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Editorial

Impact of Newer Molecular Tests on the Diagnosis of Drug Resistant TB

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Diagnosis of drug resistant TB has been a challenge, particularly in resource limited countries like India. During the early days of RNTCP, quality controlled diagnosis of drug resistant TB (DR-TB) was available only in the four National Reference Laboratories (NRL). However, moving towards programmatic management of drug resistant TB (PMDT), the country charted a long term plan to develop state level reference laboratories, the intermediate reference laboratories (IRL). PMDT started in India in 2006 (the term used in the initial days was DOTS plus)[1] and initially the diagnosis of DR-TB was done using the traditional LJ medium culture and sensitivity. This method had major problems, which included long time periods for the results to be available (often 2 - 3 months).

Soon newer technology became available in the country and set up different criteria for screening of suspects for MDR / DR TB. Criteria A was for those states which had access only to solid culture (LJ media). In such areas only patients who failed an RNTCP regime had access to diagnostic services for DR-TB. Criteria B was in states where there was access to Line Probe Assay (LPA). In such places, patients who were smear positive during follow-up smear examination while on treatment and smear positive re-treatment patients were offered testing for MDR TB. Criteria C was in states where liquid culture and / or Cartridge Based Nucleic Acid Amplification Test (CB-NAAT) was available. Here all patients starting a re-treatment regime, any patient positive on follow-up sputum examination and all HIV TB patients were offered testing for drug resistance.[1]

Since those days, the country has moved on and now the greater

availability of molecular technologies has resulted in CBNAAT being used for the diagnosis of smear negative TB as well as universal drug susceptibility testing (DST). Universal DST as per RNTCP implies that all diagnosed TB patients are offered DST to at least Rifampicin.[2]

The availability of the two molecular technologies has revolutionised the diagnosis and treatment of TB in India. Due to the availability of CBNAAT, a high proportion of smear negative patients in India are now diagnosed as "microbiologically confirmed TB". This allows for early diagnosis of TB and even patients with minimal lesions can be now diagnosed with certainty. The two tests also allow for early diagnosis of drug resistance. LPA can diagnose MDR in three days and CBNAAT in 2 hours as opposed to the three to four months that the traditional LJ medium culture and sensitivity used to take. During the early years of DOTS plus, when LJ medium culture and sensitivity was the diagnostic modality for DR-TB, almost 10% of patients used to die before treatment could be initiated in Kerala. The early detection of TB and MDR was expected to significantly bring down mortality among TB patients.

The study by Anjana et al in this issue of Pulmon clearly highlights the utility of these tests. The proportion of patients being tested for MDR / DR-TB has increased with the use of LPA and more with the use of CBNAAT. Testing of more TB patients has also resulted in increased diagnosis of MDR TB. However this increased diagnosis is a result of a large number of patients being tested.

However with increasing testing being done using the new tests, the capacity of the newer tests to provide the advantages promised is often called to question. CBNAAT is a test which in theory provides results of both presence of mycobacterium tuberculosis (MTB) and rifampicin (Rif) resistance in two hours. However testing of large number of patients has resulted in results often coming very late, often as late as one week to 10 days in parts of Kerala. The RNTCP diagnostic algorithm offers INH testing using LPA to all patients who are found to have Rif sensitive MTB, however limited capacity for testing in Kerala has resulted in this not being currently offered to TB patients in Kerala. A recent study in Trivandrum and Kollam district showed that while Rif resistance is less prevalent, the proportion of patients with INH resistance was 7% in the study population.[3] INH mono/poly resistance is associated with higher mortality in TB patients and in the context of the END TB strategy aiming at reducing mortality, testing for INH resistance becomes even more important.

It was expected that widespread use of molecular technology leading on to early diagnosis of DR-TB would result in lower mortality in these patients. However a study from South Africa, which was one of the first countries to roll out CBNAAT services to all TB patients showed that while pre-treatment mortality reduced significantly after

the expanded CBNAAT coverage, there was no significant difference in mortality after treatment was initiated.[4] In India too, the mortality of DR-TB on treatment in the cohort reporting outcomes in 2011 was 12%[5] whereas the mortality was 20% in the cohort that was reported in 2018.[6] Hence the diagnostic services have to be linked to quality treatment services for the diagnostic technology to have an impact. Only 35850 MDR TB patients could be initiated on treatment in 2017 in India when the WHO estimated incidence of MDR TB in 2017 was 135,000. Hence the diagnostic services are still not accessed by a high proportion of TB patients. There is an urgent need to increase the diagnostic capacity in India and Kerala, probably by providing more machines. Or an alternate way could be introduction of newer technologies which are cheaper and locally developed. A new technology developed by the Sree Chithra Tirunal Institute of Medical Sciences in Kerala (GeneDot) holds great promise and is currently under validation.[7]

There is a possibility that the current CBNAAT - "Xpert MTB/RIF" may be replaced with "Xpert MTB/RIF Ultra" which promises higher sensitivity at a cost of lower specificity. Use of the newer technology in low TB burden setting like Kerala can result in a higher proportion of false positive TB diagnosed if all TB patients are tested upfront with CBNAAT.[8] Current RNTCP guidelines however offer testing with CBNAAT only in patients who have a lesion suggestive of TB on a chest Xray, which would increase the positive predictive value of the test. However there are many scenarios where the test is often offered to all TB suspects and in such scenarios, the fact that there could be significant number of false positive cases diagnosed should be kept in consideration.

To conclude, the newer molecular tests, CBNAAT and LPA, have made the diagnosis of TB and DR-TB easier for treating doctors. However there are many programmatic and technical issues regarding these valuable tests which need to be addressed as well as an urgent need to increase the diagnostic capacity. There is also an urgent need to take up operational research studies related to the utility of the newer technologies in our setting for optimal benefit to TB patients and to help the state in eliminating TB.

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Review Article

Acute Exacerbation of Interstitial Lung Disease - A Clinical Event with High Mortality in the Natural Course of the Disease

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Abstract

Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is a often fatal clinical event and is defined as an acute, clinically significant deterioration that develops within less than 1 month without obvious clinical cause like fluid overload, left heart failure, or pulmonary embolism. Radiologically it presents as diffuse, bilateral ground-glass opacification on high-resolution computed tomography (HRCT). AE-ILD can affect all patients with interstitial lung disease (ILD) but generally occurs more frequently in patients with an underlying usual interstitial pneumonia pattern. The etiology of AE-ILD is not fully understood, but there are distinct risk factors and triggers like infection, mechanical stress, and microaspiration. In general, AE-ILD has a poor prognosis and is associated with a high mortality within 6 to 12 months. In clinical practice, AE-ILD is often treated with a high dose corticosteroid therapy and antibiotics. This review article provides a brief summary of the clinical features, diagnosis, risk factors and management of AE-ILD.

Introduction

Interstitial lung disease is a heterogeneous group of diseases characterized by varied clinical presentation, disease progression as well as prognosis and the common feature of most of these ILDs is end stage fibrotic destruction of the lung parenchyma. Within the clinical course of ILD, an acute exacerbation of ILD is an important clinical event in the natural course of the disease which can occur at any time and is associated with significant morbidity and mortality.[1-5] Hence considering the serious outcome of this clinical entity, early recognition and aggressive treatment of acute exacerbation of Interstitial Lung Disease (AE-ILD) could impact the survival of patients positively.

Definition

There is no official approved definition for Non IPF ILD and since an acute exacerbation of Non IPF ILD resembles that of an acute exacerbation of IPF (AE-IPF), in a clinical setting it is reasonable to extend the definition of Acute exacerbation of IPF to all Non IPF Acute exacerbation of ILD.[8,10-12]

Acute exacerbation of Idiopathic Pulmonary Fibrosis (AE-IPF) is defined as an acute and significant clinical deterioration which develops within less than 1 month in the absence of fluid overload, left heart failure or pulmonary embolism.[8]

Clinical features of Acute exacerbation of ILD

The usual clinical presentation is a rapid deterioration of respiratory symptoms with worsening dyspnea within less than 1 month with associated cough, increased sputum production, fever and flu like symptoms[7]. Most of these patients show significant hypoxaemia on admission; and often require admission to ICU and may require assisted ventilation. ABG shows a PaO2/FiO2 ratio of less than 225 or a decrease in PaO2 of >10 mm of Hg overtime [1,10,11,13]. Most of the time establishing a diagnosis of AE-ILD poses a challenge. To get an accurate diagnosis various diagnostic tests should be carried out to rule out other diagnosis like myocardial infarction, Pulmonary Embolism or fluid overload.

Evaluation by an HRCT chest upfront is required and should be performed in all clinically stable patients[6,10,12].

HRCT findings in Acute exacerbation of ILD

HRCT chest typically show newly developed bilateral Alveolar infiltrates like Ground Glass Opacities with or without consolidation. Three suggested HRCT pattern are peripheral, multifocal and diffuse ground glass opacities. The extent of disease on HRCT seems to be linked to clinical outcome. If there is no previous HRCT available for comparison, bilateral ground glass opacities and or consolidation on a background of Usual Interstitial Pneumonia (UIP)pattern is sufficient to confirm the radiographic diagnostic criteria of acute exacerbation of Idiopathic Pulmonary Fibrosis[1,14-16]

The term suspected Acute Exacerbation of IPF is used when there are only unilateral ground glass opacities.

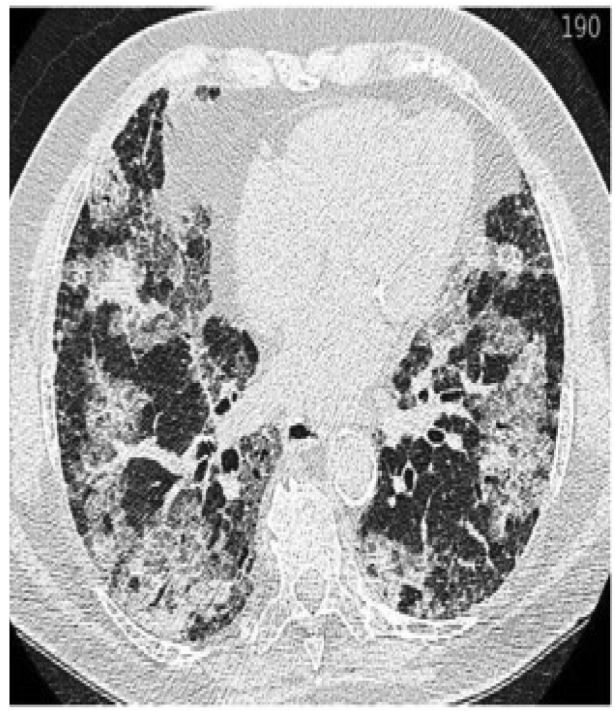

Fig 1 : HRCT of an acute exacerbation of IPF showing widespread bilateral ground glass opacities

Epidemiology

Acute exacerbation of ILD can occur at any time of the clinical course of the disease and in some patients it can be the first presenting manifestation of ILD[10,13]. The exact frequency of Acute exacerbation of ILD is unknown and the reported incidence rates of AE-ILD vary which is likely to be due to difference in definition, type of ILD and disease severity. A meta analysis of six RCTs identified a weighted average of 41 Acute Exacerbation-of IPF per 1000 patient years[20]. As for as the data on AE of Non IPF ILD is concerned there is much less frequency data. Moreover majority of studies indicate that patients with IPF are at increased risk of exacerbation than non IPF ILD. And among non-IPF ILD , those with a UIP like pattern are more at higher risk of exacerbation.[24-26]

Pathogenesis and Etiology

The exact pathogenesis is uncertain. Acute exacerbation may be triggered by an intrinsic factor causing the progression of underlying disease or external triggers such as infection, aspiration and mechanical injuries such as post operative /post procedural or both could cause [6,8].

