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Editorial

Environmental Causes of Interstitial Lung Disease (ILD) Is There a Big Elephant in the Room?

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A number of exposures have been linked to the development of ILD, particularly Idiopathic pulmonary Fibrosis (IPF) with usual interstitial pneumonia (UIP) pattern.

One of the well-recognized risk factors for the development of IPF is cigarette smoking and ever having smoked remain a risk factor for IPF even after cessation of smoking, pointing that the fibro-proliferative process or response (Eg.Gene expression profile) induced by cigarette smoking related injury may at some point become self-sustaining.[1]

In the case of Familial Interstitial Pneumonia (FIP) which has a strong genetic basis also, cigarette smoking is the strongest associated risk factor. This indicate that even a disease with strong genetic predisposition, cigarette smoking contributes significantly to the disease development which signifies the importance of gene-environment interaction for the expression of a full-blown clinical disease. Therefore, smoking cessation and keeping the living environment free of cigarette smoke including second hand smoking will go a long way in preventing the development of Pulmonary fibrosis in susceptible individuals.

The significant association between metal and wood dust exposure and IPF have been established in several parts of the world such as United states, Japan and Britain through epidemiological studiies.[2,3,4,5,6]

Similarly, studies have focused attention on the role of certain viruses and drugs in the pathogenesis of ILD. The most significant and consistent evidence involves Epstein-Barr virus, Cytomegalovirus, Hepatitis C and Human Herpes virus-8.[7,8,9] It is interesting to note that one or more of these viruses have been detected by polymerase chain reaction (PCR) or immunohistochemistry in the lungs of up to 97% of tested patients with IPF.[7,10] Presence of Epstein - Barr virus has been detected in 40% of patients with IPF in another study.[11]

A search of the data base www.pneumotox.com of the Dijon University hospital in France yielded as high as 42 drugs with a known side effect of pulmonary fibrosis. The chemotherapeutic agent bleomycin induced lung fibrosis is a well-known fact and have a known mechanism of action. More intriguing are reactions by drugs that are in common use but whose actions may be more insidious or warrant a particular degree of susceptibility to lead to IPF. It is surprising to note that several studies have linked commonly used drugs like beta blockers and antidepressants to the development of ILD.

The etiology of most chronic disease is complex with a mix of genetic and environmental influences interacting with each other over time resulting in disease. We know that extensive lung injury can result in pulmonary fibrosis (eg.Asbestosis). It may be noted that a lot of variability in the extent of pulmonary fibrosis exist between those individuals exposed to similar concentrations of fibrogenic factors.

In this issue of Pulmon a study has been published titled "Environmental allergens in idiopathic interstitial lung disease and role of skin prick test". This study looked at the prevalence of increased absolute eosinophil count and increased serum IgE levels in newly diagnosed cases of idiopathic interstitial lung disease. The other objective was to find the most common environmental agent responsible for hypersensitivity by skin prick test in those patients with idiopathic interstitial lung disease. This is an interesting study as this is probably the first study in Kerala which made an attempt to find the environmental influences on the pathogenesis of Idiopathic interstitial pneumonia. This study showed that among Idiopathic Interstitial pneumonia (IIP) patients with elevated absolute eosinophil count and serum IgE, over 66% showed a positive reaction to at least one antigen. So it is logical to limit the exposure of these patients with IIP having an elevated absolute eosinophil count (AEC) and serum IgE to antigens tested positive by skin prick test, eventhough this finding could not prove a causal-effect relationship in IIP which the investigators cited as the limitation of the study.

To determine the cause of complex diseases like ILD an under standing of how environmental exposures and genetic factors interact to alter biological function is essential.

To conclude we know that multiple exposures such as cigarette smoking, metal and wood dusts, viruses, drugs, radiation injury and fibrogenic dusts can all cause ILD that is indistinguishable from many of the classic forms of ILD. In short, these findings suggest that different forms of ILD may be related to each other by genetic predisposition and that other factors mostly environmental, operate to affect distinct clinical phenotype in each patient.

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Review Article

Bronchiolitis Obliterans among Workers of Coffee Processing Units

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Abstract

Bronchiolitis obliterans is the disease affecting small airways leading to severe respiratory dysfunction. This is frequent among young children due to viral infections. Bronchiolitis obliterans among adults are mainly due to drugs and chemicals. It is also reported in organ transplant recipients. Volatile organic compounds (VOC) such as diacetyl (2,3-butanedione) is known to cause bronchiolitis obliterans and is reported among workers of microwave popcorn plants (Popcorn Lung) and coffee processing units. This article reviews bronchiolitis obliterans among workers involved in roasting and grinding of coffee beans and highlights the importance of screening of patients for this entity among workers involved in coffee cultivation and coffee processing.

Key words

Bronchiolitis obliterans, Diacetyl, Coffee processing, Popcorn lung.

Background

Diacetyl induced bronchiolitis obliterans is first reported in workers of a microwave popcorn plant in Missouri in 2002[1]. The flavoring agent,diacetyl was used to give the popcorn a buttery taste[2]. Inhaling this chemical agent contributed to the development of this lung disease. This clinical entity was thus termed as "Popcorn Lung". Later it was reported that this flavouring agent is extensively used in e-cigarettes leading to the development of similar condition among those who use e-cigarettes. It is also proved that this chemical is a natural byproduct in coffee roasting and coffee grinding processes. Hence unacceptable levels of diacetyl in these units may cause a disease similar to popcorn lung. Bronchiolitis obliterans is associated with symptoms of cough and shortness of breath, similar to that seen in patients with chronic obstructive pulmonary disease (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. These symptoms develop slowly, progressing to more disabling symptoms over time. Lung function testing (spirometry), chest X-rays, and CT scans usually are done to reach a preliminary diagnosis. Lung tissue biopsy is necessary to confirm the diagnosis of bronchiolitis obliterans.

Bronchiolitis obliterans

In 2004, The US Centers for Disease Control and Prevention (CDC) reported several cases of bronchiolitis obliterans in workers of a microwave popcorn plant [1,3, 4]. After investigation by the NIOSH (National Institute of Occupation Safety and Health), it was disclosed that a flavoring agent termed diacetyl (2,3Butanedione) was used to give the popcorn a buttery taste[2]. Inhalation of this flavoring chemical is the likely cause of this lung disease.

A study published in 2015 showed that harmful chemicals associated with "popcorn lung" are present in many types of flavored e-cigarettes, particularly those with flavors like fruit and candy[5]. Of the 51 flavored e-cigarettes tested, flavoring chemicals were found in 47 and diacetyl specifically in 39 samples. This suggests a potentially dangerous level of exposure via e-cigarettes to chemicals that can cause severe lung damage.

Diacetyl and 2,3-pentanedione (acetyl propionyl) are VOCs known as alpha-diketones that are added as ingredients in food flavorings used in some food products such as microwave popcorn, bakery mixes, and flavored coffee[6,7]. Diacetyl, 2,3-pentanedione, other VOCs, and gases such as CO and CO2 are naturally produced and released during the coffee roasting process[8]. Grinding roasted coffee beans produces a greater surface area for off-gassing of these compounds[9]. Often, coffee roasting facilities pack newly roasted coffee in permeable bags or in bags fitted with one-way valves to allow the coffee to off-gas after it is packaged. Sometimes, newly roasted coffee is placed in bins or containers and allowed to off-gas before packaging. According to a recent report from the Centers for Disease Control and Prevention (CDC), these potentially harmful chemicals were found at higher-than-expected levels at some coffee processing facility[7].The CDC evaluated the respiratory health of 16 workers at a facility which roasts, grinds, and pack coffee. Investigators collected air samples as well as roasted coffee beans to measure the emission levels of alpha-diketones such as diacetyl and 2,3-pentanedione. In their report, the CDC confirmed that occupational exposure to diacetyl and 2,3-pentanedione can cause bronchiolitis obliterans and loss of lung function.

Occupational bronchiolitis obliterans has been identified in flavor manufacturing workers and microwave popcorn workers who worked with flavoring chemicals or butter flavorings[10]. It has also been identified in employees at a coffee roasting and packaging facility that produced unflavored and flavored coffee. A NIOSH health hazard evaluation at that facility found diacetyl and 2,3-pentanedione in high concentrations in the air.They identified three sources: 1) flavoring chemicals added to roasted coffee beans in the flavoring area; 2) grinding unflavored roasted coffee beans and packaging unflavored ground and whole bean roasted coffee in a distinct area of the facility, and 3) storing roasted coffee in hoppers, on a mezzanine above the grinding/packaging process, to off-gas[8]. At the time of the health hazard evaluation, workers had shortness of breath and obstruction on spirometry, both consistent with bronchiolitis.

A new type of extrinsic allergic alveolitis was reported in a person who worked for more than 20 years in a coffee-roasting factory and developed lung lesions. By immunological investigations it was proven that there were circulating antibodies against coffee-bean dust in the patient's serum. Immunofluorescence of the lung biopsy demonstrated deposits of IgG and complement along the alveolar capillaries[11]. This case was reported as "coffee workers lung". This entity should be differentiated from bronchiolitis obliterans in coffee processing units due to the fact that this is a hypersensitivity reaction to coffee beans rather than due to chemical like diacetyl.

Clinical features

Bronchiolitis obliterans is a serious, often disabling, lung disease that involves inflammation and narrowing of the small airways (bronchioles). Bronchiolitis obliterans often present with symptoms of cough and shortness of breath, similar to that seen in patients with chronic obstructive pulmonary disease (COPD) and asthma. These symptoms develop slowly, progressing to more disabling symptoms over time. This pathology is irreversible and progressive and there is no definite treatment.

Diagnosis

Diagnosis is often delayed due to nonspecific clinical features and is initially treated as asthma or

COPD. X-Ray chest PA view shows hyperinflation and may have reticular shadows or nodular shadows, bilaterally. This is often difficult to distinguish from COPD. HRCT thorax is more specific with features of air trapping, bilateral reticulo-nodular opacities and tree in bud shadows. These features favour small airway involvement in the form of respiratory bronchiolitis. Honey comb shadows are obviously absent. Spirometry in typical cases show features of small airway dysfunction in the form of reduced MMEF 25-75% with a normal FEV1 and FVC. Histopathological confirmation is needed for a firm diagnosis. Epidemiological studies involving estimation of diacetyl at coffee processing units and periodic surveillance of workers for early clinical signs are mandatory to prevent this rare occupational bronchiolitis obliterans.

