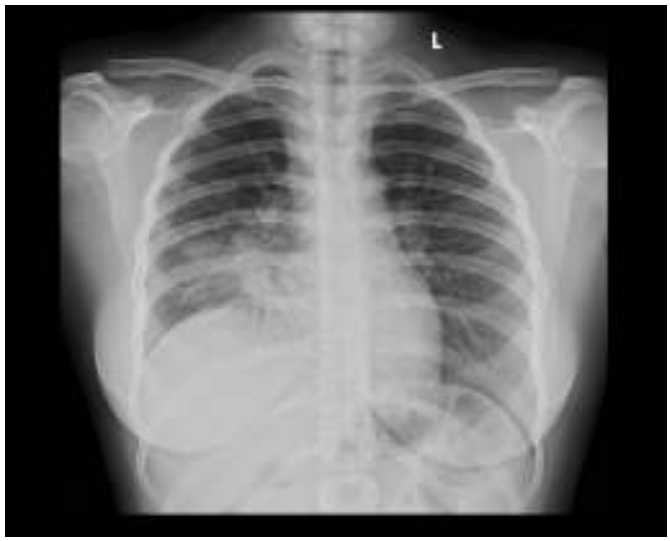

Fig 1: CXR-PA view showing right lower zone non homogenous opacity.

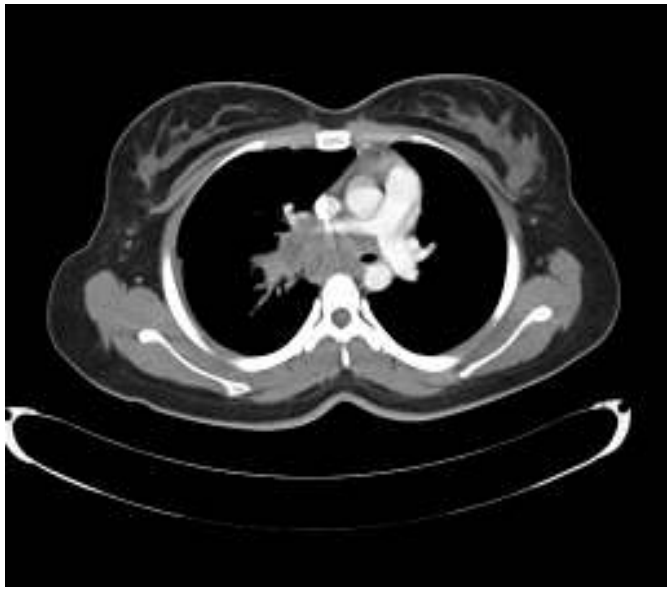

Fig 2: CT Chest mediastinal window showing enlarged sub carinal and right hilar nodes.

and right main pulmonary artery; with collapse consolidation of right lower lobe and multiple hypoenhancing lesions in liver with mild right pleural effusion. Bone scan showed multiple lytic lesions involving left scapula, right clavicle, multiple spine and left iliac bone. AFP, Beta HCG and serum LDH were normal.

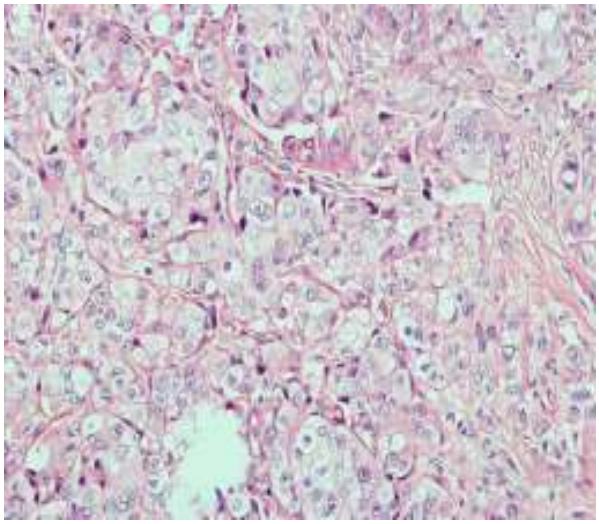

Fig 3: Cervical node biopsy specimen showing neoplastic cells with increased nucleus to cytoplasm ratio, prominent nucleoli and features suggestive of adenocarcinoma H and E x200.

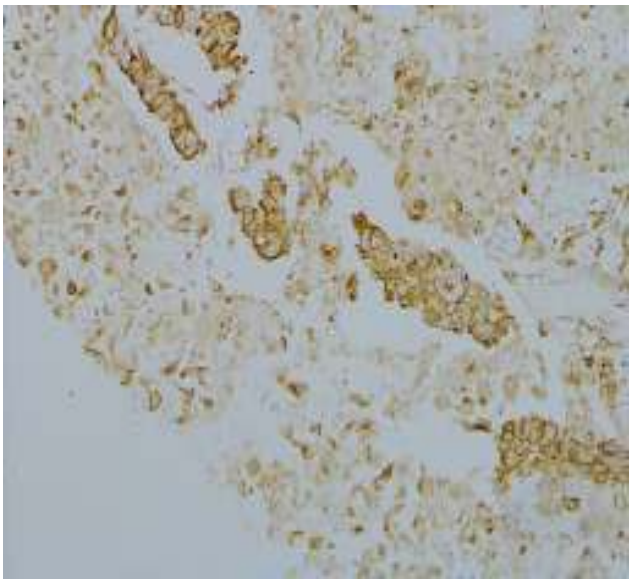

Fig 4: Immunohistochemistry showing positivity for Napsin

HPR (fig 3) and IHC (fig 4) of excision biopsy of right supraclavicular lymph node confirmed lung adenocarcinoma.The case was discussed in multi disciplinary tumour board and started on systemic chemotherapy with pemetrexed and carboplatin. Further mutation studies were done and it came as positive for ROS1 mutation. Hence she was started on crizotinib therapy. She tolerated the treatment well and was symptomatically better on review.