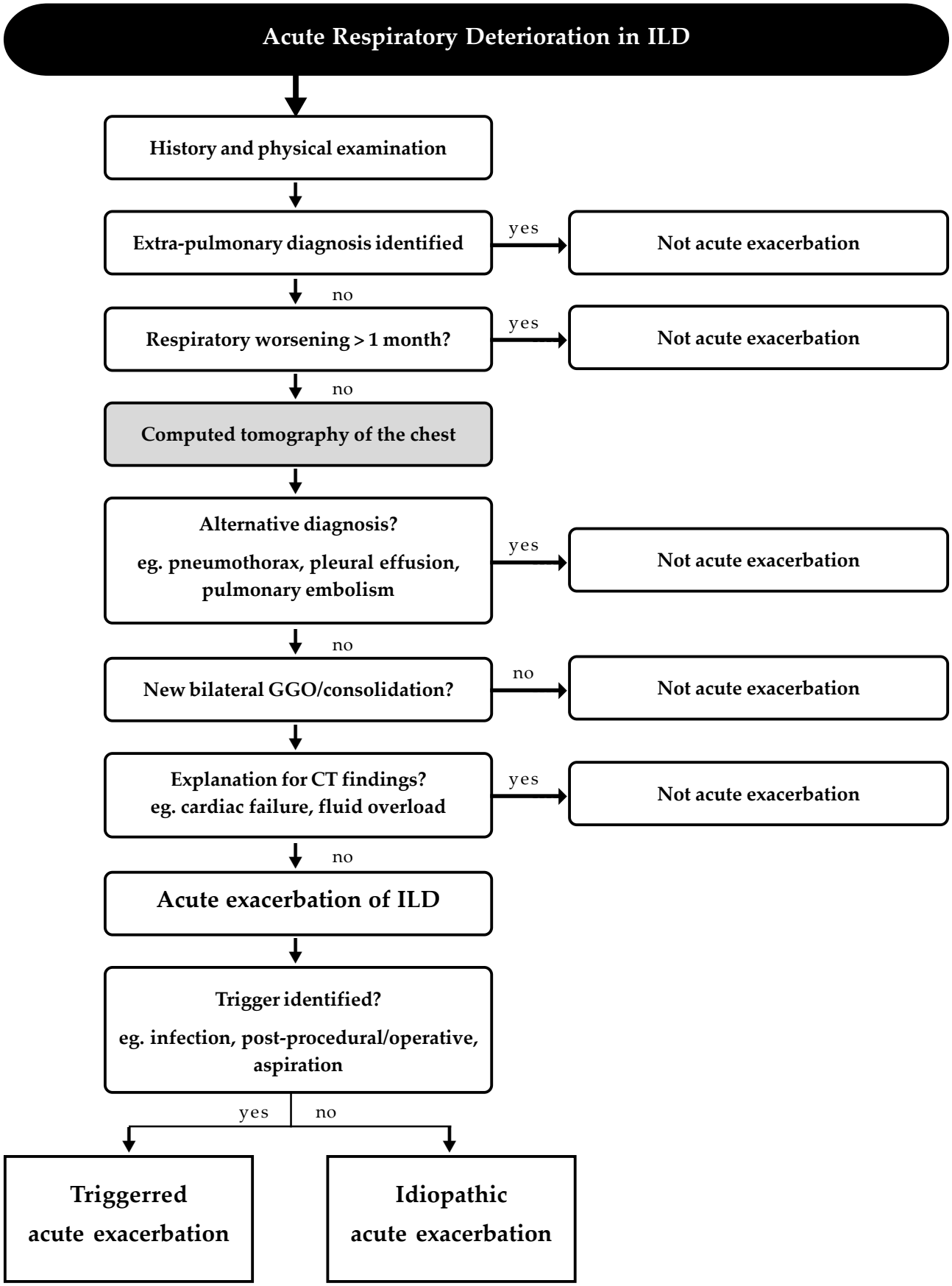

Fig 2 : flow diagram showing diagnostic approach to Acute Exacerbation of Interstitial Lung Disease

Infection

There is growing number of findings indicating the role of infection both viral and bacterial which might be involved in some cases of ILD. There is markable change in the microbiome of respiratory tract, showing an increased bacterial burden in BAL during exacerbation. Patients with Acute exacerbation of IPF has shown an increase in the campylobacter species, stenotrophomonas species and a significant decrease in the veilonella species in the respiratory tract compared to stable IPF.[18] Majority of studies have shown that an immunosuppressive therapy increased the risk of Acute exacerbation of IPF[19,23,27]

Microaspiration

Microaspiration may also play a role as shown in the post-hoc analysis of placebo treated IPF patients in three clinical trials in whom no one was treated with antiacid therapy.[28]

Other Clinical risk factors

Advanced clinical stage of the disease with low FVC is a stable risk factor. In addition a recent decline in FVC, a low DLCO, low total lung capacity, low 6 minute walking distance, impaired baseline oxygenation and increased dyspnea also could place the patient at risk of exacerbation[2, 17, 19, 21, 22]

Though Acute exacerbation of ILD can occur in different histological forms of ILD,UIP like pattern on HRCT is associated with higher risk of exacerbation among Non IPF ILD such as hypersensitivity pneumonitis and Connective tissue associated ILDs (CTD-ILD).[7, 10]

Prognosis

Acute exacerbation of ILD is a fatal clinical event and mortality is high. The in-hospital mortality in AE-IPF is estimated to be over 50%. The existing data suggests that IPF patients have a worse survival outcome compared to Non IPF ILD patients. However Acute exacerbation of ILD in non –IPF ILD is also a fatal event and the highest overall mortality rate of Acute exacerbation of ILDs is seen in hypersensitivity pneumonitis (75-100%) and mortality in other non –IPF ILD vary from 34-83%. (5, 12)

Treatment

Optimal therapy for AE-IPF has not been established. All patients require supportive care to relieve hypoxemia and alleviate symptoms of shortness of breath and cough.

Evidence based data's on effective therapies in AE-ILD are lacking. In clinical practice Acute exacerbation of ILD is often treated with a combination of high dose intravenous corticosteroids and broad spectrum antibiotics.[7, 10, 12]

In Acute exacerbation of IPF, the current international guidelines give a weak recommendation on treatment with corticosteroid stressing that the recommendation is based on anecdotal reports of benefit and the high overall mortality in acute exacerbation of IPF.[6]

Supportive measures

Routine - Supportive measures for all patients with AE-IPF include provision of supplemental oxygen and relief of dyspnea. Standard measures for prevention of venous thromboembolism and stress gastropathy are prudent.

Oxygenation - Patients with AE-IPF often have a high oxygen requirement to maintain pulse oxygen saturation above 88 percent and their high inspiratory flow rate may make oxygenation with standard low-flow nasal cannula difficult.

High-flow oxygen therapy by nasal cannula may be a reasonable alternative for patients with acute hypoxemic respiratory failure without hypercapnia who are not able to achieve an adequate SpO2 with low-flow oxygen.

Relief of dyspnea - For some patients, treating hypoxemia with supplemental oxygen is sufficient to treat dyspnea, but dyspnea due to IPF may be refractory. Palliative care strategies may help alleviate dyspnea

Prevention of venous thromboembolism - Patients who are hospitalized with an AE-IPF are at increased risk of

venous thromboembolism and appropriate thrombo prophylaxis should be undertaken.

Anti-acid therapy - since acid aspiration has been implicated as a potential contributor to AE-IPF anti reflux and anti acid therapy should be instituted upfront.

Mechanical ventilation - The role and efficacy of noninvasive positive pressure ventilation and low tidal volume mechanical ventilation have not been formally studied in AE-IPF. Mechanical ventilation is of limited value in the IPF patient with an acute deterioration without a defined treatable trigger, based on high mortality rates and the poor outcomes reported for mechanical ventilation in IPF.

Glucocorticoids - The international evidence-based guidelines for AE-IPF suggest administering systemic glucocorticoids in the majority of patients with AE-IPF. The steroid of choice is either predinisolone in the dose of 1 mg per kg body weight or IV methyl-predinisolone 1 gram per day for three days followed by a taper, based on severity of disease and response to therapy. For those individuals who appear to a have a clinical response to glucocorticoids, try to taper them slowly over the course of weeks to months ensuring there is no recurrence with close follow up.

Multiple reports outline glucocorticoid use as monotherapy. On the other hand, some investigators have reported an immunosuppression-free approach with similar outcomes in AE

Antibiotics - Broad-spectrum antibiotics are typically initiated upon presentation as the radiographic findings overlap with pneumonia. Given the severity of disease and poor prognosis, many experts complete a seven day course even if all cultures are negative.

Biologic markers, such as procalcitonin and C-reactive protein (CRP), are sometimes used to try to distinguish between bacterial and nonbacterial causes of pneumonia. One randomized trial evaluated the use of procalcitonin (PCT)-guided antibiotic treatment versus standard clinician determined care in 61 patients with AE-IPF [29]. This trial demonstrated shorter duration of antibiotic use with PCT monitoring while the duration of mechanical ventilation and overall mortality were unchanged.

Nintedanib and pirfenidone - The antifibrotic agent, nintedanib, may help prevent AEs. However the value of adding or continuing nintedanib or pirfenidone during an AE has not been properly evaluated. The current practice is to continue the patient on their established therapy. For patients not on one of these agents, it may be reasonable to initiate one of the antifibrotic agents after resolution of the AE.

Palliative care

Palliation of dyspnea is an important component of end-of-life care. Palliative strategies to reduce dyspnea in an individual patient may include relaxation techniques, facial cooling with a fan, opiates, benzodiazepines, and sometimes noninvasive ventilation. There may be a role for noninvasive ventilation to reduce dyspnea, although this requires a clear discussion of goals of care, especially in patients who prefer not to pursue life-prolonging treatments.

There are many clinical trials which looked at effectiveness of medications other than steroid monotherapy including combination of steroids and Tacrolimus, Cyclosporin and steroids, rituximab and steroids along with therapeutic plasma exchange and intravenous immunoglobulin in severly ill IPF patients and some of these interventions have shown an improved survival outcome and reduction in re-exacerbation rates.

Conclusion

Acute exacerbation of ILD is a fatal clinical event in the natural course of the ILD and awareness of such an entity among Pulmonologists is of paramount importance in instituting early treatment and supportive care, which could potentially impact the survival outcomes. Though the clinical presentation of Acute exacerbation of ILD is similar both in IPF and Non IPF ,acute exacerbation of ILD is less common and the severity of exacerbation is also less fatal compared to IPF. The decision to ventilate the patient or not during an exacerbation needs to be taken on a case to case basis and the need to ventilate the patient to be discussed together with the physician, the patient and family and in accordance with the individual goal of care.

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Original Article

Impact of Frozen Section Evaluation of Pleuroscopic Biopsy in Management of Pleural Effusion

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Abstract

Aims and Objective : To find out Impact of frozen section evaluation of pleuroscopic biopsy in management of pleural effusion

Materials and Methods : This is a Hospital record based Cross Sectional Study done at KIMS hospital. 129 subjects who presented with moderate to massive pleural effusion were subjected to pleuroscopy and then frozen section and final histopathology results were analysed.

Results : Out of the 53 cases studied by frozen section, a conclusive result was obtained in 41 cases. 21 cases were malignancy (19 - adenocarcinoma, 1-squamous cell carcinoma, 1-poorly differentiated carcinoma), 20 cases were tuberculosis. All the frozen section results were concordant with final histopathology reports. For tuberculosis, sensitivity was 75.9% and specificity was 100%; and for malignancy, sensitivity was 77.8 % and specificity was 100%. Median duration of hospital stay is 5 days for those who underwent frozen section and was 8 for those who did not undergo frozen section which is statistically significant (p value 0.016). Duration of ICD was 4 days for those who underwent frozen section and 4.5 days for those who did not undergo frozen section which is not statistically significant.

Conclusion : Frozen section is an invaluable tool in pleuroscopic evaluation of pleural effusion resulting in significant reduction in hospital stay in patients undergoing the procedure.