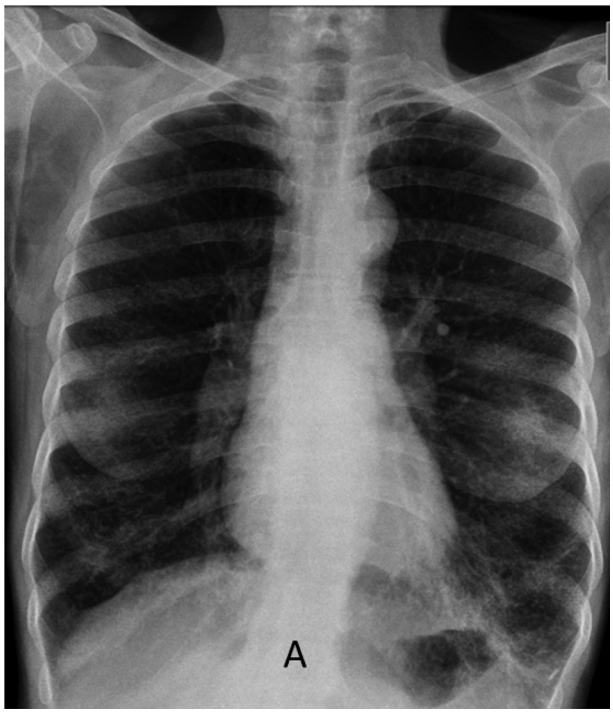

Fig 1 (A)

A 52 year old female, non smoker presenting with cough and progressive breathlessness for 10 years. She is being treated as asthma. She used to work in domestic small scale coffee processing unit where roasting, grinding and packing of coffee bean is done . Fig-1 (A) : X ray chest PA showing hyperinflation and fine reticulo-nodular shadows in the mid and lower zones. Fig-1 (B) HRCT Thorax showing reticular shadows, nodular shadows and air trapping. Tree in bud appearance is also seen.

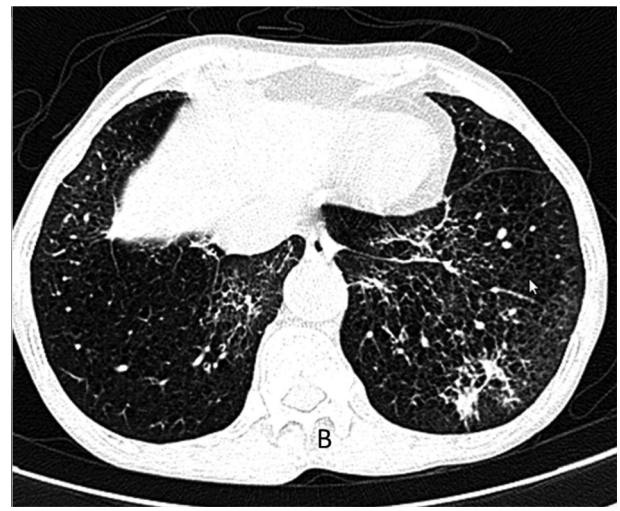

Fig 1 (B)

Parameter	Pred	LLN	Pre Best	%Pred	Post Best	%Pred
FVC [L]	2.72	2.12	2.43	89	2.59	95
FEV1 [L]	2.02	1.51	1.72	85	1.76	87
FEV1/FVC [%]	74.6	64.9	70.7	95	68.2	91
FEF25-75% [L/s]	1.91	0.71	1.11	58	1.01	53
PEF [L/s]	6.85	5.11	4.36*	64	6.23	91
FET [s]	-	-	5.6	-	6.0	-
FIVC [L]	2.72	2.12	2.68	98	2.96	109
PIF [L/s]	-	-	5.55	-	7.10	-

Caution: Poor session quality. Interpret with care
* Indicates below LLN or significant post change.

Fig 2 : Spirometry shows normal FEV1, FVC and FEV!/ FVC ratio. However the FEF25-75 is considerably reduced pointing to small airway disease

Management

Early clinical suspicion on the background of occupational exposure is important in the management. Surveillance of emission levels of diacetyl and removal from exposure are important measures to prevent progression to disabling disease. Mainstay of treatment is systemic corticosteroids and immuno-suppressants to control airway inflammation.

Summary

Occurrence of bronchiolitis obliterans in workers of coffee processing facility is reviewed here. Eventhough this entity is treated as either asthma or COPD due to its nonspecific clinical symptoms; it is a distinctive clinical syndrome with small airway dysfunction. Exposure to diacetyl during the process of roasting and grinding of coffee bean is considered as a possible cause for bronchiolitis obliterans. To establish a causative link further research is needed. Clinical and radiological features are similar to that of popcorn lung. Many cases treated as asthma or COPD may be suffering from bronchiolitis obliterans and a proper history of exposure may help in establishing the diagnosis.

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Original Article

Environmental Allergens in Idiopathic Interstitial Lung Disease: Role of Skin Prick Tests

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Abstract

Introduction : Idiopathic interstitial pneumonias (IIP) include a group of diseases where the cause is unknown and prognosis remains poor.

Aims & Objectives : a) To find the prevalence of increased absolute eosinophil count and increased IgE level in newly diagnosed cases of idiopathic interstitial lung diseases. b) To find the most common environmental agent responsible for hypersensitivity by Skin Prick Test (SPT) in those patients.

Methods : This is a cross sectional study done in our department, over a period of 18 months. Sixty-nine patients diagnosed with IIP by HRCT and histopathology were selected for study by consecutive sampling. The demographic patterns of these patients were described. Absolute eosinophil count (AEC) and IgE were evaluated in these patients. Skin prick tests were done in these patients with allergens including inhaled, food and mites. The method used was logistic regression and the results were expressed in proportion.

Results : In this study, 69 patients diagnosed with IIP belonged to the age group of 45- 55 years(mean age of 49.62 years) with a female dominance. IPF was the most common IIP identified (39.1%) closely followed by unclassifiable group (31.9%). Absolute eosinophil count was elevated in 8 patients (11.6%) and serum total IgE was elevated in 12 patients (17.4%). Out of the 18 patients with elevated IgE or AEC, 12 patients showed positivity to at least one allergen (66.67%). The most common allergen identified was grape and Lepidoglyphus destructor (storage mite) which were positive in 4 patients.

Conclusion : The prevalence of raised absolute eosinophil counts and IgE in IIP is comparable to that of normal population. But in patients with raised AEC or IgE, there is a high positivity to environmental allergens.

Keywords : Idiopathic interstitial pneumonia, environmental allergens, skin prick tests

Introduction

Interstitial lung diseases are a heterogeneous group of about 200 distinct disorders involving lung parenchyma leading to variable degrees of fibrosis. Previously thought to be a disease limited to lung interstitium, but now it is considered to be one that involves the interstitium and extending to the alveoli, hence the terminology "Diffuse parenchymal lung disease (DPLD)" is more appropriate. Lung is an organ which is continuously exposed to environmental agents and is susceptible to injury from air borne or blood borne causes. The injury can be acute like cryptogenic organizing pneumonia where lung function will return to normal or conditions like IPF that invariably progress over varying periods of time.[1]

The diagnosis of DPLD is a multidisciplinary approach including clinical, radiological and histopathological findings.[2]

Patients present with gradually progressive dyspnea, non-productive cough and exercise induced desaturation. As much as possible, an accurate diagnosis is to be made so that appropriate therapy can be given.[3]

Routine investigations include blood investigations, serological studies to identify the presence of a connective tissue disorder, radiology (both X ray and HRCT) to assess the pattern of lung disease. A histological diagnosis may become essential for accurate diagnosis and this can be achieved by trans bronchial lung biopsy or surgical lung biopsy.[3]

In this study we have tried to find the prevalence of sensitization to common environmental allergens in patients with idiopathic interstitial lung disease. The prevalence of increased eosinophil count and IgE is assessed to identify whether there is an underlying allergic pathology and to identify the allergen by means of skin prick tests.

Background

Epidemiology

There are limited studies regarding the incidence and prevalence of ILD. The pioneer study in ILD was conducted by Coultas et al from an ILD registry in New Mexico, USA[4]. The incidence and prevalence of ILD vary significantly from place to place. DPLD was regarded as a rare disease in India until Jindal et al in 1979 published data on cases of DPLD seen over 5 yrs[5]. In 2004, a series of 97 patients was published by Subhash et al and IPF was found to be the major disorder in 45% of patients[6]. One of the largest series in India was done by Senet al . In reported cases of 274 patients with histopathological diagnosis, IPF was found in 43 % patients[7].

Recently a study was conducted in India (March 2012- June 2015), hypersensitivity pneumonitis was found to be the most common new onset ILD followed by connective tissue ILD and IPF[8]. A similar study to identify the spectrum of ILD in a tertiary care center in northern India was done and sarcoidosis was identified as the most common(42.2%) followed by IPF (21.2%)[9].

Relevance

The incidence of interstitial lung disease is increasing in the recent years. There are many studies being done in this subject to identify the epidemiological pattern, pathogenesis and the response to treatment. Idiopathic interstitial pneumonias are a group of diseases where the exact pathogenic mechanism is less understood. Number of studies in these patients are lower compared to interstitial lung diseases of known etiology, especially in India. Due to lack of knowledge regarding the key mediator of interstitial fibrosis, the current treatment is not very effective in reducing the morbidity and mortality of the disease. Current recommendations include the use of antifibrotic agents like pirfenidone and nintedanib to prevent progression of fibrosis and worsening of lung function. These drugs act by inhibiting fibroblasts and their mediators. Where the pathogenic mechanism got deranged or what initiated the fibroblastic process is still unknown. In a large multicentric study in India, hypersensitivity pneumonitis was found to be the major ILD. Lung is one organ that bears the consequences of allergic reactions in the body.

In our study we tried to find out whether patients with IIP are sensitized to environmental allergens and to find the common allergen by SPT if sensitized. The evidence of sensitization is checked by

increased eosinophil count or elevated IgE values. Eosinophil is known to produce fibrosis of many organs. These patients might have had fibroblastic process triggered by mediators released by eosinophil or mast cell activation. If any such significant sensitization is identified, these patients may benefit from avoidance of the allergen along with antifibrotic agents. The possible benefit from anti IgE therapy or newer modalities like anti IL5 and IL5 R can also be studied in IIP.

Objectives

a. To find out the prevalence of increased absolute eosinophil count and increased IgE level in newly diagnosed cases of idiopathic interstitial lung diseases

b. To find out the most common environmental agent responsible for hypersensitivity by SPT in those patients

Methods

This is a cross sectional study done in the department of Respiratory Medicine, Amala Institute of Medical Sciences over a period of 18 months from June 2016 to Dec 2017.After getting approval from institutional ethical committee, 69 patients who came for treatment in our department, both as inpatient and outpatient, who were recently diagnosed with idiopathic interstitial pneumonia were included in the study.