Discussion

The ROS1 rearrangement in non small cell lung cancer (NSCLC) was discovered by Rikova et al[4].ROS1, originally discovered as the human homologe of the chicken proto-oncogene c-ros, is a gene located in the chromosome 6, encoding an orphan receptor tyrosine kinase, closely related with ALK and LTK. Rearrangement leads to fusion of a portion of ROS1 that includes the entire tyrosine kinase domain with 1 of 13 different partner proteins.The fusion partners include CD74, SLC34A2, SDC4, EZR, FIG,TPM3, LRIG3, KDELR2, LIMA1, MSN, CLTC, CCDC6, and TMEM106. Among these, CD74 is the most common fusion partner in NSCLC. ROS1 (ROS1 protooncogene receptor tyrosine kinase) is activated by chromosomal rearrangement in a variety of human cancers, including NSCLC, cholangiocarcinoma, gastric cancer, ovarian cancer, and glioblastoma multiforme[4-8]. The resulting ROS1 fusion kinases are constitutively activated and drive cellular transformation.

Patients who harbour ROS1 gene rearrangement can benefit from treatment with TKIs. Crizotinib, a small molecule ATP-competitive ALK inhibitor, was approved for use in NSCLC patients with active ROS1 signalling by the United States Food and Drug Administration on March 11, 2016. Crizotinib has shown to be an effective drug for improving the prognosis of

NSCLC patients with ROS1 rearrangement. A previous study reported an objective response rateof 72% and median progression-free survival of 19.2 months[9]. It has been reported that ROS1-positive NSCLCs may be associated with increased sensitivity to Pemetrexed-based chemotherapy[10].

References

1. Bergethon K, Shaw AT, Ou SH, Katayama R, Lovly CM, McDonald NT, Massion PP, Siwak-Tapp C, Gonzalez A, Fang R, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J ClinOncol 2012; 30(8):863-70; PMID:22215748; http://dx.doi.org/10.1200/JCO.2011.35.6345
2. Kim HR, Lim SM, Kim HJ, Hwang SK, Park JK, Shin E, et al. The frequencyand impact of ROS1 rearrangement on clinical outcomes in never smokers with lung adenocarcinoma. Ann Oncol2013;24:236470.
3. Acquaviva J, Wong R, Charest A. The multifac eted roles of the receptor tyrosine kinase ROS in development and cancer. BiochimBiophysActa2009;1795:3752.
4. Rikova K, Guo A, Zeng Q, Possemato A, Yu J, Haack H, et al. Global survey of phosphotyrosinesignaling identifies oncogenic kinases in lung cancer. Cell 2007;131:1190203.
5. Charest A, Lane K, McMahon K, Park J, Preisinger E, Conroy H, et al. Fusion of FIG to the receptor tyrosine kinase ROS in a glioblastoma with an interstitial del(6)(q21q21). Genes Chromosomes Cancer 2003;37:5871.
6. Gu TL, Deng X, Huang F, Tucker M, Crosby K, Rimkunas V, et al. Survey of tyrosine kinase sig naling reveals ROS kinase fusions in human cholangiocarcinoma. PLoS One 2011;6:e15640.
7. Lee J, Lee SE, Kang SY, Do IG, Lee S, Ha SY, et al. Identification of ROS1 rearrangement in gastric adenocarcinoma. Cancer 2013;119:162735.
8. Birch AH, Arcand SL, Oros KK, Rahimi K, Watters AK, Provencher D, et al. Chromosome 3 anomal ies investigated by genome wide SNP analysis of benign, low malignant potential and low grade ovarian seroustumours. PLoS One 2011;6:e28250.
9. Shaw AT, Ou SH, Bang YJ, Camidge DR, Solomon BJ, Salgia R, Riely GJ, Varella-Garcia M, Shapiro GI, Costa DB, et al. Crizotinibin ROS1-rearranged non-small-cell lung cancer. N Engl J Med 2014; 371(21):1963-71; PMID:25264305; http:// dx.doi.org/10.1056/NEJMoa1406766
10. Riess JW, Padda SK, Bangs CD, Das M, Neal JW, Adrouny AR, Cherry A, Wakelee HA. A case se ries of lengthy progression-free survival with pemetrexed-containing therapy in metastatic non–small-cell lung cancer patients harboring ROS1 gene rearrangements. Clin Lung Cancer 2013; 14(5):592-5; PMID:23810364; http:// dx.doi.org/10.1016/j. cllc.2013.04.008

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