Key words : frozen section, pleurodesis, pleuroscopy

Introduction

A pleural effusion is excess fluid that accumulates in the pleural cavity. Clinical features includes cough which is usually dry in nature, breathlessness and pleuritic chest pain.

On the basis of pathophysiology it can be classified into two types, transudative and exudative. Conditions associated with transudative pleural effusions include congestive heart failure, liver cirrhosis, severe hypo albuminemia, nephrotic syndrome, acute atelectasis, myxoedema, obstructive uropathy and end-

stage kidney disease. Conditions associated with exudative pleural effusions include pneumonia, malignancy, tuberculosis, pulmonary embolism, pulmonary infarction, pancreatitis and rheumatoid arthritis.[1]

The diagnosis of a case of pleural effusion requires chest x-ray PA view and decubitus view. If decubitus view shows a thickness >10 mm, then diagnostic or therapeutic thoracocentesis is investigation of choice.[2] Pleural fluid analysis is usually done to differentiate exudative or transudative effusion. Pleural fluid samples should be sent for total count, differential count, glucose, ADA, albumin, LDH, protein, culture, gram stain, AFB smear, AFB culture and cytological analysis.[3]

Pleuroscopy, also known as medical thoracoscopy, is a minimally invasive procedure which is used to perform a biopsy of the pleura and to perform therapeutic interventions. It can be done under conscious sedation. Diagnostic accuracy of this procedure approaches 100% in malignant and tuberculous pleural effusions. Complication rates are low (2%-5%) which includes subcutaneous emphysema, bleeding and infection. Mortality rates are less than 0.1%. Chemical pleurodesis can be performed for recurrent, symptomatic malignant pleural effusion, with success rates approaching 90 %.[4]

The frozen section procedure is a pathological laboratory procedure to perform rapid microscopic analysis of a specimen. It is also known as cryosection. The quality of slides produced by frozen section is of lower quality than formalin fixed paraffin embedded tissue processing. Since studies about frozen section in pleuroscopic biopsy are very less, this study has been taken to determine impact of frozen section in evaluation of pleuroscopic biopsy in management and outcome.

Materials And Methods

This study, conceptualised as a hospital record based cross sectional study, was conducted in the setting of the Department of Respiratory Medicine, KIMS Hospital, Trivandrum, Kerala. Patients who presented with undiagnosed moderate to massive pleural effusion and were subjected to pleuroscopy from January 2008 - June 2018, were included in the study. During the initial period of the study, frozen section was not available for patients undergoing pleuroscopy. This procedure was introduced for the patients undergoing pleuroscopy in 2012 owing to the obvious benefits of the investigations. Hence the initial cases in the series did not undergo frozen section.

All patients who were subjected to pleuroscopy were included in the study. The frozen section results and final histopathology report were collected and analysed. Outcome of frozen section was analysed by calculating number of days with hospital stay.

With the permission of hospital administration, data was collected from electronic database of the KIMS hospital. Collected general characteristics of patient included age, sex, side of effusion, nature of effusion and cellularity of effusion. Other data collected included details about frozen section, whether conclusive result obtained or not, final diagnosis, days of hospital stay, days of ICD duration and whether pleurodesis done or not.

For the procedure, the patient was positioned on the healthy side in a lateral decubitus position with the involved side up. Axillary point of entry was taken as standard. Entry was done through the mid axillary line at the level of fourth or fifth intercostal space to allow for complete thoracic cavity inspection.[4]

The single-puncture technique was the commonest method used. Vertical incision was made with a scalpel through skin and subcutaneous tissue, appropriate to size of trocar to be used. Trocar was inserted in a cork screw motion until sudden release of resistance was felt. When the trocar reached the pleural cavity, it was removed and the cannula kept 1-3 cm within pleural cavity, held in position by an assistant. Then thoracoscope was placed in the cannula and advanced into pleural cavity under direct vision. Whenever necessary, pleural fluid was removed with a suction catheter.[4]

Suspicious areas were biopsied through the working channel of thoracosope/ pleuroscope. If lesions were present on the parietal pleura rather than visceral pleural lesions, these were biopsied, thereby avoiding risk of prolonged air leak. Typically two to six biopsies of a suspicious pleural lesion was taken.[4]

Whenever frozen section was done from the biopsy sample, if the diagnosis came as malignancy, talc insufflation was done and if it came as granuloma, pleurodesis was avoided.

Data collected were entered into excel spread sheet and results were analysed with the help of Epi info7 software. With regard to ethical considerations, being a record based study, permission of gate keeper of information was obtained and patient identifiers not extracted.

Results

The mean age group of the study was 55.51 years with a standard deviation of 15.39years. 62.02% of the study group were males and 37.98% were females. Right sided effusion was present in 58.91% of cases. Exudative effusion was there in 92.31% of patients. Cellularity of effusion revealed non- lymphocytic variety to be more common (74.36%). The general characteristics of the patients recruited can be seen in Table 1.

		Number	Percent
Age	below 45 yrs	32	24.81%
	45 to 55 yrs	29	22.48%
	55 to 65 yrs	37	28.68%
	65 yrs and above	31	24.03%
Sex	Male	80	62.02%
	Female	49	37.98%
Side of effusion	Left	53	41.09%
	Right	76	58.91%
Nature of effusion	Exudative	119	92.31%
	Transudative	10	7.69%
Cellularity of effusion	Lymphocye predominant	33	25.64%
	Non-Lymphocyte predominant	96	74.36%

Table 1 : General characteristics of the study population

Final diagnosis obtained after histopathology report showed malignancy (46.51%) as the most common diagnosis and followed by tuberculosis (29.46%). Among the patients, inconclusive result was present in 24.03% which included both patients with an inconclusive report and also patients referred from other hospitals, who chose to do their histopathology in the referring hospital and no feedback was obtained. The details can be seen in Table 2.

FINAL DIAGNOSIS	Frequency	Percent	95% CI Lower	Higher
Tuberculosis	38	29.46%	21.76%	38.12%
Malignancy	60	46.51%	37.69%	55.50%0
Inconclusive	31	24.03%	16.95%	32.34%

Table 2 : Final diagnosis obtained on histopathology section

Frozen section was done in 53 cases, of which 21 cases yielded malignancy and 20 cases yielded tuberculosis. Among those with malignancy, 19 were adeno carcinoma, 1 was squamous cell carcinoma and 1 was poorly differentiated carcinoma. Inconclusive results were obtained in 12 cases, of which on final histopathology evaluation, 6 cases were determined to be tuberculosis and 6 cases to be malignancy. All the frozen section results were concordant with final histopathology reports.

	Number	Percent
Tuberculosis	20	37.7%
Malignancy	21	39.2%
Inconclusive	12	22.6%

Table 3 : Diagnosis made on frozen section biopsy in the 53 patients who underwent pleuroscopy during the period during when frozen section facility became feasible

The mean duration for hospital stay was 7.38 days with standard deviation of 4.7 days. Median duration of hospital stay was 5 days for those who underwent frozen section and 8 days in those who did not undergo frozen section which was statistically significant (p value 0.016). Duration of ICD was 4 days for those who underwent frozen section and 4.5 days for those who did not undergo frozen section which was not statistically significant. The details can be seen in Table 4.

	Patients who underwent frozen section		Patients who did not undergo frozen section		P Value
	Median	IQR	Median	IQR	
Duration of hospital stay	5	(3-7)	8	(5.5-10)	0.016
Duration of ICD insertion	4	(2-7.5)	4.5	(2-6)	0.05

Table 4 : Difference in median hospital stay and median duration of ICD insertion among patients who underwent frozen section as opposed to those who did not

After analysing diagnostic accuracy of frozen section with final histopathology as a gold standard, sensitivity of malignancy was found to be 77.8% and specificity of 100%.Frozen section for the diagnosis of tuberculosis showed sensitivity of 75.9% and specificity of 100%. The details can be seen in Table 5.

	Sensitivity	Specificity
Malignancy	77.8%	100%
Tuberculosis	75.9%	100%

Table 5 : Sensitivity and specificity of FS in the diagnosis of malignancy and TB with final histopathology as the gold standard

Discussion

Sensitivity of frozen section was 77.8% for malignancy and 75.9% tuberculosis and specificity yielded 100% for both. A study done by David Fielding, Peter Hopkins and David Sersier yielded a 75% accuracy for frozen section.[5] A study done by Georgia Karpathiou et al showed a final sensitivity of 96.26% and specificity of 97.87% in detecting malignant pleural lesion. In that study, 149 frozen sections were done, of which 144 cases yielded a diagnosis. There were 96 malignant lesions and 48 benign conditions diagnosed.[6] This is better than the results obtained in our study, which may be due to the high proportion of inconclusive results obtained in our study.

Among those who underwent frozen section pleuroscopic biopsy and those who did not, we analysed duration of hospital stay and ICD duration and concluded that there was decrease in hospital stay in those who underwent frozen section, which was statistical significant also. (p value 0.016). We could not find any significant association between the median duration of ICD placement with frozen section being done or not. If malignancy was detected in the frozen section study, the advantages include earlier talc insufflation, which would lead to better outcome of the pleurodesis and also by decreasing hospital stay would result in associated decrease in morbidity and cost of hospital stay. Also, if the frozen section showed a granulomatous lesion, there was an advantage of

initiating ATT immediately and the ICD would be removed either the same evening or next morning. This would facilitate a shorter hospital stay and a shorter duration of ICD placement, which has a significant cost saving advantage.

Conclusion

Frozen section is an invaluable tool in pleuroscopic evaluation of pleural effusion resulting in significant reduction in hospital stay in patients undergoing the procedure.

Acknowledgement

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Original Article

Impact of Introduction of Rapid Diagnostic Techniques on Testing for Drug Resistant TB and Detection of MDR TB in Ernakulam District

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Abstract

Background : India accounts for 24% of global multi drug resistant TB (MDR TB) burden. Spread and mortality due to MDR TB can be prevented by early detection of MDR TB and successful early initiation of effective drug regimes for MDR TB. Availability of rapid diagnostic techniques on MDR TB case detection and policy related to use of these tests have been made in Kerala, however the impact of these policy changes have not been documented.

Objectives : To explore whether changes in MDR TB suspect criteria in the light of availability of newer diagnostic techniques like line probe assay (LPA) and cartridge based nucleic acid amplification tests (CBNAAT) resulted in increased detection of MDR TB, as compared to conventional culture methods in Ernakulam district.

Methods : This is a secondary data based cross sectional study conducted in tuberculosis patients in Ernakulam district between May 2009 and June 2018.

Results : The mean number of patients tested for drug resistance in Ernakulam district during the period when LJ media culture and sensitivity was being done was 21per quarter as opposed to 303 per quarter once molecular technologies were introduced for testing for drug resistance. This difference in means is statistically significant. Higher proportions of TB patients were being screened for Rif resistance over the last 10 years. The mean number of MDR TB / Rif Resistant TB diagnosed per quarter in the three phases, LJ Media culture, LPA and CBNAAT were 3.9, 7.3 and 9.3 respectively.