Inclusion criteria

1. Age : 20 - 69 yrs
2. PFT restrictive pattern
3. HRCT features suggestive of ILD

Exclusion criteria

1. Patients in cardiac failure (assessed by ECHO).
2. Dermatitis / dermagraphism
3. Past history of hypersensitivity reactions

Sample size

Over a period of 18 months, a total of 69 patients with idiopathic interstitial lung disease were studied.

The aim of the study was to identify the role of skin prick tests in identifying sensitization to environmental allergens in patients with idiopathic interstitial pneumonia. The levels of peripheral blood eosinophils and IgE were also studied in those patients as a screening for allergen sensitization.

Procedure

Patients who presented to OPD with symptoms of progressive dyspnea and cough were evaluated by chest x ray and spirometry. If an interstitial pattern was seen on X ray, HRCT thorax was done in them. If HRCT patterns were suggestive of ILD they were evaluated by detailed history and physical examination to rule of connective tissue diseases and hypersensitivity pneumonitis. Immunological diseases were ruled out by relevant antibody work up. In patients where a definite diagnosis could not be made by HRCT, they were subjected to TBLB if patients were willing for the same and histopathological diagnosis was warranted.

In those patients who were diagnosed to have idiopathic interstitial pneumonia, previous history of allergic diseases, parasitic infections and atopy were ruled out by history. Cases were selected by consecutive sampling. After getting written informed consent, these patients were tested for total serum IgE and absolute eosinophil count. In patients with any of the above elevated underwent skin prick tests. An AEC > 400 cells/ mm3 and serum total IgE> 150 IU/ litre were considered as elevated.

Patients were seated in a chair with arms and forearms in supine position. Skin was cleaned with alcohol and allowed to dry. Negative control (saline) and positive control (histamine) were given first. Skin is pricked with lancet provided by the manufacturer. After 20 minutes, reaction is read to rule out dermagraphism. Allergens were then applied over the volar aspect of arm and forearm 3 cm apart and pricked with lancet. All precautions to deal with anaphylaxis were taken while performing test. Emergency ICU care if needed was also available nearby though none of our patients had

anaphylactic reaction during our study. Test results were read after 20 minutes of skin prick and were recorded. Maximum diameter of the wheal reaction was read. Any value more than 3 mm from the negative was taken as a positive reaction.

Results

There were 69 patients recruited to the study. The general characteristics of the patients is described in table 1.

		No.	Percentage
Age	20-29 yrs	1	1.45%
	30-39 yrs	3	4.35%
	40-49 yrs	18	26.09%
	50-59 yrs	29	42.03%
	60-69 yrs	18	26.09%
Sex	Male	24	34.78%
	Female	45	65.22%
Occupation	Unskilled	24	34.78%
	Skilled	10	14.49%
	Professional	5	7.25%
	Business	30	43.48%
Spirometry	Restrictive	44	64.71%
	Mixed	24	35.29%
Predominant lung zone	Upper zone	2	2.90%
	Lower zone	11	15.94%
	Upper and mid		
	zone	18	26.09%
	Mid and lower		
	zone	22	31.88%
	All zones	16	23.19%
Predominant pattern	Reticular	19	27.54%
	Nodular	2	2.90%
	Reticulonodular	10	14.49%
	Groundglass	20	28.99%
	Traction		
	bronchiectasis	1	1.45%
	Honey combing	17	24.64%

Table 1 : General characteristics of the patients

In 27 out of 69 patients, a definite diagnosis was made by HRCT as UIP pattern and hence 39.1 patients were diagnosed with IPF. 22 out of 69 patients (31.9%) were grouped into unclassifiable ILD. 26.1 % patients had NSIP pattern. 2 patients (2.9%) were diagnosed with cryptogenic organizing pneumonia. The proportions of various IIPs diagnosed in given in Table 2.

			95% CI	
	Number	Percent	Lower	Higher
Idiopathic Pulmonary Fibrosis	27	39.13%	27.60%	51.63%
Non-Specific Interstitial Pneumonia	18	26.09%	16.25%	38.06%
Cryptogenic Organizing Pneumonitis	2	2.90%	0.35%	10.08%
Unclassifiable	22	31.88%	21.17%	44.21%

Table 2 : Diagnosis of the IIP

Among 27 IPF patients, 19 were females and 8 were males. NSIP was also more common in females. COP was seen equally in both genders. Among males, the most common idiopathic ILD was unclassifiable.

8 patients among 69 (11.6 %) showed an increase in absolute eosinophil count and majority of patients (88.4%) had normal eosinophil values. None of the patients had a value more than 1000. 57 patients (82.6%) had a normal IgE value. 14.5 % cases showed an increased IgE value between 150 - 1000 and 2.9 % cases (2 out of 69) showed IgE value > 1000. Mean Absolute eosinophil count was 158.42 with standard deviation of 149.79 and Serum IgE was 105.58 IU/ ml (standard deviation 176.368).

		No.	Percentage
Absolute	<400	58	84.06%
Eosinophil			
count			
	400 to 1000	11	15.94%
IgE	<150	57	82.6%
	150 to 1000	10	14.5%
	>1000	2	2.9%

Table 3 : Investigation results

Skin Prick Test Results

Skin prick test was done for the 18 patients who had a elevated AEC or IgE. The pattern of positivity of various allergens is given in Table 4.

The overall results of the skin prick test as well as the allergens positive to each of the individual IIPs is given in Table 4.

	Positive			Diagnosis	
	Number	**%**	**IPF**	**NSIP**	**Unclassifiable**
Dermatophagoidsfarinae	3	16.7	1	2	-
Dermatophagoidapteronyssinus	3	16.7	1	2	-
Bermuda grass	1	5.6	-	-	1
Corn	0	0			
Timothy grass	0	0			
Mug wart	1	5.6	-	1	-
Peanut	0	0			
Banana	1	5.6	-	-	1
Pineapple	1	5.6	-	-	1
Orange	1	5.6	1	-	-
Egg yolk	0	0			
Hens egg	0	0			
Chicken	0	0			
Mussel	0	0			
Salmon	1	5.6	-	1	-
Cod	1	5.6	-	1	-
Wheat flour	0	0			
Shrimp	2	11.1	-	1	1
Cow epithelia	1	5.6	-	-	1
Rhizopusnigricans	0	0			
Penicilliumnotatum	0	0			
Cladosporiumherbarum	0	0			
Aspergillus fumigatus	0	0			
Alternaria tetanus	0	0			
Botrytis cinerea	0	0			
Rag weed	2	11.1	-	2	-
Lamb's quarter	1	5.6	-	-	1
Kentucky blue grass	0	0			
Walnut	2	11.1	-	1	1
Cow's milk	2	11.1	-	1	1
Potato	0	0			
Barley	0	0			
Lobster	1	5.6	-	-	1
Carp	1	5.6	-	1	-
Tuna	2	11.1	-	1	1
Cauliflower	3	16.7	-	3	-
Pea	0	0			
Spinach	0	0			
Rye grass	0	0			
Cat epithelia	1	5.6	1	-	-
Mutton	1	5.6	-	1	-
Grape	4	22.2	-	3	1
Acarussiro	2	11.1	1	1	-
Lepidoglyphus destructor	4	22.2	1	1	2
Tyrophagusputrescentiae	2	11.1	-	1	1
Beef	0	0			
Oats	0	0			

Table 4 : Results of Skin Prick Test

Skin prick test was done in 18 patients out of 69 who had an increased eosinophil count or IgE. Among 18 patients the most common allergen identified was grape and Lepidoglyphusdestructor (storage mite). 4 out of 18 patients showed a positive reaction to each of the above allergens (22.2%). 3 patients showed a positive reaction to cauliflower, Dermatophagoidsfarina and DermatophagoidaPteronyssinus, i.e. 16.7 % each. 2 patients (11.1%) had a positive reaction to shrimp, Tyrophagusputrescentiae, Acarussiro, walnut, cow's milk, tuna, rag weed.

Discussion

Idiopathic interstitial lung diseases include a variety of clinically, radiologically and pathologically different entities. The successful management of a patient depends on the exact diagnosis. Since the pathogenic mechanisms are not clearly outlined, the exact cause is not known in most of the cases. The treatment of ILD has not improved markedly even after the use of newer agents that inhibit fibroblast proliferation like pirfenidone and nintedanib. The aim of our study was to identify the role of skin prick test in identifying the sensitization to environmental allergens after screening for elevated eosinophil counts and IgE levels.

In the present study, 69 patients who were newly diagnosed with idiopathic interstitial lung disease were included. Among them, 45 patients (65.2%) were females and 24 patients were males (34.8%). A study done to identify the epidemiological pattern of ILD in Kerala has shown that 36 (51.4%) were females and34 (48.6%) were males.[11] In a multicentric study done in India recently, 501 out of 1087 patients were males (46.2%).[12] To identify the incidence and prevalence of ILD in greater Paris, a study was conducted and among the 848 patients studied, 428 were females (50.4%) and 417 were males (49.17%) were males.[13] Hence a female predisposition was identified in ILD patients at our centre comparable to Indian and international data.

In this study, patients aged 38-55 yrs were included. Age above 55 yrs were not included because SPT positivity decreases with age and wrinkling of skin may give false results. The mean age was 49.62 yrs. Maximum number of patients (60 patients, i.e.87 %) was in the age group of 45-55 years. In the above cited study from Kerala, the mean age was 52.4 years.[11] In a study done by Korean Interstitial Lung Disease research group,out of the total 1663 IPF patients, majority were more than 70 yrs of age (44.5%).[14] In a study from Ahmadabad , the age group with maximum number of ILD was 50-70 yrs[15]. Thus, the mean age of our study group was comparable with that of Kerala. Hence the demographic features suggest that the prevalence of idiopathic interstitial lung disease is more in females and in the age group of 45-55 years.

43.5% of our study group were unemployed. This may be either because of female predisposition and majority of females in our area are home makers. It may also be due to poor health that they stopped working. 34.8 % patients were unskilled workers, mostly manual laborers. In the study done by Palat P et al, 60% were house wife (15 out of 25)[15].