Conclusion : Higher numbers of TB patients are being screened in 2018 as compared to 2008 for MDR TB in Ernakulam district resulting in more and early diagnosis of MDR TB

Key words : MDR TB, diagnosis, case detection, molecular diagnostic tests

Introduction

Tuberculosis (TB) is one among the top 10 causes of death globally and is the single leading infectious cause of death. India accounts for 27% of the global TB burden with an annual incidence of 2.74 million cases in 2017. According to the global TB report 2018, India is included in the list of high burden countries in all the three categories, including TB incidence, HIV TB and Multi drug resistant TB (MDR TB).[1]

In 2016, the world moved from the STOP-TB strategy to the END TB strategy. This strategy has ambitious goals, including reduction of TB mortality by 95% by 2035, reduction of incidence by 90% by 2035 and zero catastrophic expenditure for TB patients. However, the emergence of drug resistant tuberculosis is one of the major threats to Global TB control efforts. In 2017, the World Health Organisation (WHO) estimated an incidence of 558000 new case of rifampicin resistant tuberculosis world wide. India accounts for 24% of the global MDR TB burden. The estimated prevalence of MDR TB in India is 2.8% among new cases and 12% among the previously treated cases. The estimated incidence of MDR TB in India in 2017 is 135000.[2]

Primary transmission of DR TB can be prevented only by early detection and successful early initiation of effective treatment. PMDT services were launched in India in 2007. At the start of the programmatic management of drug resistant TB (PMDT) in India, diagnosis of MDR TB was based on traditional LJ media culture and sensitivity in quality-controlled laboratories. Later newer molecular technologies like line probe assay (LPA) and cartridge based nucleic acid amplification test (CBNAAT) were introduced. LPA was introduced in intermediate reference laboratories in 2011-2012, including in Kerala; and CBNAAT was introduced in 2016 in Kerala.

Based on the availability of technology, the suspect criteria for screening patients for drug resistant TB have evolved in India. Initially drug sensitivity testing was offered to patients with the highest risk of developing drug resistant TB, which only included those failing new and retreatment regimes (Criteria A). Later, with the availability of LPA, even those patients who were smear positive at any point during follow-up AFB smear examination during treatment and all previously treated AFB smear positive patients were offered diagnostic services for drug resistant TB (Criteria B). With the availability of CBNAAT, and diagnostic services at district level, all patients are being screened for drug resistance since 2017. As a part of scaling up of diagnostic strategy according to the national strategic plan (NSP) goal to achieve rapid decline in the burden of TB, morbidity and mortality, universal DST has been introduced, so that all new TB patients are now offered CBNAAT for detection of Rif resistance. In 2016, the national TB control program of India modified its diagnostic algorithm and CBNAAT is offered to sputum smear negative TB suspects, whose chest X-ray was suggestive of TB so as to improve diagnosis of TB, however this also allows for early detection of Rif resistance.[2]

The present study was undertaken to understand the impact of changes in MDR-TB suspect criteria and introduction of rapid diagnostic methods on the screening of TB patients and detection of MDR-TB patients.

Objective

To explore whether changes in MDR TB suspect criteria in the light of availability of newer diagnostic techniques, viz, LPA and CBNAAT resulted in increased detection of MDR TB, as compared to conventional culture methods in Ernakulam district, Kerala.

Methodology

Study Design : Secondary data based cross sectional study

Study Setting : The study was conducted in Ernakulam district with a mid-year population 3326,724 and with a tuberculosis notification of about 2000 cases per year.

Study population : Tuberculosis patients residing in Ernakulam District

Study Period : Data from 1st May2009 to 31st Dec 2017

Interventions of interest based on which the periods selected for differential analysis included:

Changes in MDR TB screening criteria subsequent to introduction of LPA

Changes in MDR TB screening criteria subsequent to introduction of CBNAAT

b. Comparator : Conventional culture-based diagnosis techniques for MDR TB

c. Outcomes : Diagnostic yield of LPA, CBNAAT and conventional culture-based diagnosis techniques for MDR TB

Data sources : Data was obtained from the quarterly reports available at the District Tuberculosis Centre, which were collated from the reports submitted by the individual tuberculosis units within the district, after obtaining permission from the District TB Officer.

Data Collection and Storage : The data obtained as mentioned above was manually entered into Microsoft Excel spreadsheets and the same were stored safely with the researchers under standard 128-bit encryption.

Data Analysis : Data was analysed using Microsoft Excel and EpiInfo7. Appropriate statistical tests of significance like chisquare for trend were used.

Results

Ernakulam district started implementation of PMDT in 2008On an average about 2000 TB patients are notifiedin the district. The drug susceptibility testing data during the study period was analysed. The mean number of patients tested for drug resistance in Ernakulam district during the period when LJ media culture and sensitivity was being done was 20.6 patients per quarter as opposed to 303.4 patients per quarter once molecular technologies were introduced for testing for drug resistance. The median number of patients tested per quarter was 17.5 and 189.5 respectively before and after the introduction of molecular testing for drug resistance. (This difference was statistically significant, $p<0.001$). The mean and medial number of patients tested in the periods of LJ media testing, testing using line probe assay and CBNAAT are given below in table 1. The difference between the periods was statistically significant.

Period	Diagnostic strategy	Patients screened for drug resistance		Significance in difference in medians	Mean number of patients diagnosed as MDR/ Rif resistant	Significance in difference in means
		Mean	Median			
2008 - 2011	LJ media culture	20.6	17.5		3.92	
2011 - 2016	Criteria B of RNTCP (LPA)	197.9	182.5	p <0.001	8.27	p <0.001
2016 -	Use of CBNAAT at district level for diagnosis of TB as well as drug susceptibility testing	883.2	890.5		9.25	

Table 1 : Difference in screening of DR suspects and diagnosis of MDR / RR with various strategies of testing for every quarter in the years 2009 - 2018

Ethical considerations : Permission to use the secondary data available in the District TB Centre was sought and obtained from the DTO. The data used for this study was only in the aggregated form and did not contain any personal identifiers with respect to any of the MDR TB patients diagnosed during this period in the district.

Trend chart was plotted for the total number of patients being tested for drug resistance (Figure 1). The number was highest in the last 4q2017 with almost 900 patients being screened for drug resistance. The trend graph shows an increase in the years after 2011 when LPA was introduced but a steep increase in the patients tested can be seen after 2016 when CBNAAT was introduced and testing started at district level.

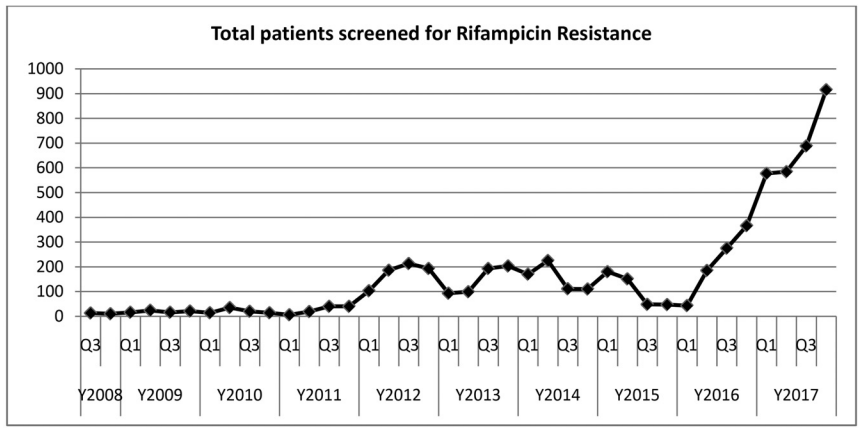

Fig 1 : Trends in testing of TB patients for drug resistance in Ernakulam district

Trend chart was also plotted for the total number of MDR TB / Rif Resistant TB patients diagnosed (Figure 2). The number of MDR / Rif resistant TB diagnosed shows a first increase when the criteria changed due to the introduction of LPA in 2011 and a second increase when the criteria changed from B to C due to introduction of CBNAT in 2016.

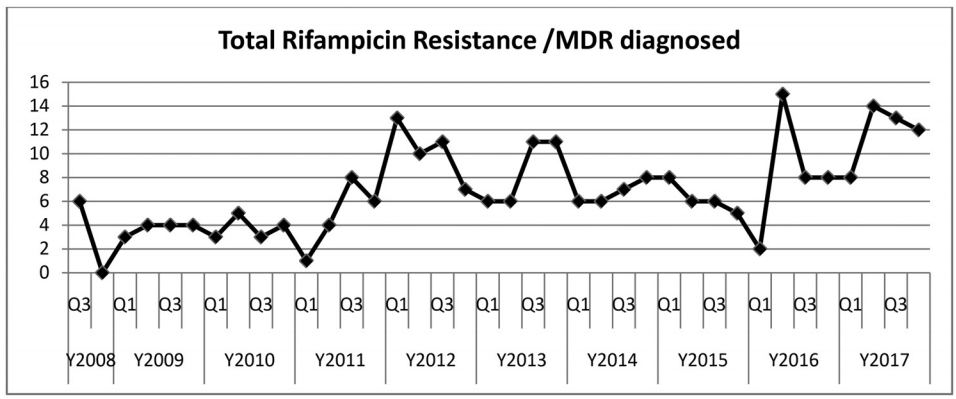

Fig 2 : Trends in diagnosis of MDR TB / Rif resistant TB in Ernakulam district

Trend chart was also plotted for the total number of patients being tested for drug resistant TB for every 1000 TB patients diagnosed (Figure 3). The number of MDR / Rif resistant TB diagnosed shows a first increase when the criteria changed due to the introduction of LPA and a second steep increase can be seen when CBNAT was introduced in 2016. The numbers screened for resistant TB were more than the number of TB patients diagnosed since 2017 since smear negative TB suspects were being simultaneously tested for both TB diagnosis as well as drug susceptibility by CBNAAT.

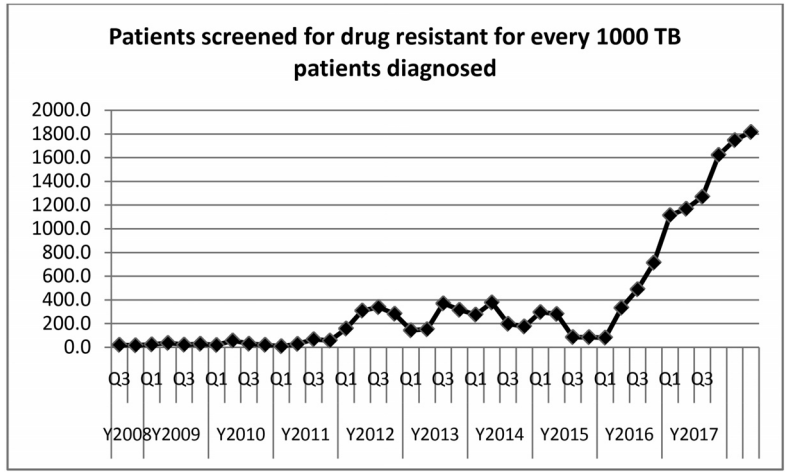

Fig 3 : Patients screened for drug resistant TB as a proportion of every 1000 TB patients diagnosed

Trend chart was also plotted for the total number of MDR TB / Rif resistant TB patients being diagnosed for every 100 TB patients notified(Figure 4). This also shows a first increase when the criteria changed due to the introduction of LPA and a second increase can be seen when CBNAT was introduced in 2016.

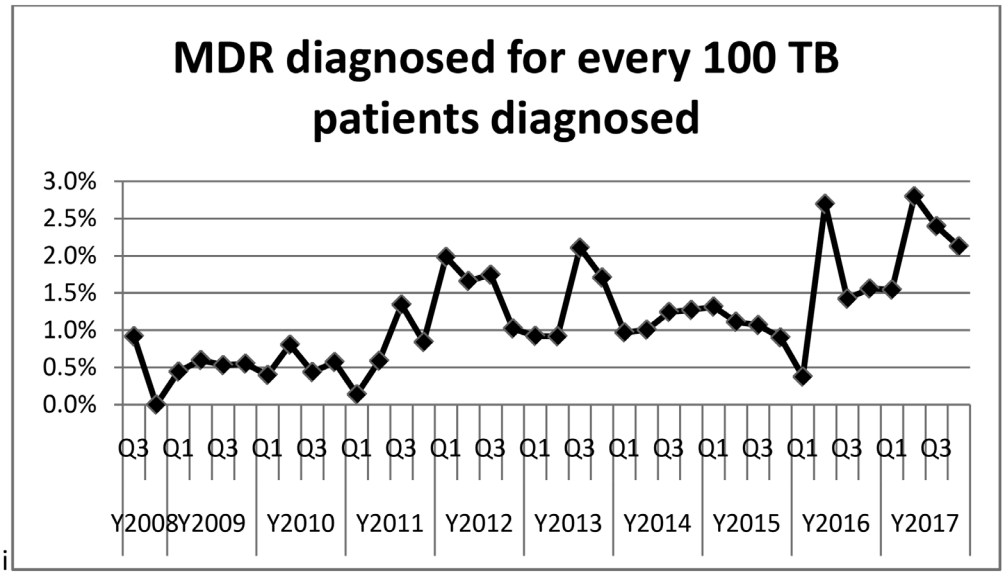

Fig 4 : MDR TB / Rif resistant TB diagnosed for every 100 TB patients diagnosed

After subjecting all notified patients for universal DST, 3% of them were found to have MDRTB. With LPA and criteria B, we were missing half of the MDRTB cases and with LJ, nearly two third.

Discussion

In India multi drug resistance poses a challenge in the control of tuberculosis. WHO endorses the strategy of early diagnosis of tuberculosis with universal DST as a critical component of end TB strategy. Initially at the start of the PMDT services, the diagnosis of drug resistance was based on culture methods and according to the national programme guidelines MDR TB suspect was defined as those TB cases with previous history of anti TB treatment, TB cases on treatment with positive sputum smear result at any follow up smear examination, diagnosed TB cases with HIV-co-infection and all pulmonary TB cases who are contacts of a known MDR TB case.[3] In Kerala, Line probe assay was introduced in November 2011 and our study shows a significant increase in the number of MDR TB / Rif resistant TB patients diagnosed thereafter. However the spectacular jump in the number of the MDR / Rif resistant TB diagnosed in the first quarter after introduction of LPA is due to the results of LJ media culture of the previous quarter and the LPA results of the same quarter coming in together. Our numerators are not derived from the denominator, denominator is the patients tested during the quarter and numerator is the patients diagnosed during the quarter. Thus, there is cohort miss match. However the plateau after the initial peak shows that the increase in diagnosis was a sustained one. In February 2016, CBNAAT was introduced at the district level and in September 2017 universal DST was implemented. Our study results show an increase in the number of patients tested for drug resistance and the number of MDR TB patients diagnosed after the introduction of line probe assay and CB NAAT.

The results of MDR diagnosed for every 100 TB patients diagnosed should be interpreted with caution, as the numerator is the MDR TB / Rif resistant TB patients diagnosed in a quarter and the denominator is the total TB patients diagnosed in that quarter. The MDR / Rif resistant cases may not be among the same cohort of the TB patients diagnosed, hence the proportions in Figure 4 may not represent the MDR rate among TB cases in Ernakulam. However, the fact that the number of MDR / Rif resistant cases diagnosed has increased when compared to the TB cases diagnosed, indicates that use of molecular tests results in increased diagnosis of MDR TB when offered upfront. Similar findings were shown by Sachdeva et al[4], who

showed that there was a substantial increase in the detection of rifampicin resistance by offering an upfront CBNAAT to all presumptive TB cases instead of high-risk groups. Similar findings were obtained in studies conducted in South Africa, Uganda and India[5]. In Raizada's study[6] in India, it was shown that introduction of CBNAAT in public health settings significantly increased the case notification rates of bacteriologically confirmed cases by 30% and rifampicin resistant case notification by fivefold. Widespread deployment of CBNAAT would help in curtailing the MDRTB epidemic. In our study there is an increase in the number of rifampicin resistance after introduction of rapid diagnostic techniques. However, the reasons for only a modest increase in the number of rifampicin resistance diagnosed after introduction of universal DST (over and above that diagnosed by LPA) needs further analysis and further studies. According to the national anti TB drug resistance survey in 2016, the prevalence of MDT TB in new cases in Kerala is 1.84% and in previously treated cases is 11.04%.[7] The lower prevalence of drug resistance among new TB patients could be the reason for this modest increase in case detection which should be validated by further studies.

Conclusion

The introduction rapid molecular diagnostic tests and decentralisation of CBNAAT has resulted in enhanced patient screening for drug resistance and has significantly increased the MDR TB case detection.

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Radiology Pearl

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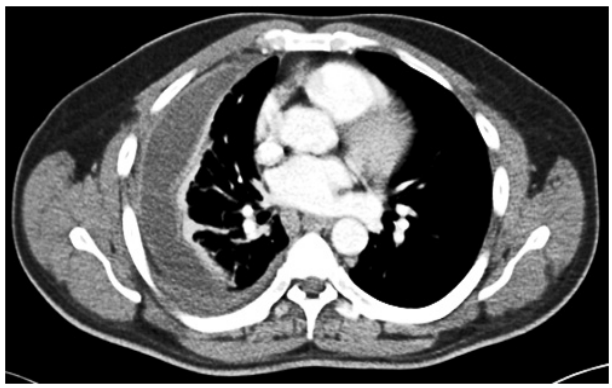
What is the radiological sign?



Answer : Split pleura sign

Split pleura sign is seen in contrast enhanced chest computed tomographic (CT) images[1]. CT image in split pleura sign is described as enhancement of the thickened inner visceral and outer parietal pleura separated by a collection of pleural fluid. The sign results from fibrin coating both the parietal and visceral surfaces of the pleura with resulting ingrowth of blood vessels which leads to contrast enhancement[1,2]. Both layers of the pleura can then be visualised as linear regions of enhancement that come together at the margins of the collection.

Split pleura sign is daignostic of empyema which most commonly occurs due to bacterial pneumonia[2]. Empyema can also lead to extrapleural fat stranding and thickening of extrapleural soft tissues which can be visualesed in contrast enchanced CT scan[3]. Rarely similar changes can also occur in mesothelioma, hemothorax, post lobectomy and following talc pleurodesis[4,5].

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Case Report

A Unique Case of Pleural Effusion

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Abstract

Pleural effusion may occur as a complication following trauma. Its most prominent feature is a high eosinophil count in pleural fluid. Only few cases of post traumatic non-eosinophilic pleural effusions[1] have been reported in literatures. Here we report this unique case of non-eosinophilic delayed post traumatic pleural effusion ,which is a rare entity.

Key words

Post traumatic effusion, Non-Eosinophilic effusion

Introduction

Post traumatic pleural effusion is an understudied complication of chest wall trauma. It can also occur post procedures like thoracentesis or thoracotomy. It is usually associated with a high eosinophil count in pleural fluid. However non eosinophilic pleural effusion cases have rarely been reported.

Case Report

A 50 year old male, non-smoker with no known co-morbidities presented with complaints of left sided pleuritic chest pain, non-productive cough and exertional dyspnoea(MMRC grade 2) of two weeks duration. There was no history of fever, hemoptysis, prolonged immobilisation, orthopnoea/paroxysmal nocturnal dyspnoea or chronic drug intake.

He gave a history of RTA with chest trauma and multiple rib fractures six weeks ago which was managed conservatively. There were no features of pleural effusion or pneumothorax in Chest Xray (Fig:1). He also sustained fracture of left humerus for which open reduction and internal fixation was done. His post operative period was uneventful.

On examination his vitals were stable and respiratory system examination was suggestive of left sided pleural effusion which was confirmed with chest xray (Fig:2) and thoracic ultrasound.

Routine blood investigations , Rheumatoid factor and TSH values were unremarkable. Computed Tomography (CT) thorax showed multiple rib fractures on left side (ribs 3 to 8) and pleural effusion with passive atelectasis.

Thoracentesis and analysis revealed straw coloured, lymphocyte predominant exudative effusion with ADA value of 17. Pleural fluid cytology was negative for malignant cells. Fluid AFB smear and Gene Xpert were also negative .

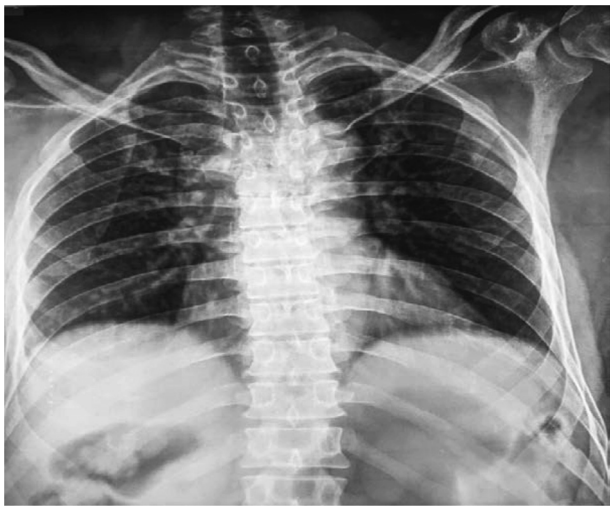

Fig 1 : Chest Xray following trauma

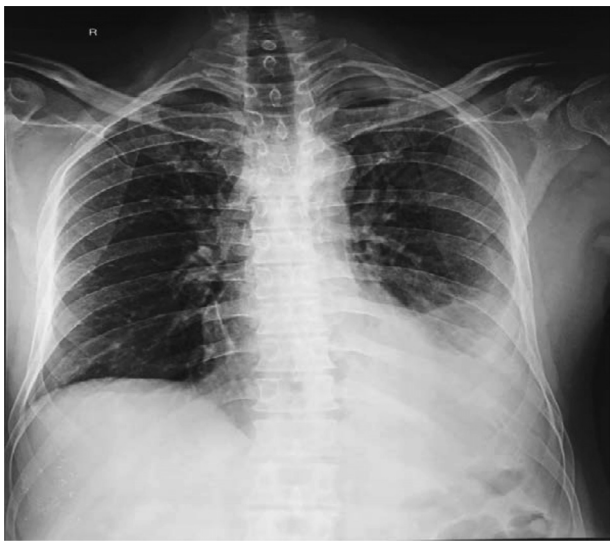

Fig 2 : Chest Xray on presentation

He was re assessed after a period of three weeks and follow-up chest x-ray showed increase in size of effusion which was confirmed with thoracic ultrasound. He was then subjected to pleuroscopy which revealed multiple whitish plaque like lesions and some areas of brownish patches in parietal pleura on costovertebral areas(Fig :3). Biopsies were taken for further investigations. Histopathology examination was suggestive of chronic inflammation and fibrosis with AFB smear and culture negative.

A repeat chest xray after 2 weeks showed resolution of effusion (Fig:4).

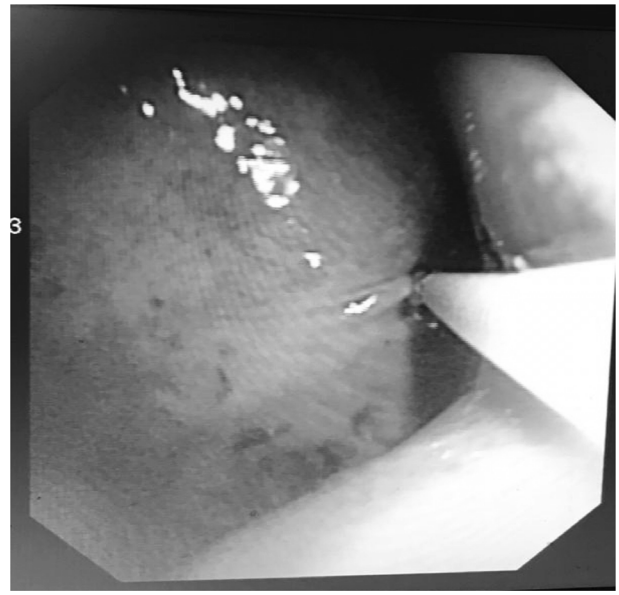

Fig 3 : Pleuroscopy Image

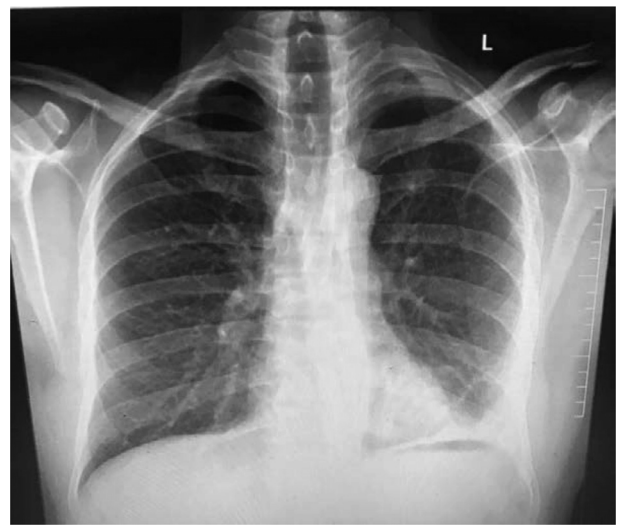

Fig 4 : Chest Xray 2 weeks post Pleuroscopy

Final Diagnosis : Post traumatic non eosinophilic delayed pleural effusion

Discussion

Eosinophilic pleural effusions constitute approximately 10 per cent of pleural effusions , 20 per cent of which is traumatic. Post-traumatic pleural effusion is a rare entity that is probably related to subpleural trauma or dissection. The etiology of eosinophilic post-traumatic pleural effusion is attributed to immune complex reaction, probably related to the presence of air or blood in the pleural space. There may be activation of the classical pathway of complement system and a recruitment of inflammatory cells like eosinophils.