In our study, the predominant lung zone affected was mid and lower zones (39.1%) followed by upper and mid zones (26. 12%). The predominant pattern identified in our study was ground glass opacities (GGO) in 29 % cases followed by reticular shadows. In a study done by Gayathri et al, ground glassing was seen in 53.84 % cases and honeycombing was noted in 73 % cases[17]. In another study from India by Pankaj Badarkhe-Patil et al, reticular shadows were found to be the most common HRCT pattern (64%of cases).[18] A study from a tertiary care centre in Kerala, GGO was seen in 46% cases[11]. Since there is significant overlap between the patterns, an exact comparison cannot be made. Though 53.8 % patients in the study by Gayathri et al showed GGO, ours may be comparable to that. In our study only the predominant pattern in a patient was analyzed.

In this study the most common ILD identified is IPF, 27 out of 69 patients (39.1%) were diagnosed radiologically or by multidisciplinary approach. Recently, in a study from Kerala by Kumar et al, IPF was the most common ILD (34.14%)[19]. The prevalence of IPF was 76 % in a study done by Gayathri Devi et al[17]. Another study from India, by Pankaj Badarkhe-Patil et al showed that the most common ILD in their centre was IPF (36%) which is comparable to our study[18]. ILD registries in various parts of the world shows that IPF is the most common pattern. But very recently a multicentric study

from India, Singh et al has shown that hypersensitivity pneumonitis (47.3%) was the most common ILD. IPF contributed only 13.7%. These patients were exposed to air coolers (48. 1%). This finding cannot be generalized as majority of patients in our area do not use air coolers[12]. Hence the type of ILD in our study is comparable with studies from various parts of the world.

In 22 patients a definite diagnosis could not be obtained. This was partly because they were not willing for an invasive procedure like TBLB or SLB and partly biopsy was inconclusive in another set of patients who underwent biopsy. So we have put them into unclassifiable category. Hence they made a significant proportion (31.9%). In a resource scarce setting like India most of the cases are diagnosed based on clinical and radiological features. In the study done by Singh et al only 7.5 % of the 1084 patients actually underwent lung biopsy. Hence the number of patients who underwent histopathological examination was comparable to the Indian standards.

NSIP pattern was found in 26.1% cases. In the study by Gayathri et al 7 % patients had NSIP pattern[17]. In a study conducted in Greece by Karalatsani et al , the incidence of NSIP was 3.9 %(20). In a study from Paris by Boris Duchemann et al, the prevalence of NSIP was 13.7 %(38) as compared to 26.1 % in our study. Hence the prevalence of NSIP was higher in our study.

Cryptogenic organizing pneumonia was seen in 2 patients (2.9 %). This is comparable to a study where COP was seen in 4 % of patients[36]. The exact incidence and prevalence is unknown. A review of cases over a period of 20 yrs in Iceland showed the incidence was around 1.97 / 1,00,000 population[21].

In this study, IPF was seen more in females (70%). NSIP also showed a similar pattern, 83.3 %. Unclassifiable ILD was seen more in men as compared to females. In a study done by Singh et al, IPF was more in men (73.6%).[12] In a study by Kishaba et al (Japan), out of 54 IPF patients, 66 % were men. Hence in our study more number of females had IPF as compared to other studies.

In the study done by Singh et al NSIP was seen more in females (53.3%). In our study the diagnosis of NSIP was also much higher in females. The disparity may be because in the studies cited above, the number of males and females enrolled in the study were almost equal, but in our study, 70 % were females. This may be the reason for female predilection of IPF and NSIP in our study.

IPF was seen most commonly in the age group of 45-55 years. The peak incidence of IPF is after 50 years and slightly later in males[22,23]. Hence the observation in our study is comparable to studies in different countries. NSIP was also seen in the same age group. In the study by Singh et al , the mean age of NSIP was 55.6 years.[12]

Majority of our subjects showed a restrictive pattern (63.7%).In a study from India, out of 25 patients, all patients showed a restrictive pattern[15]. 24 patients in our study showed a mixed pattern. The history of smoking (active or passive) was not taken into account in our study. Most of the mixed pattern in spirometry was seen in unclassifiable and majority in this group were males. Smoke exposure may be a confounding factor in the analysis that is responsible for the mixed pattern obtained. Many of the patients could not perform acceptable spirometry due to cough, which may also be the reason why the data obtained in our study is not comparable with other studies.

Peripheral blood eosinophilia and serum IgE are considered as two parameters that indicate the level of allergic diseases in a patient. In an article by Anna Kovalszki et al, Absolute eosinophil count more than 450 microliter was considered significant[24]. Peripheral blood eosinophilia is considered as a minimally invasive marker of corticosteroid responsiveness in asthmatic patients. It was considered to be 71 % sensitive and 77 % specific[25] in asthma patients. In a study by J. Hosper's et at in Netherlands, peripheral blood eosinophilia (>275/ mm3) and a positive skin test were studied in patients with asthma and COPD. Eosinophilia was associated with an increased mortality independent of gender, smoking, age, FEV_1 %[26].

We evaluated the absolute eosinophil count in patients newly diagnosed with idiopathic interstitial lung disease. The role of eosinophils and its mediators in fibrosis of various organs have already been discussed. There are lot of researches ongoing in the pathogenesis of interstitial pneumonias especially IPF. But the

mediators like interleukins, TGF, MMP etc. cannot be measured in every patient.

In our study an increased absolute eosinophil count > 400 was seen in 11.6 % of patients. There are no studies to compare the level of eosinophilia studied in idiopathic interstitial pneumonia. In a study done by Rimpi Bansal et al in rural areas of Punjab over a period of one month, eosinophilia was seen in 10.7 % of the population. This included patients with all diseases who visited the hospital[27]. This is almost comparable with the eosinophilia in our study group. Comparing to that study, absolute eosinophil count is not significantly elevated in patients with idiopathic interstitial pneumonia.

It is found that about 1/5th of world's population suffered from some type of IgE mediated lung disease[28]. In our study, a value of IgE more than 150 IU/ml was considered as significant. Out of 69 patients, 12 patients had elevated IgE (17.4%). 14.5 % had IgE 150 -1000 IU/ml and 2.9 % had IgE> 1000.

The normal value of IgE varies in different populations. In a study by Rasheed et al from Saudi Arabia, a value more than 190 IU/ml was considered significant[29]. In a study conducted in Taiwan to identify reference value of IgE in Asian children, a value of 77 IU/ml provided the modest sensitivity and specificity. They concluded that even though the accuracy in diagnosing allergy is low, a low value rules out allergic disease.[30] We considered a value more than 150 IU/ml as significant. In a study by AnjaMediatyet al, there is a statistically significant reduction in IgE values as age advances.[31] In a study done in 1985 , the normal value of IgE in non-allergic people less than 17 yrs was done. No significant differences seen in male - female patients. They found that IgE levels > 100 IU/ml can be taken as a cut off limit.[32] Serum total IgE is highly nonspecific. Due to significant overlap between atopic and non atopic individuals, its diagnostic utility is low, yet can be used as a screening tool to rule out atopy.[10]

The mean IgE value obtained in our study was 105.58 IU/ml. In a study from India published in 2010 by Thirunavakkarasu et al, mean IgE in normal subjects was 151.95 IU/ml as high as 1045.32 IU/ml in asthmatics. In another study , the mean IgE of the population was 106.6 IU/ml as compared to 280.2 IU/ml in asthma patients[33]. A study to compare the IgE levels in idiopathic interstitial pneumonias was lacking. As observed from other studies in asthma and general population, in our study, an IgE level in patients with idiopathic interstitial pneumonias were comparable to that of general population and is not elevated like in asthma which is the typical allergic disease.

In our study all patients with elevated eosinophil counts and IgE underwent skin prick test with common environmental antigens. Forty seven antigenic preparations were used in our study including inhaled allergens, food, plants, fungal antigens and certain mites. It is said that in India in every 200 km, the aero allergen profile changes and antigens should be made after consulting with the local aerobiological studies[10]. Since this was not possible, we used internationally accepted antigenic preparations from MerckAllergopharma. Out of 47 antigens 25 antigens were positive in at least one patient. Grape and Lepidoglyphus destructor were the ones common, in 4 patients.

In our study, 18 patients who had either elevated eosinophil count or IgE underwent SPT. Among them, 12 patients showed a positive reaction to at least one antigen. This means, 12 patients out of 69 subjects (17.3 %) had at least a positive reaction in SPT. This is very low compared to a study from Kerala where 130 of 139 patients with asthma (93.5%) showed positivity to at least one allergen.

In IPF patients, 6 allergens were found to be positive. 17 allergens were positive in patients with NSIP. None of the allergen showed positivity in COP patients. 13 antigens were positive in the unclassifiable group.

In a study done by Mishra et al, most common allergen in united airway disease was found to be dust mite (21.66%). In our study, out of 18 patients who underwent SPT dust mites (Dermatophagoids farina and Dermatophagoida Pteronyssinus were positive in 33.3 % of cases. In another study from central Kerala, house dust mite was positive in 23% of cases.[34] In the same study, the most common food allergen identified was prawn followed by potato. In our study, the most common food allergen identified was grape (22.2%) cases.

In another study the prevalent allergen was

studied in Asian and European population. Dust mites were identified as the most prevalent allergen.The prevalence was more common in Asian population[35]. In a study published in chest 2002, the prevalence of positive SPT was 54 % in patients who attended orthopedics department[35]. In UK , the prevalence of a positive SPT to at least one antigen was seen in 15-40 % of normal individuals [35, 36, 37].

The positive finding if considered in the whole study population, 17.39% patients showed a positive reaction which is comparable to SPT positivity in general population. But among 18 patients who had IgE or eosinophil count elevated, 12 patients (66.67%) showed a positive reaction. Similar studies are lacking in literature.

Conclusion

In our study, IPF was found to be the most prevalent idiopathic interstitial pneumonia which is comparable to studies from other parts of the world. A female dominance was seen in our study. The most common age groups found in our study were also similar to the epidemiological patterns seen in India and internationally. Since a histopathological diagnosis was not obtained in many patients, unclassified idiopathic interstitial pneumonia constituted a large group. The prevalence of increased eosinophil count was not as high as in other allergic diseases and was almost comparable to that of the general population. Similarly, no marked elevation of serum immunoglobulin E was noted when compared to the general population. The prevalence of a positive skin prick test varies in different geographic regions and that obtained in our study subjects were almost similar to that of healthy subjects. In IIP patients with elevated IgE and AEC, 66.67 % showed a positive reaction to at least one antigen. The most common allergen identified was grape and Lepidoglyphus destructor (storage mite). In those patients with elevated IgE and AEC, SPT seems to be logical to get rid of exposure to positive antigens though it is not proved that the positive antigen has caused the disease which is a limitation of our study.