In our case the absence of eosinophils in pleural fluid could be due to non violation of pleural space. The diagnosis of post traumatic pleural effusion can be guided by the history of trauma to chest wall, with clinical signs of effusion and radiological findings. It can also be diagnosed by exclusion using clinical, laboratory and radiological examinations and thus eliminating other etiological possibilities of effusion likeTB, malignancy, empyema, pulmonary embolism, other systemic diseases.

Conclusion

Post traumatic effusions are usually associated with high eosinophils in pleural fluid. However lymphocyte predominant post traumatic effusions should also be considered after ruling out other causes of effusion. This condition may recur and be treated with pleural drainage if necessary.

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Case Report

A Two-in-one Pathology Sequentially Progressing to a Three-in-one Disease

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Abstract

Pulmonologists are often called in to assess asymptomatic pre-operative patients with abnormal chest radiographs. Such incidental findings, on many occasions, prompt the diagnosis of an otherwise occult disease, possibly at an earlier stage in the natural history. We share the case of a middle aged lady who was planned to undergo surgical treatment of a thyroid nodule, but was referred to us on account of an abnormal chest radiograph. Further evaluation revealed her to be harboring parenchymal and mediastinal sarcoidosis which was therapeutically handled as per current norms. After excellent clinical and radiological response, stormy events ensued with the development of tuberculous pleuritis. The challenges of sequential multiple diseases developing in the same patient at varying time frames are brought to light as we discuss the secular follow up of the subject. Utmost emphasis and stress is given to good clinical judgement, interdisciplinary co-ordination and clinico-pathological correlation.

Key Words

Follicular carcinoma of thyroid, tuberculosis, sarcoidosis, dual pathology

Initial presentation

(Rajesh V.)

A 58 year old lady presented to the pulmonary OPD referred from pre-anesthetic checkup clinic. She had no prior medical comorbidities. She initially presented to the ENT / head and neck department with a painless neck swelling. A diagnosis of thyroid nodule was made on clinical grounds by the ENT surgeon and an ultrasound guided fine needle aspiration cytology from the nodule was ordered. Results revealed a follicular neoplasm and surgical excision was being

contemplated under general anesthesia. Evaluation by the anesthesiologist revealed an abnormal chest radiograph and a pulmonary opinion was sought. The representative chest radiograph PA view at presentation to pulmonary OPD is shown below (Fig 1). What were the possibilities considered and how was the approach planned?

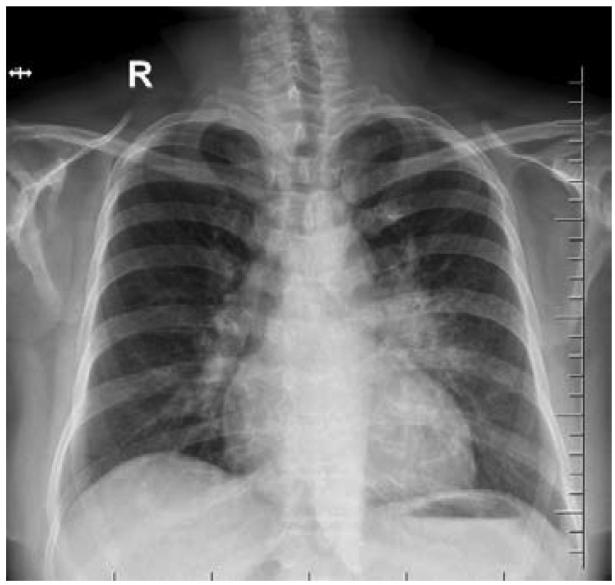
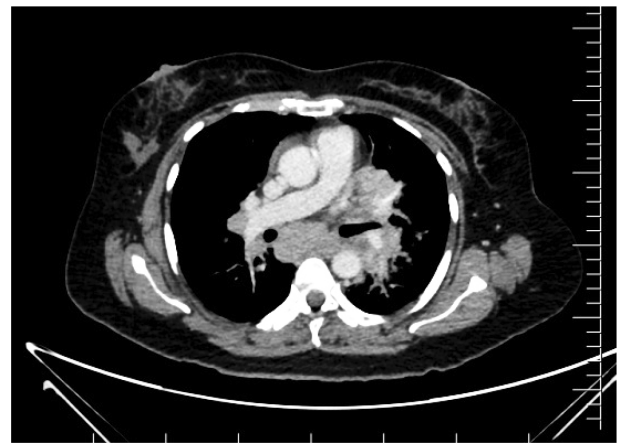


Fig 1 : Postero-anterior chest radiograph at presentation

Subsequent Evaluation

(Jolsana Augustine, Danny George)

The initial chest radiograph shows bilateral hilar prominence, mediastinal widening and left mid-lower zone reticular opacities with some superposed alveolar shadows. In the clinical background, metastasis of the thyroid neoplasm was considered high on the cards. Possibility of an unrelated second etiology like sarcoidosis, tuberculosis, second primary malignancy in the lung etc were thought of. We proceeded to a contrast enhanced CT scan of the chest, the representative images of which are depicted (Fig 2a and 2b). Multiple enlarged mediastinal lymphnodes involving multiple stations with mild enhancement on contrast injection was noted. Parenchymal window showed interlobular and intralobular interstitial thickening with perilymphatic nodules and peribroncho vascular interstitial thickening. Some hypo enhancing areas were visualized within the lymph nodes. Mantoux test was negative (transverse diameter of induration of 0 mm). Possibilities of metastasis with lymphangitis carcinomatosa, sarcoidosis and primary lymphoma were entertained at this juncture, although sarcoidosis would have been a clear-cut first radiological possibility if the subject had no history of malignancy.[1] Perilymphatic nodules in an HRCT image considerably narrow the differential diagnosis.[2] Decision was made to proceed with bronchoscopy, mediastinal lymph nodes sampling and brochoalveolar lavage (BAL) studies for microbial agents.



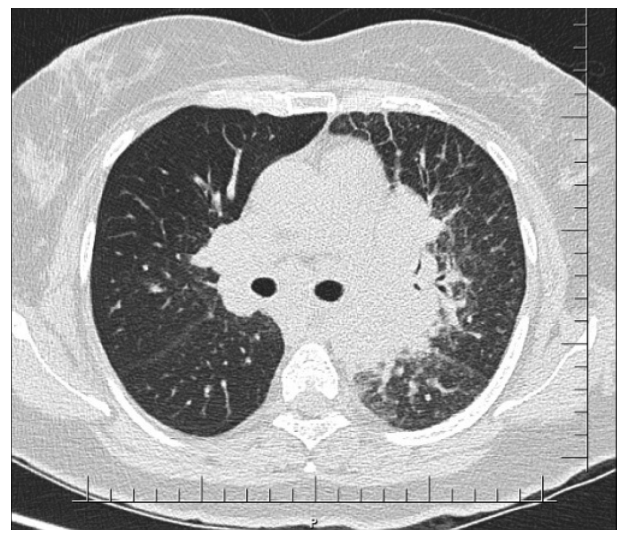


Fig 2a&2b : Representative CT chest images at presentation

Opinion from Medical Oncologist

(Sanju Cyriac)

How common is lung and mediastinal lymph node involvement in thyroid malignancies? Follicular thyroid neoplasms characteristically are uninodular in contrast to their counterpart, papillary thyroid cancer. Vascular invasion with consequent hematogenous metastasis is frequently encountered with follicular cancer, whereas spread to lymph nodes is distinctly

infrequent, occurring in only 8 to 13 percent of cases.[3] As an exception to this, lymph node involvement is more common in Hürthle cell variant of follicular cancers.[4] In contrast, lymph node involvement is very common in papillary thyroid cancer. Given the common hematogenous spread, distant metastases occur in 10 to 15 percent of patients with follicular cancer irrespective of tumor size, although metastatic disease is rarely reported in tumors <2 cm in size. Common sites of distant metastases are bone (with lytic lesions) and lung; less commonly, brain, liver, bladder, and skin are involved.[5]

Pathologist into the Picture

(Latha Abraham)

Bronchoscopy revealed nodularity of main and lobar bronchi. BAL microbial tests including CB-NAAT were unrewarding. Endobronchial lung biopsy was done which showed granulomas composed of epithelioid histiocytes and multinucleated giant cells with some crystalline inclusions (Fig 3). A tightly packed central area composed of macrophages, epithelioid cells, multinucleated giant cells,and lymphocytes surrounded by lamellar rings of hyaline collagen was seen. Special stains for acid fast bacilli and fungi were negative. Transbronchial needle aspiration cytology specimen from the subcarinal lymph nodes was richly cellular and revealed multiple well-formed non-caseating granulomas. Coupled with the negative Mantoux test and elevated serum angiotensin converting enzyme levels, a diagnosis of sarcoidosis was made with reasonable certainity. The confident distinction between tuberculosis and sarcoidosis remains challenging even to the astute clinician and pathologist. The relationship between sarcoidosis and tuberculosis remains an enigma. Even the earliest description by Caesar Boeck of a case of 'multiple benign sarkoid of the skin' was thought to be allied in some way to tuberculosis.[6] Mycobacterium tuberculosis (MTB) as a putative cause of sarcoidosis has been extensively studied with conflicting reports.[7] Remarkable clinical similarities make the differential diagnosis of the two conditions difficult. Some distinguishing features, although might help[8] (Table 1) and may be utilized by clinicians.

The decision for initiating treatment in sarcoidosis is also controversial. Although asymptomatic, our patient had hypoxia (resting peripheral oxygen saturation of 93% on room air) and hypercalcemia (serum calcium 11.8 mg / dl). These aspects coupled with the fact that she had to undergo a surgery under general anesthesia prompted us to go ahead with the decision to initiate corticosteroids up-front.