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Original Article

Expiratory Central Airway Collapse, a Retrospective Descriptive Study in a Tertiary Health Care Centre

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Abstract

Background

Expiratory Central Airway Collapse(ECAC) is a syndrome comprising of 2 different pathophysiological entities-Tracheobronchomalacia(TBM) and Excessive Dynamic Airway Collapse(EDAC) where former have weakness of cartilage and latter have laxity of posterior tracheal membrane. Bronchoscopy is the gold standard in diagnosis but dynamic CT Chest have equal sensitivity.

The aim of the study was to assess the clinical profile of patients diagnosed as ECAC in a tertiary care centre.

Method

A descriptive study was carried out in 22 patients who were diagnosed as ECAC during the period 2016-2018. A detailed clinical history was taken. Dynamic CT Chest, Bronchoscopy and Spirometry findings were taken into account.

Results

ECAC was found to be slightly more common in males (54.5%).TBM (72.7%) was found to be more common compared to EDAC (27.3%).The mean age of diagnosis was found to be 65.91 years. Cough was the predominant symptom and was present in 90.9% patients with ECAC. 16(72.7%) patients were diagnosed cases of obstructive lung disease but having uncontrolled symptoms.

Conclusion

ECAC which is by far an unrecognised entity must be considered as a differential diagnosis in uncontrolled asthmatics and COPD patients especially when they present with severe intractable cough not responding to higher permissible inhalational medications. CPAP should be the first way of management before going for surgical procedure.

Keywords: ECAC, Cough, Bronchoscopy, CPAP

Abbrevations: CT-Computerised Tomography, CPAP- Continuous Positive Airway Pressure

Introduction

Expiratory Central Airway Collapse (ECAC) is a syndrome comprising of 2 different patho physiological entities - Tracheobronchomalacia (TBM) and Excessive Dynamic Airway Collapse (EDAC). EDAC is found in 22% of patients with obstructive lung disease.[1]

Weakness of cartilage is seen in TBM whereas laxity of posterior tracheal membrane is seen in EDAC. Weakness of anterior wall of cartilage produce crescent-shaped TBM, where as weakness of lateral wall produce Saber-sheath TBM. In EDAC, Antero-Posterior diameter will be decreased by >50%.[1]

Symptoms include brassy cough, dyspnoea and recurrent respiratory infections. Wheeze resistant to corticosteroids and bronchodilators is also seen. Bronchoscopy is the gold standard in diagnosis but dynamic Computerised Tomography (CT) Chest is equally sensitive for diagnosis.[2,3]

ECAC may be the cause of some of the cases presenting as cough but misdiagnosed as asthma or Chronic Obstructive Lung Diseases (COPD). Those not responding to conventional treatment must be evaluated for ECAC also.

Keywords

ECAC, EDAC, TBM, CT Chest, Bronchoscopy.

Aim and Objective

To assess the clinical profile of patients diagnosed as ECAC in a tertiary care centre.

Material and Methods

A retrospective descriptive study was carried out in both in-patients as well as outpatients in the department of Respiratory Diseases, Kerala Institute of Medical Sciences, Trivandrum, Kerala during the period, July 2016 to June 2018 who were subsequently diagnosed as ECAC. Their clinical History was noted. Spirometry based on American Thoracic Society/ European Respiratory Society (ATS/ERS) guidelines was reviewed. 64-slice 1.1mm thickness multidetector High Resolution Computerised Tomography (HRCT) chest scans were reviewed by qualified radiologist to classify ECAC. Flexible fibreoptic Bronchoscopy was performed in those cases where CT chest was inconclusive but ECAC was still suspected.

Results

In our study, 12 (54.5%) patients were males and 10 (45.5%) were females and the Mean age of diagnosis of ECAC was 65.91 years with a Standard Deviation (SD) of 11.65. Mean age of diagnosis of TBM was 64.6 years and EDAC was 69.3 years.

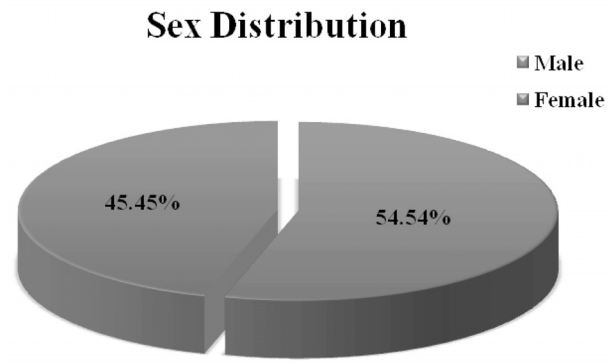

Fig 1 :

A total of 22 cases diagnosed as ECAC during this period was analyzed, out of this 16(72.7%) patients had TBM and 6 (27.3%) had EDAC. (Fig. 1, Fig. 2, Fig. 3, Fig. 4)

All 6 cases of EDAC was noted in diagnosed cases of asthmatics and out of which 3 were males and 3 were females.

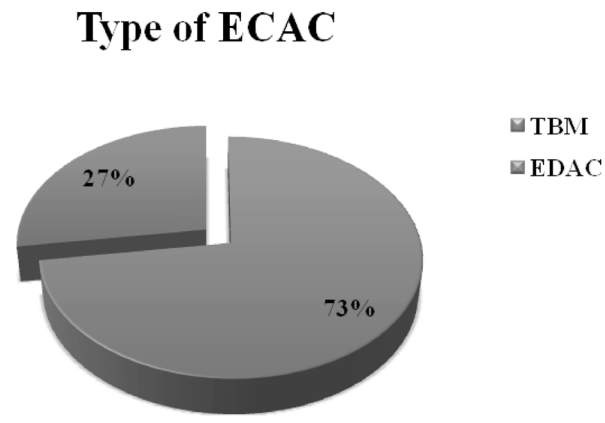

Fig 2 :

13 patients (59.1%) had persistent cough as the main symptom, 7 (31.8%) had cough along with dyspnoea as the main symptom and 2 patients (9.1%) had persistent dyspnoea only as their main symptom in spite of using maximum dose of inhaled medications.

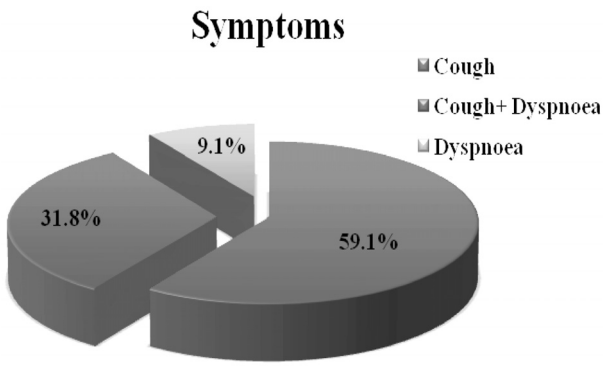

Fig 3 :

14 (63.6%) patients were non-smokers and 8 (36.4%) patients were Smokers. 6(75%) out of 8 smokers had TBM.

11(50%) patients were diagnosed cases of asthma, 5(22.7%) patients were diagnosed cases of COPD but symptoms persisted in spite of giving maximum permissible dose of inhaled medications.. All asthmatics and COPD patients satisfied the ATS/ ERS standards.

4 (18.2%) patients had normal spirometry and were being treated as cough variant asthma but symptoms persisted in spite of giving maximum permissible dose of inhaled medications and later turned out to be ECAC, precisely TBM. 2(9.1%) patients were managed as Laryngopharyngeal Reflux Disease (LPRD) but later turned out to be ECAC. 2 (9.1%) patients were admitted and intubated for various other conditions but latter presented with persistent cough, spirometry showed obstruction with no reversibility, but didn't improve with aggressive management later CT chest revealed ECAC, probably acquired ECAC due to instrumentation.

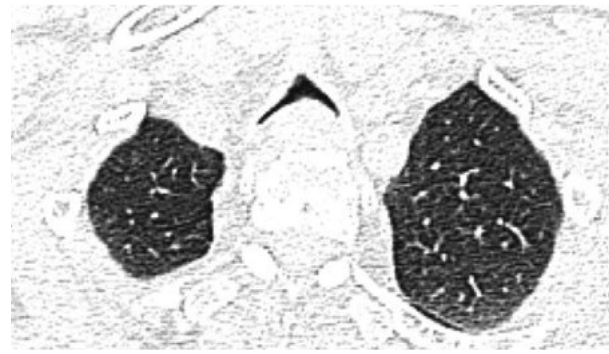

Fig. 4 : Ct thorax showing expiratory collapse of trachea

The mean exacerbation rate of these patients in the previous year was 2.89 with a SD of 2.03. 12(54.5%) patients had Diabetes Mellitus (DM) as well as Hypertension (HTN) as their co-morbid illness.

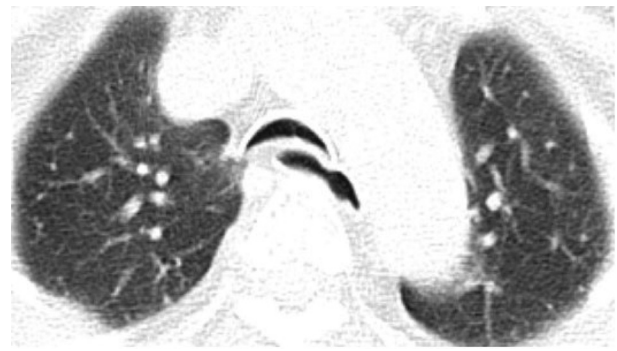

Fig 5 :

14 (18.2%) patients had normal CT chest but bronchoscopy revealed ECAC.

All 22 patients were tried on Continuous Positive Airway Pressure (CPAP) which reduced their symptoms as well as use of inhalers.

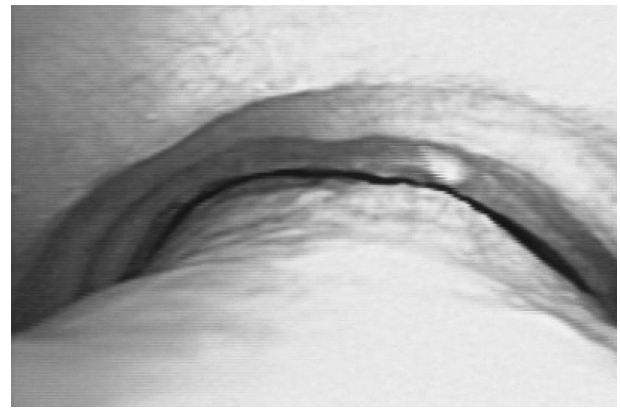

Fig. 6 : Expiratory tracheal collapse during bronchoscopy

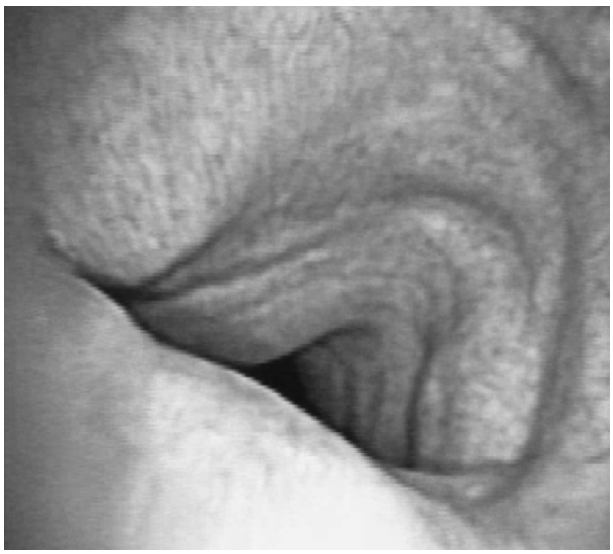

Fig. 7 :

Discussion

In our study ECAC was found to be slightly more common in males (54.5%).TBM (72.7%) was found to be more common compared to EDAC (27.3%).The mean age of diagnosis was found to be 65.91 years. Age of presentation of TBM (64.6 years) was found to be slightly earlier compared to EDAC (69.3years). Cough was the predominant symptom and was present in 90.9% patients with ECAC.

Non smokers (63.6%) were more compared to smokers in our study. 6(75%) out of 8 smokers had TBM. 5(22.7%) COPD patients were there in our study and all 5 were found to have TBM. According to a study by McHenry et al. TBM is more common in COPD having a smoking history This result is in concordance with our result.[4]

11(50%) asthmatics were there in our study. 6(54.5%) patients out of this had EDAC even though all cases of EDAC was seen only in asthmatics. According to Dal Negro et al. EDAC is more common in asthmatics and in females.[5] In our study even though EDAC was seen only in asthmatics, both males and females were equally found to have EDAC.

4(18.2%) cases were misdiagnosed and treated as cough variant asthma but later found out to be TBM.

2(9.1%) patients were found to have TBM following post mechanical ventilation. Similar cases have been reported by Kandaswamy et al.[6]

Bronchoscopy is the gold standard in diagnosis of ECAC which is clearly evident from the fact that 4 patients who had a normal dynamic CT chest later proved to have ECAC after performing bronchoscopy. According to Carden et al. and Masters et al. bronchoscopy is the gold standard in the diagnosis of ECAC. [2,3]

All the patients who were diagnosed to have ECAC were started on CPAP therapy with which they showed significant improvement in their symptoms and we were able to reduce the dose of their inhaled medications. According to Kandaswamy et al. and kalra et al. CPAP should be used as the initial treatment modality in ECAC.[7,8]

During expiration airway is prevented from collapsing by the tone of the smooth muscles but in chronic respiratory diseases, expiration becomes an active process to overcome the loss of elasticity of the airways. Thus as the air flow advances through the obstructed airways pressure of the airways decreases (Bernoulli effect) which generates a transmural pressure gradient that results in EDAC.[1]

FEMOS [Functional class (F), Extent (E), Morphology (M), Origin (O), and Severity of Airway collapse (S)]: It is the classification system used to monitor the progression of disease as well as treatment outcome.[9]

Current treatment guidelines include treating underlying cause and use of CPAP. If it fails, Stenting with silicone airway stents is an option, but persistent symptoms is an indication for tracheobronchoplasty. Surgical central airway stabilization with posterior tracheobronchial splinting using a polypropylene mesh improves respiratory symptoms, health-related quality of life, and functional status in highly selected patients with severe symptomatic TBM.[10,11,12,13,14]

Conclusion

ECAC must be considered as a differential diagnosis in uncontrolled asthmatics and COPD patients especially when they present with severe intractable

cough not responding to higher permissible inhalational medications. All such patients must be subjected to Dynamic CT chest and if inconclusive they must undergo a bronchoscopy. CPAP should be the initial treatment modality and if not getting controlled, surgical interventions must be thought of.

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Radiology Pearl

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History and presentation

A 57 year old lady was referred to pulmonary medicine OPD for preoperative pulmonary evaluation. Her history was remarkable for long standing systemic hypertension, type 2 diabetes mellitus and stage 5 chronic kidney disease. She was on intermittent haemodialysis (twice weekly) for 2 years now via a left radial arteriovenous fistula. Altruistic donor renal transplantation was being contemplated. She had no other major respiratory symptoms. A chest radiograph PA view done as part of preoperative work up is depicted below. What are the possibilities and how should she be worked up?

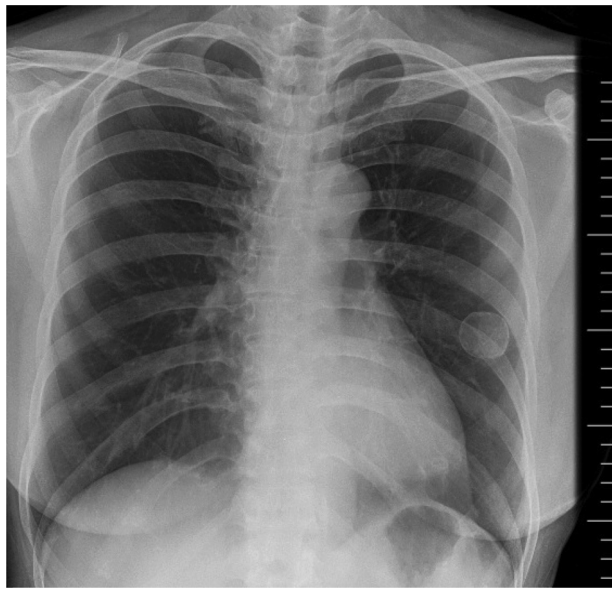

Fig 1 : Chest x ray PA View

Clinical Evaluation and Further work up

Chest x ray showed a well circumscribed rounded lesion left lower zone. This lesion showed heterogeneous calcification with peripheral predominance. It tends to partially obscure by overlying the anterior edge of 5th rib which gives a suspicion of chest wall origin of lesion. Left breast examination revealed a hard nodular lesion. Retrospectively, she gave a history of trauma to her left breast 15 years back. A mammogram was requested, which revealed features of calcified traumatic fat necrosis.

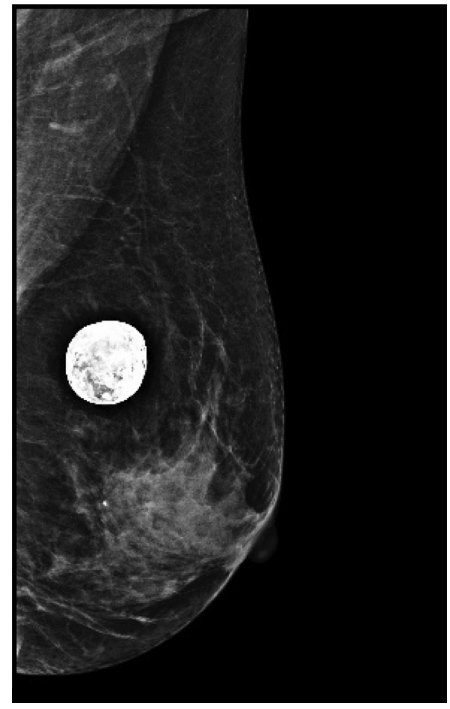

Fig 2 : Mammogram image

Final diagnosis

Calcified breast nodule secondary to fat necrosis.

Discussion

The first step in evaluation of a solitary nodule imaged in a postero anterior chest radiograph is to confirm the intrapulmonary location of the lesion. Due to the 2 dimensional nature of the imaging, lesions of skin and subcutaneous tissue, breast, pleura etc can have opacities in posteroanterior chest radiograph mimicking an intraparenchymal lesion. Physical examination (inspection and palpation of chest), chest radiograph lateral view etc aid in this differentiation. The importance of lateral view chest radiograph in confirming the intraparenchymal location of the radio-opacity cannot be overemphasized in such cases.In the given subject, left breast examination clinched the intramammary location of the lesion and further imaging with mammography established the diagnosis.

Calcified lesions are not uncommon in breast. Although majority of the calcified breast nodules are benign akin to their pulmonary counterparts, a small minority of malignant breast lesions show calcification[1]. Breast cysts, fibro adenoma, infections, fat necrosis secondary to trauma or any surgery etc are common differentials. Carcinoma breast, ductal, cutaneous or vascular calcification are less common, but occasionally encountered aetiologies. Rarely ointments, creams and deodorants applied on chest wall can cause radio opacity in chest x ray.[2]

The pattern of calcifications is the most important factor in the differentiation between benign and malignant breast lesions[3]. Benign patterns of calcification include rod like, popcorn, egg shell, and punctate calcifications. Amorphous, coarse heterogeneous, pleomorphic, linear branching calcifications are indeterminate and often have a potential for malignancy; lesions having these calcification patterns should be biopsied. The change in size of lesion over time is an important factor and lesion growth from any previously available images should be assessed.

Fat necrosis can have variable appearances in mammogram.[4] The lesions can be seen as lipid cysts, focal asymmetries, or spiculated masses. Calcifications are frequent and micro calcifications are common with coarse calcifications being less frequent. The chronicity of the lesion and the exuberance of fibrous response determine the mammographic features. If minimal fibrosis occurs, the mass appears as a radiolucent mass or as an oil cyst. These lipoid lesions have a predictable radiographic course,with linear and curvilinear calcifications developing early and central calcifications visualized later[5]. Sometimes fully calcified lesions are the only mammographic finding of traumatic fat necrosis, as occurs in our case. Calcifications related to fat necrosis are usually smooth and round or curvilinear. However, fat necrosis calcifications with indeterminate patterns like branching, rod like, or angular calcifications have been described. Atypical features include oil cysts with fat-fluid levels or serous-haemorrhagic contents and oil cysts containing spherical densities that may represent fibrin balls.[6]

In this patient the mammogram was highly suggestive of calcified traumatic fat necrosis and combined with the trauma history the diagnosis was settled. A previously available chest radiograph image 5 years back confirmed lesion stability. Hence she was kept under clinico-radiological follow up.