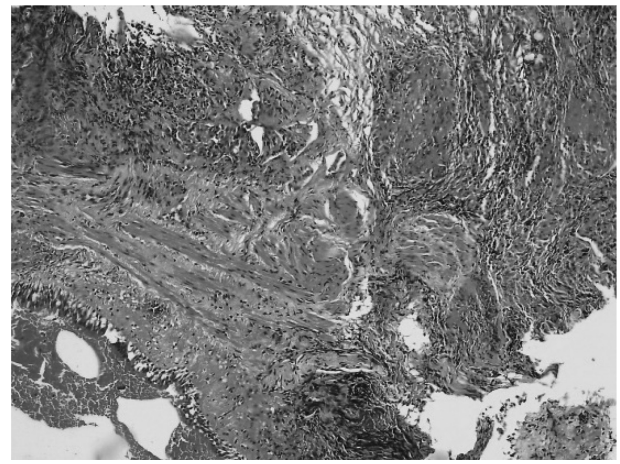


Fig 3 : H&E 400 x, endobronchial nodule biopsy showing non caseating compact granuloma

Back To the Surgeon

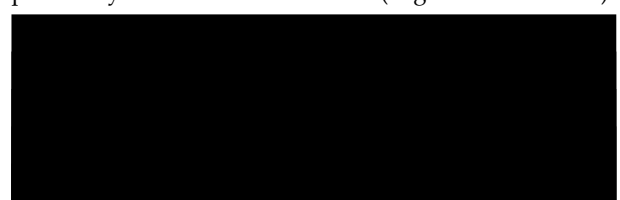
(Dhanya E.K.)

With a diagnosis of coexisting dual disease (sarcoidosis overlapping with follicular neoplasm of the thyroid), we went ahead with a total thyroidectomy. The histopathology revealed follicular carcinoma of the thyroid - Hurthle cell variant. The patient had an unremarkable perioperative period and was discharged home on the 5th post-operative day. After multi disciplinary discussion, it was decided to proceed with radio iodine ablation and thyroid hormone replacement after that. Therapy for sarcoidosis was initiated with prednisolone at a dose of 40 mg / day.

Multidisciplinary follow up

(Divya R.)

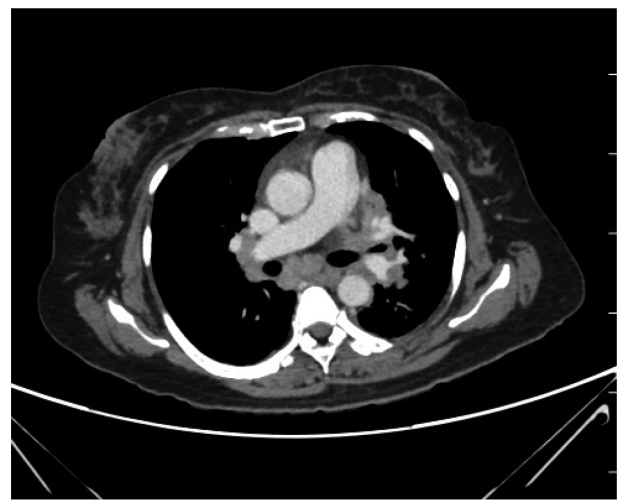
The lady remained under close clinico radiological follow up after iodine ablation and was put on tapering dose of prednisolone. She exhibited good clinical, radiological and spirometric improvement in the subsequent months. Her follow up chest radiographs and CT images are depicted here. Significant reduction in lymph node size was noted along with resolution of parenchymal abnormalities (Fig 4a and 4b).



FEATURE	FAVOURS TUBERCULOSIS	FAVOURS SARCOIDOSIS
Constitutional symptoms	More common, but mild	Less common, but severe when present
Nature of cough	Productive; often, hemoptysis	Dry; hemoptysis rare
Thoracic LN involvement	Asymmetrical; conglomerate and often hypodensities	Bilaterally symmetrical hilar LN; paratracheal LN; solid / discrete
Extrathoracic LN involvement	Cervical and axillary LN often seen	Occurs in < 10% cases
Lacrimal, parotid and myocardial involvement	Very rare	Commonly seen
Necrotising pneumonia, cavitation and pleural effusion in CXR	Commonly seen	Distinctly uncommon
HRCT findings (in diffuse disease)	Centrilobular / random nodules Tree in bud lesions	Perilymphatic nodules
Clinicoradiological dissociation	Less likely; patient symptomatic	Often seen; asymptomatic patient with abundant radiological findings
Tuberculin test	Often positive unless immuno compromised	Almost always, negative
Elevated serum ACE levels	No or mild elevation only	Often significantly elevated
Hypercalcemia or calciuria	Distinctly uncommon	Often seen
Microbial tests for M.tuberculosis in Sputum / BAL / Biopsy specimen	Often positive; confirmatory	Always negative (unless coexistent TB)
Morphology of granuloma	Caseating; ill formed; abundant inflammatory cells; AFB may be seen	Non-caseating; compact; "naked"; inclusion bodies
Response to anti TB drugs	Usually excellent response (Unless primary MDR TB)	No response (Spontaneous resolution possible)
Response to Steroid Therapy	Clinicoradiological worsening	Usually excellent response

Table 1 : Features that help to distinguish tuberculosis from sarcoidosis

This excellent therapeutic response corroborated the diagnosis of sarcoidosis. The smooth clinical course took a head-on turn at the fifth month of steroid therapy with the lady developing progressive severe dyspnoea and left sided chest discomfort over a period of 5 days. The chest radiograph revealed an opaque left hemithorax. (Fig 5). At this point of time, we thought of malignant pleural effusion as an extremely probable diagnosis given her background thyroid carcinoma coupled with rapid development of large effusion. Diagnostic thoracentesis revealed a serosanguinous fluid with negative cytology for malignant cells and borderline adenosine deaminase values. (38 U / ml)



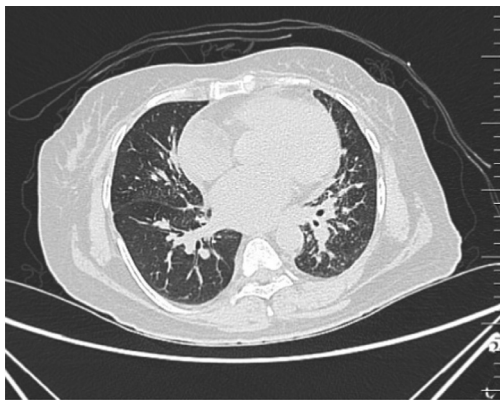


Fig 4a & 4b : Representative CT images after 3 months of steroid therapy showing reasonable resolution

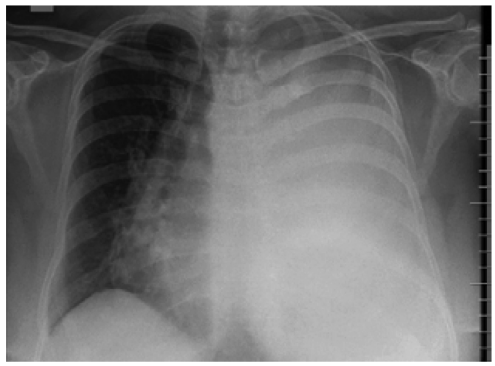


Fig 5 : posteroanterior chest radiograph at 5 months of steroid therapy when the patient became acutely dyspnoeic showing massive left side effusion

Determining the etiology of pleural effusion

(Paramez A.R.)

How do we proceed further to determine the etiology of pleural effusion? Medical thoracoscopy has a valuable role in determining the etiology of undiagnosed exudative pleural effusion by obtaining pleural tissue specimens under direct visualization, which may be subjected to microbial and histopathological examination. About 25% of pleural effusions remain undiagnosed despite primary tests such as biochemical tests, thoracocentesis and biopsy[9]. We went ahead with diagnostic medical pleuroscopy under local anesthesia supplemented by conscious sedation. The parietal pleural surface was studded with nodules of varying sizes, some having a necrotic surface (Fig 6). Biopsies were taken from multiple nodules and sent for histopathologic as well as microbial evaluation. (Bacterial culture, fungal culture and mycobacterial tests). The procedure was completed uneventfully and 2400 ml of serosanguinous pleural fluid was drained. 24 gauge intercostal drainage tube was inserted. Medical thoracoscopy in experienced centres has high yield and low complication rate. A previous study done in Kerala with 25 subjects revealed a diagnostic yield of 80%.[10].

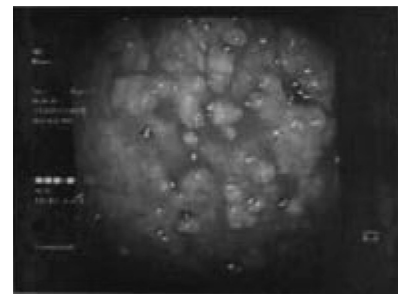


Fig 6 : Representative thoracoscopic image showing parietal pleural nodules

Pathologist once again to the Rescue

(Sunitha Thomas)

The pleural biopsy revealed multiple granulomas with caseation (Fig 7). The granulomas, as opposed to the previous lymph node specimen, showed evidence of caseation and special stains demonstrated the presence of acid fast bacilli. Differentiation of granuloma in tuberculosis versus sarcoidosis can be challenging, but some general rules prevail.[11] The presence of necrosis in the granuloma is not a fool-proof feature in distinguishing tuberculosis from sarcoidosis,[12] but the finding of acid fast bacilli does secure the diagnosis for all practical purposes. As further reports became available in subsequent days, microbial tests revealed growth of M. Tuberculosis. A conclusive diagnosis of tubercular pleuritis was made.

The Final Turn of Dice

(Rajesh V. and Jolsana Augustine)

Antituberculosis treatment was initiated with standard regimen. Steroids were rapidly tapered and stopped in subsequent days. Monitoring for hypo cortisol state was periodically monitored. Fast resolution of the effusion was observed with no reaccumulation of fluid. Serial chest radiographs and CT images (not shown) ensured complete resolution of effusion and mediastinal nodes remained subcentimetric. Anti TB chemotherapy was continued for 6 months till completion. The chest Xray at treatment completion was interpreted as a near normal image (Fig 8). At 5 months of completion of anti TB therapy, she fares well without further medical setbacks.

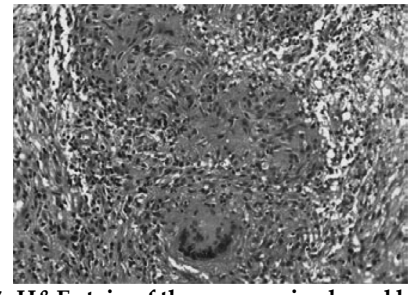


Fig 7 : H&E stain of thoracoscopic pleural biopsy specimen demonstrating caseating granulomas

As discussed previously, the distinction of tuberculosis from sarcoidosis poses a real challenge in countries where mycobacterial disease is endemic. The situation is further complicated as the two diseases can coexist in the same individual.[13] Adding to the misery, immunosuppression induced by steroid therapy in sarcoidosis predisposes to reactivation of latent tuberculosis. Terminologies like tuberculous sarcoidosis has been employed by some authors[14], but has been challenged. Vigilant clinical supervision for therapeutic response is mandatory after institution of chemotherapy for tuberculosis as well as immunosuppression for sarcoidosis.

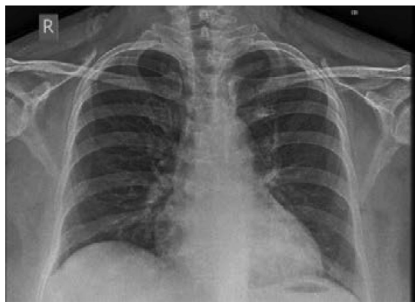


Fig 8 : posteroanterior chest radiograph at the end of anti TB treatment showing complete clearance

Case Summary and Conclusion

In short, we had a middle aged lady who presented with a malignant thyroid nodule. Pre-operative anesthetic work up revealed mediastinal adenopathy with reticular lesions in chest radiograph. Bronchoscopy with evaluation of pathological specimens coupled with ancillary tests led to a diagnosis of sarcoidosis. Total thyroidectomy and radio iodine ablation was done followed by initiation of steroids for sarcoidosis, which was tapered based on response. Sudden development of large left sided pleural effusion 5 months down the line evoked a high index of suspicion of pleural metastasis from thyroid malignancy, but thoracoscopic pleural biopsy revealed the etiology to be tuberculosis. Complete response to anti TB therapy was noted and the patient continues to be in follow up.

The case re-emphasises a lot of time honored clinical pearls and provides learning points.