Learning Points

1. Any nodule seen in the posteroanterior chest radiograph needs to be confirmed with regard to its intrapulmonary location or otherwise with clinical examination and limited ancillary tests

2. The differential diagnosis of calcified thoracic / chest wall nodules is wide, but as a general rule specific patterns of calcification suggest benign aetiologies

3. Traumatic fat necrosis can have variable mammographic and sonographic appearances

4. Lesion stability over a reasonable length of time has therapeutic implications and justifies a wait and watch approach

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Radiology Quiz

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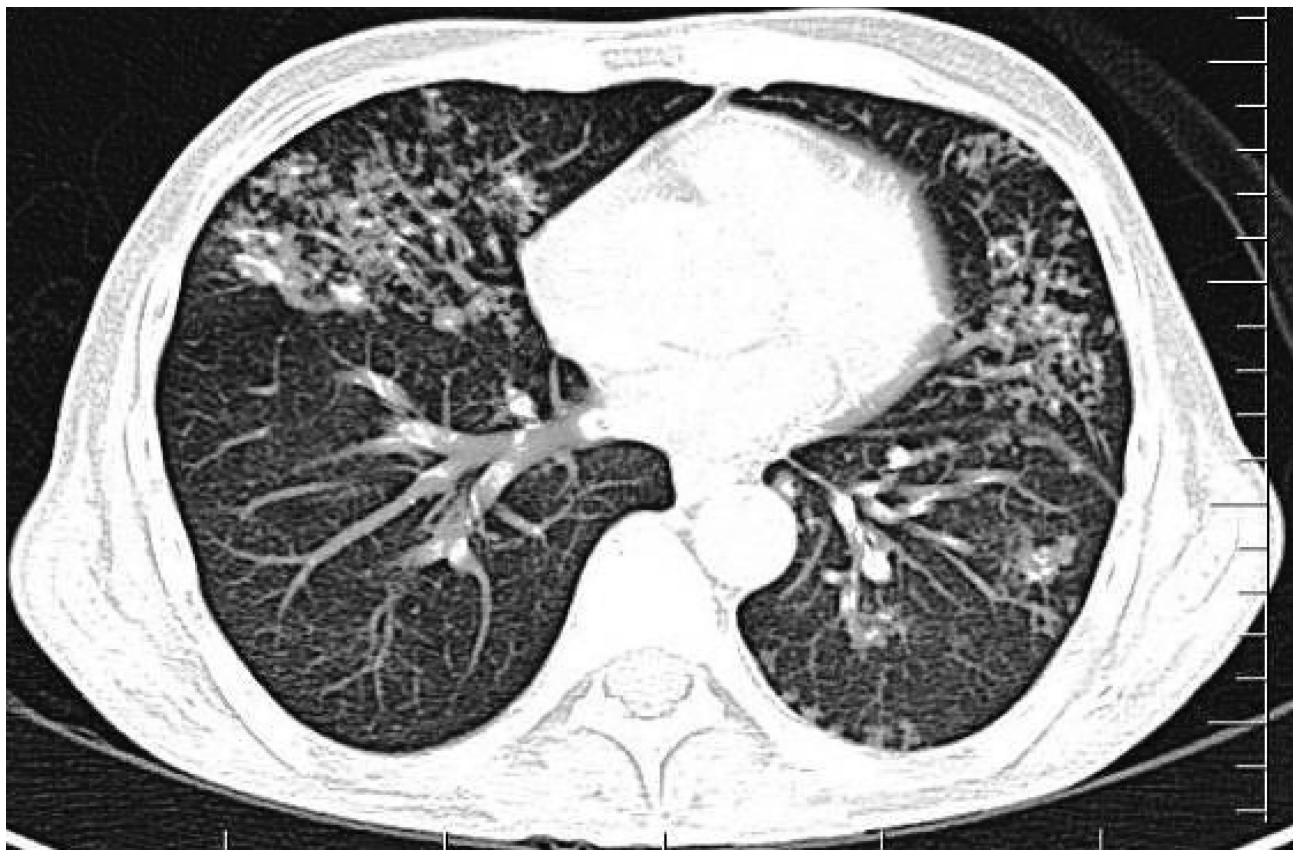

Question 1

What is the radiological sign in this image?

1. Bronchiectasis
2. Pulmonary tuberculosis
3. Viral pneumonia
4. Allergic bronchopulmonary mycosis (ABPM)

Question 2

Tree in bud appearance was initially described in which of the following condition?

5. Sarcoidosis

Ans. 1

Tree in bud appearance.

Ans. 2

Pulmonary tuberculosis

The "tree-in-bud" (TIB) pattern is a high resolution CT scan is characterized by small centrilobular nodules of soft-tissue attenuation connected to multiple branching linear structures of similar caliber originating from a single stalk[1]. This was initially described in cases of endobronchial spread of Mycobacterium tuber culosis.

Tree-in-bud appearance represents endo bronchial spread of infection[1]. It indicates dilatation of bronchioles and filling of bronchioles with mucus, pus, or fluid. Thus the bronchioles resemble a branching or budding tree and are usually somewhat nodular in appearance[1, 2].

Causes for tree in bud appearance:

Infective Bronchiolitis

- Pulmonary tuberculosis
- Atypical Mycobacterial infections
- Viral pneumonia
- Fungal pneumonia
- Allergic bronchopulmonary aspergillosis (ABPA)
- Pneumocystis pneumonia
- Aspiration pneumonia

Congenital

- Cystic fibrosis
- Immotile cilia syndrome
- Yellow nail syndrome

Connective tissue disorders

- Rheumatoid arthritis
- Sjögren's syndrome

Bronchial diseases

- Obliterative (constrictive) Bronchiolitis
- Diffuse panbronchiolitis
- Follicular Bronchiolitis

Neoplastic (i.e. carcinomatous endarteritis or Broncho vascular interstitial infiltration)

- Bronchioloalveolar cell carcinoma
- Distant metastatic disease (e.g. breast, liver, ovary, prostate, kidney)
- Primary pulmonary lymphoma
- Chronic lymphocytic leukemia
- Tumor emboli to centrilobular arteries (or carcinomatous endarteritis)

e.g. from breast cancer, stomach cancer

- Bronchovascular interstitial infiltration

e.g. Sarcoidosis, lymphoma, leukemia

TIB opacities are most often a manifestation of infections or aspiration. Patterns of disease can provide clues to the most likely diagnosis[5]. Consolidation and bronchopneumonia pattern with TIB is usually due to bacterial infection or aspiration. Predominant lower lobe distribution and esophageal abnormality with TIB opacities is associated with aspiration. Chronicity of findings with fibrosis, cavitation with TIB is associated with mycobacterial infection. Acuteness of findings is associated with bacterial infection.

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Case Report

All those Miliary Shadows in Diabetic Gentlemen are not Tuberculosis !

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Abstract

Miliary mottling in a chest radiograph is encountered in a variety of conditions, although miliary tuberculosis ranks high among the differentials in an appropriate clinical setting. We share the case of a 67 year old diabetic gentleman who presented with persistent cough, loss of appetite and loss of weight who had miliary mottling in chest radiograph. Tubercular etiology was high in the consideration, but blood investigations showed leucocytosis with eosinophilia and high Ig E levels. Transbronchial lung biopsy revealed eosinophilic tissue infiltration and serology for microfilarial antibodies returned positive in high titres. His symptoms, blood eosinophilia and pulmonary lesions responded to antifilarial chemotherapy. The radiological manifestations of tropical pulmonary eosinophilia are briefly reviewed.

Key words

Tropical pulmonary eosinophilia, miliary lesions, reticular shadows, diethyl carbamazine

Radiograph is almost always the time honoured first investigation requested in subjects with symptoms and signs of pulmonary disease, this modality often being the most yielding as well as cost effective one. Miliary shadows in chest radiology refer to bilateral, usually symmetric diffuse micro nodular opacities. Of the various radiographic patterns encountered in pulmonary tuberculosis, miliary mottling is one that has grave implications since it suggests advanced disease with hematogenous spread and needs to be diagnosed and treated promptly. The causes of miliary pattern on chest radiographs are many and require careful clinical, radiological and laboratory correlation.

India being a tuberculosis–endemic country, miliary shadows in chest imaging is often attributed to tuberculosis without further etiological confirmation.[1] Patients are started on empirical anti tubercular therapy (ATT) with alternative diagnoses being considered only in the absence of therapeutic response. While this

approach will prove correct in majority of cases, failure occurs in a significant fraction. Our case illustrates an important, although less commonly encountered cause of miliary mottling on chest radiograph which was diagnosed with simple tests. Specific management was instituted with good clinical response.

Case Summary

A 67 year old gentleman, reformed smoker and a known case of type 2 diabetes mellitus for the last 18 years with poor glycemic control, presented to the pulmonary OPD with complaints of persistent cough,shortness of breath, loss of appetite and loss of weight for past 3 months. He had no allergic background or asthma. He denied history of fever or expectoration. Extra pulmonary symptoms were conspicuously absent.He was a reformed smoker with a smoking history of 85 pack years. He had no cardiac disease or renal disease. He was not dyspnoeic on examination. On auscultation, bilateral crackles were heard in lung bases and neck was supple. Cardiovascular, gastro intestinal and central nervous system examinations were unremarkable. Pulse oximetry revealed a saturation of 94% on room air. Chest radiograph revealed bilateral miliary shadows Fig. 1. A possibility of miliary tuberculosis was contemplated considering his uncontrolled diabetic status, subacute symptoms, weight loss and characteristic radiology. Given the age and smoking status, an occult malignancy with haematogenous lung metastasis was also considered.

His complete hemogram revealed a total count of 15,000 / mm3 and differential count showed 57% eosinophils. Serum IgE level was 2570 IU / ml. Urinalysis revealed proteinuria and glycosuria. A serum Creatinine of 1.8 mg / dl was noted. Liver functions and lipid profile was normal. CT thorax confirmed the radiograph findings. Bilateral uniform micro nodules with random distribution were seen. (Fig 2) No pleural, endobronchial or mediastinal lesions were seen. Ultrasonography of the abdomen showed features of early diabetic nephropathy with no hepatosplenomegaly. An adequate sputum specimen for AFB testing was not obtained despite sputum induction. A fibreoptic bronchoscopy was performed which revealed an unremarkable bronchial tree. BAL was sent for mycobacterial, bacterial and fungal tests. BAL fluid revealed 40% eosinophilia. Transbronchial biopsy was sent for histopathology which revealed intense interstitial eosinophilic infiltration. (Fig 3) All BAL microbial tests returned unrewarding. Serology for antifilarial antibodies showed positivity in high titres. A diagnosis of tropical pulmonary eosinophilia was reached upon and he was initiated on diethyl carbamazine in prescribed doses. After 3 weeks of therapy, his symptoms as well as peripheral blood eosinophilia resolved. Chest radiograph exhibited marked resolution of infiltrates. (Fig 4) He remains under follow up.

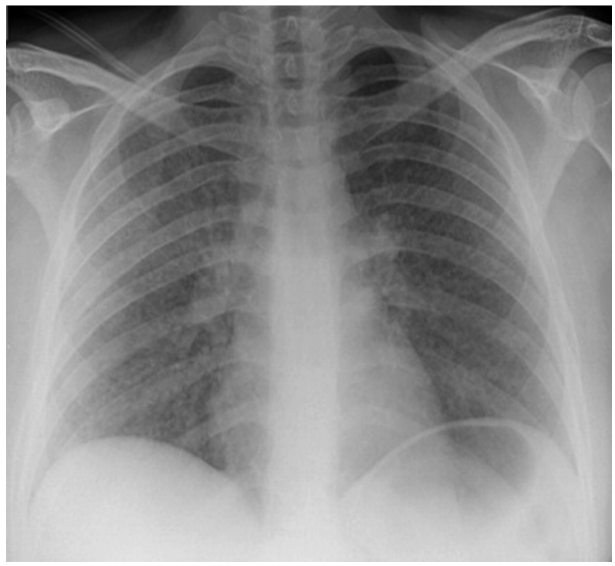

Fig. 1 : Chest radiograph at Presentation showing miliary mottling

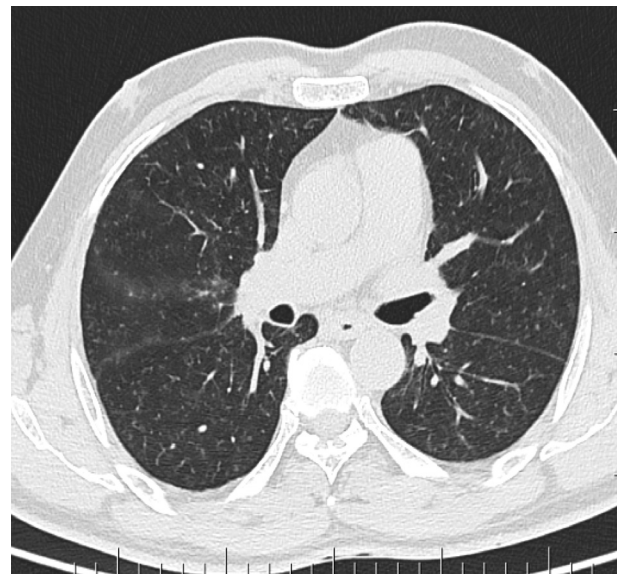

Fig. 2 : CT chest at presentation showing randomly distributed micro nodules

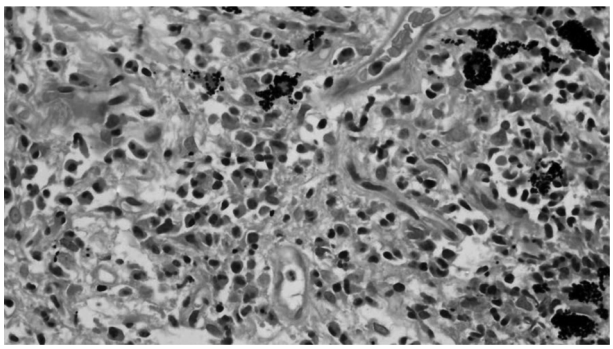

Fig. 3 : H&E staining of Transbronchial lung biopsy specimen showing intense interstitial eosinophilic infiltration

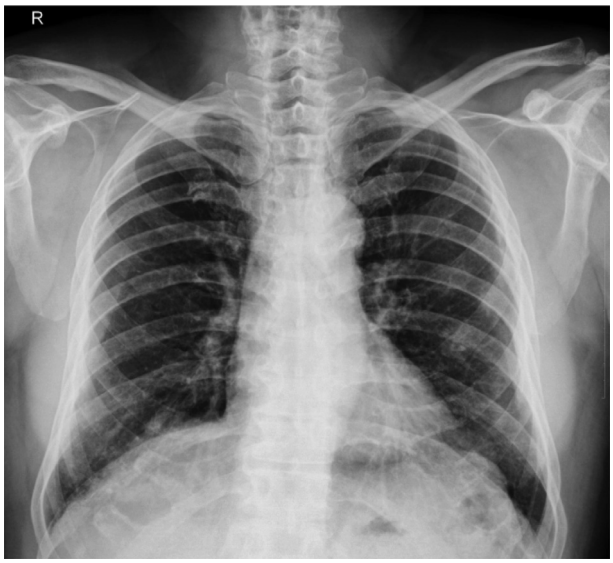

Fig. 4 : Chest radiograph after antihelminthic therapy showing marked resolution of lesions

Discussion

Miliary lesions refer to innumerable, small 1-4 mm pulmonary micro nodules scattered throughout the lungs.The nodules have a random distribution within the secondary pulmonary lobule. The common causes of miliary mottling in a chest radiograph are summarised in table 1. Since the list of differential diagnosis is long, careful attention needs to be given to correlate the clinical presentation, relevant laboratory tests and histopathology of lung biopsy specimen in selected cases.

Infections	Tuberculosis (TB) Histoplasmosis, Mycoplasma infection Nocardiosis Blastomycosis
Metastasis	Bronchoalveolar carcinoma, Hematogenous metastases from carcinoma of thyroid, kidney, breast, malignant melanoma Lymphagitis carcinomatosa
Immune and inflammatory	Sarcoidosis Hypersensitivity pneumonitis Silicosis Pulmonary siderosis Tropical pulmonary eosinophilia
Rare causes	Allergic bronchopulmonary aspergillosis (ABPA) Pulmonary alveolar microlithiasis Leiomyoma

Table 1 : Common causes of miliary nodules

Pulmonary infiltrates with eosinophilia is a broad diagnostic qualifier encompassing a variety of infectious, inflammatory, and allergic etiologies [2]. The differential diagnosis of eosinophilic lung disease includes Loeffler syndrome (secondary to helminth infection), drug reaction; allergic bronchopulmonary aspergillosis; chronic eosinophilic pneumonia; vasculitis, such as Churg-Strauss syndrome, and idiopathic hypereosinophilic syndrome[2]. (Table 2) Tropical pulmonary eosinophilia (TPE) is prevalent in filarial endemic regions of the world especially India, South-East Asia, and Africa. It is characterized by cough, dyspnea, and nocturnal wheezing with diffuse reticulonodular infiltrates in chest radiographs and marked peripheral blood eosinophilia[3]. It is caused by immunologic hyper-responsiveness to the human filarial parasites, Wuchereria bancrofti and Brugia malayi. TPE is endemic in areas with filarial endemicity. In India, it is mostly found around the coastal regions from Maharashtra to Kerala and West Bengal to Tamil Nadu[4].

Eosinophilic Lung Disease of undetermined cause	Idiopathic eosinophilic pneumonias Idiopathic chronic eosinophilic pneumonia (ICEP) Idiopathic acute eosinophilic pneumonia (IAEP) Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) Hypereosinophilic syndrome (HES) Idiopathic hyper eosinophilic obliterative bronchiolitis
Eosinophilic Lung Disease of determined cause	Eosinophilic pneumonias of parasitic origin Tropical eosinophilia Ascaris pneumonia Eosinophilic pneumonia in larva migrans syndrome Strongyloides stercoralis infection Eosinophilic pneumonias in other parasitic infections Eosinophilic pneumonias of other infectious causes Allergic bronchopulmonary aspergillosis and related syndromes Allergic bronchopulmonary aspergillosis Other allergic bronchopulmonary syndromes associated with fungi or yeasts Bronchocentric granulomatosis Drug-, toxic agent–, and radiation-induced eosinophilic pneumonias Drugs (typical, occasional, or exceptional eosinophilic pneumonia) Toxic agents (toxic oil syndrome, L-tryptophan) Eosinophilic pneumonia induced by radiation therapy to the breast
Miscellaneous Lung Diseases with Possible Associated Eosinophilia	Organizing pneumonia Asthma and eosinophilic bronchitis Idiopathic interstitial pneumonias Langerhans cell histiocytosis Lung transplantation

Table 2 : Classification of Eosinophilic Lung Disease

Chest radiograph findings can be subtle and a normal Xray can be seen in upto 20% cases of TPE. The usual radiological features include reticulo-nodular shadows more in the mid to lower zones and miliary mottling[5, 6]. Computerized tomography (CT)scan often reveals bronchiectasis, air trapping,lymphadenopathy, cavitation, consolidation or pleural effusions in addition to the miliary mottling and interstitial shadows [7].

The antifilarial agent diethylcarbamazine (6 mg/kg/day for 21 days)[8] remains the main therapeutic agent for TPE. DEC is active against both the microfilariae and adult worms. Corticosteroid therapy has been used as adjunctive therapy to reduce inflammation in the acute setting [9]. Bronchospasm can generally be managed with bronchodilators, with short-term systemic corticosteroids needed in severe cases.Relapses occur in up to 20 percent of patients [10].

The index of suspicion for miliary tuberculosis was high in our case considering the uncontrolled glycemic status, significant weight loss, subacute symptoms and miliary shadows. The peripheral blood eosinophilia gave a clue that the shadows may be manifestation of a pulmonary eosinophilic infiltration, but we wanted to conclusively rule out a coexisting mycobacterial infection. Hence, bronchoscopy was undertaken. Miliary TB is associated with interstitial involvement secondary to hematogenous spread and sputum / BAL negativity is common. Hence, we proceeded with a transbronchial lung biopsy to confirm eosinophilic infiltration and rule out granulomatous

disease.The uncontrolled glycemic status would have contributed to weight loss and strengthened the suspicion of miliary TB. The case underscores the necessity for conclusive microbial / histopathological diagnosis before initiating empirical antimycobacterial therapy.

Conclusion

Miliary lesions in a chest radiograph pose diagnostic challenge as the number of differentials is large. Careful history, physical evaluation and a focused battery of tests help us to reach an accurate diagnosis in the vast majority of cases. Tropical pulmonary eosinophilia (TPE) is a relatively common cause of reticulonodular shadows and miliary mottling is not uncommon. A high index of suspicion (in residents of endemic zones), presence of peripheral blood eosinophilia, elevated antifilarial antibody titres and tissue infiltration by eosinophils clinches the diagnosis. If appropriate therapy is initiated early, complete resolution is the rule.

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