1. *Dual etiology is possible in many clinical scenarios and need to be considered / looked for.*
2. *Whenever feasible, good clinical judgement should be corroborated by focused laboratory / microbial / pathological tests.*
3. *The distinction of tuberculosis from sarcoidosis poses a challenge to even the most accomplished clinician; careful interpretation of multiple facets of the individual patient may be needed to arrive at a working diagnosis.*
4. *Continued careful monitoring is vital in clinical practice. Unexpected turns should prompt periodic reevaluation.*
5. *All is well that ends well.*

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Case Report

Necrotizing Granulomatous Inflammation : The Greatest Masquerader

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Abstract

A 46 year old gentleman presented to us with fever, cough and scanty hemoptysis. He was treated as MDR TB outside for 7 months and he discontinued treatment due to intolerance. Chest radiograph showed right lower zone and left upper zone cavity. BAL AFB smear, culture and genexpert were negative. CT guided biopsy taken from right lower lobe cavity clinched the diagnosis

Key words

Lung nodules, necrotizing granulomatous inflammation, tuberculosis.

Case Report

We hereby report a case of 46 year old man who presented with history of intermittent low grade fever, cough with scanty haemoptysis, and loss of weight for last 2 months. Initially fever was low grade intermittent with evening rise of temperature which was changed to high grade continuous fever with chills and rigors over past two weeks. He also complained of dyspnoea on exertion. He had occasional scanty haemoptysis. He denied any history of joint pain, and oral ulcer. He was a reformed smoker with 20 pack years smoking history. Past medical records revealed that he had similar complaints two years back, and for that he was evaluated in another hospital. He was treated as multidrug resistant tuberculosis (MDR TB) under revised national TB programme on the basis of BAL Genexpert which was indeterminate. He said he felt better and had weight gain after initiating treatment, but discontinued treatment after 7 months. Family history was non contributory. On examination he was conscious oriented and had temp of 101^{O} F. His vitals were as following: heart rate 100/ min, respiratory rate 20/min, BP 110/70 mm of hg, SPO2 97% on breathing room air. His respiratory system examination was normal. Complete blood count showed haemoglobin of 12 gm/dl, white

blood cell count of 12,700 /cumm and platelet count of 466000/ cumm. Serum creatinine was elevated [1.15 mg/dl], urea 28.4 mg/dL. Urine routine microscopy was normal. Liver function tests were normal. ESR was elevated [86mm /1st hour]. C Reactive Protein was 106mg/dL. Serum procalcitonin was 0.080ng/ml. Other investigation like prothrombin time, serum electrolytes and serum calcium were within normal limit. Mantoux test was negative. Chest radiograph showed right lower zone and left upper zone cavitatory lung nodule(Fig:1). Sputum for AFB and Genexpert were negative. CT chest showed a large nodule in apicoposterior segment of left upper lobe measuring 4.4 x 5.6 cm. There was another thick walled cavitatory lesion with air fluid level measuring 5.8 x 4.3 cm, with thickness of the cavity wall of 1.2 cm in the superior segment of right lower lobe . (Fig: 2) Fiberoptic bronchoscopy was done which showed normal tracheobronchial tree. But nasopharynx showed ulcers bilaterally from where biopsy was taken. (Fig: 3). The biopsy showed mixed inflammation with a diagnostic finding. Finally CT guided lung biopsy was taken which confirmed the diagnosis (Fig: 4).

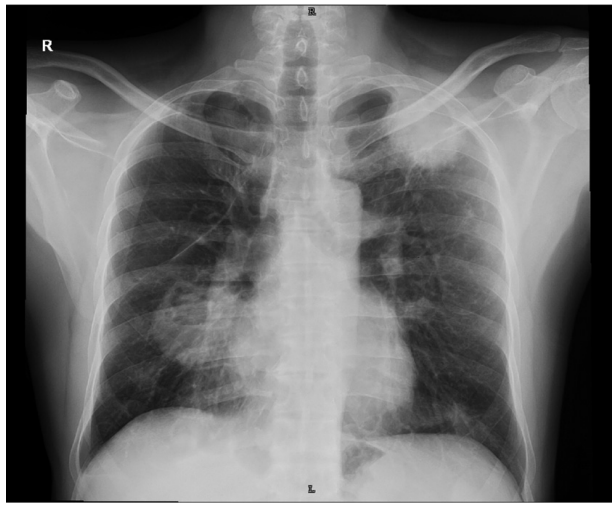

Fig 1 : Chest roentgenogram shows right lower zone and left upper lobe cavitating nodule

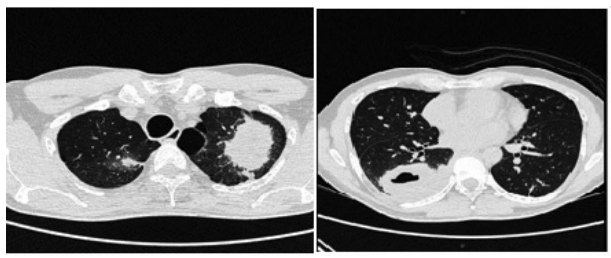

Fig 2 : Left upper lobe nodule with spiculated margins, central necrotic areas, and one a cavitatory nodule in the right lower lobe.

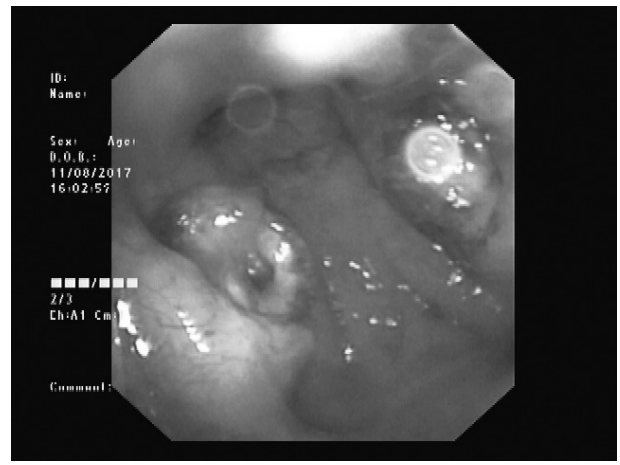

Fig 3 : Bilateral symmetrical ulcers seen on the base of nasal floor

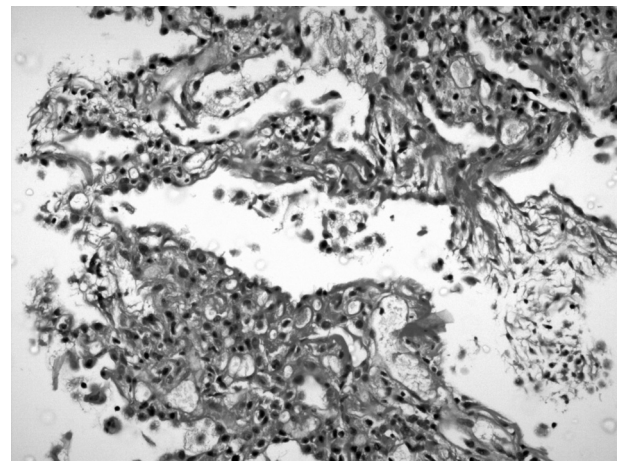

Fig 4 : Histopathology of lung biopsy showing granulomatous inflammation with necrosis (Hematoxyline-eosin, original X 10)

What is your diagnosis?

What should be the next line of management?

Before turning the page interpret the images and history and suggest a probable diagnosis.

Interpretation of radiological and bronchoscopic images:

Chest roentgenogram shows right lower zone and left upper zone cavitating nodule

CT chest: Left upper lobe nodule with spiculated margins, central necrotic areas,and a cavitating nodule in the right lower lobe.

Fiberopticbronchoscopy : Normal tracheobronchial tree. There were bilateral symmetrical ulcers on the base of nasal floor from which biopsy was taken.

Histopathology : Granulomatous inflammation with necrosis. A granuloma was visible in blood vessel, very classical of vasculitis. (Fig :5)

Final diagnosis : Granulomatous polyangitis limited to upper airway and lungs

Treatment and clinical course

He was treated with pulse methylprednisolone (1gm iv OD) for 3 days followed by 1mg /kg of body weight steroids in combination with cyclophosphamide 2mg/kg bodyweight. There was transient improvement and fever subsided. But there was no radiological resolution. So he was started on rituximab 500mg OD. He received 3 doses of rituximab 2 weeks apart and there was dramatic improvement in his symptoms as well as his chest x ray. He has been on regular follow up there after with significant relief of symptoms.

Discussion

Granulomatosis with polyangiitis (GPA), a disease characterised by necrotising granulomatous diseases, was first described in 1936 by Dr Friedrich Wegener.[1] It is a rare disease with peak incidence in the fourth or fifth decade. It is common in Caucasian (80-97%) with equal distribution among males and females. Systemic vasculitis predominantly affects the small arteries, with lesions involving the upper respiratory tract, lungs and kidneys. In 25% of the patients with GPA, involvement of the airways can be the only manifestation.[2] Common clinical presentation is haemoptysis, rhinnorrhoea and epistaxis, and few present with a vasculitic rash. Non-specific symptoms such as rash, arthralgia and malaise are also common. Kidney is affected usually in late stage of disease.[3] GPA is associated with cytoplasmic antineutrophil cyto plasmic antibodies (c-ANCA) and anti-proteinase-3 positivity aid diagnosis, which is confirmed by biopsy findings of vascular/ perivascular granulomatous inflammation.[4]

It can be challenging to differentiate GPA from TB due to the overlap in presentations of both the diseases. It can lead to misdiagnosis and subsequently inappropriate management. In countries like India, where TB is endemic a high degree of suspicion is needed to avoid missing a diagnosis like GPA. The clinical presentation of either disease may considerably overlap at some stage of the disease course. Present case highlights the need for careful clinical examination and systematic analysis of patients presenting with respiratory and upper respiratory symptoms and signs so that the diagnosis of systemic vasculitis like GPA will not be missed or delayed. If an inappropriate diagnosis of TB is made, that will result in worsening of underlying vasculitis and vice versa.[5]

Conclusion

GPA and TB has many features that can overlap. Histopathology diagnosis of necrotising granulomatous inflammation alone may not be sufficient. A high index of suspicion is necessary to ensure that the correct diagnosis is made and that TB is always considered as a possible differential diagnosis or as a coexisting pathology.

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Case Report

Elucidating the Etiology in a Subject with Undiagnosed Dyspnoea - Thinking out of the Block

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Abstract

Dyspnoea is one of the commonest presenting symptoms encountered by pulmonologists in their practice. Although a variety of pulmonary diseases can have dyspnoea as the cardinal symptom, it needs to be stressed that disorders affecting other organ systems like cardiovascular and neuromuscular diseases can also have breathlessness as a presenting feature. The astute clinician is left with the task of elucidating the etiology of dyspnoea with a careful history, focused physical evaluation and targeted battery of investigations. We share the case of a 65 year old gentleman who presented with progressive breathlessness of 6 months duration. Pulmonary and cardiovascular evaluations on multiple occasions at multiple institutions were unrewarding with regard to the etiology. A focused multidisciplinary approach at our institution established a diagnosis of multiple system atrophy as the cause of his clinical syndrome. Appropriate therapy, supportive measures and prognostication was instituted and he remains under clinical follow up.

Key Words

Multiple system atrophy, evaluation of dyspnoea, parkinsonism, autonomic dysfunction

Initial presentation

Respiration is unique in that, of all the vital functions, it alone has dual regulation. It is regulated not only by automatic centers located in the brainstem but also by voluntary signals initiated in the cortex[1]. As an offshoot, individuals have some control over their own breathing; as a corollary, sensations arising from various sites do affect the rate and pattern of breathing as well as the individual's subjective sensation of breathing. Dyspnoea, along with cough and chest pain, rank as the top three presenting symptoms to the pulmonologist. The mechanism(s) and pathways of this sensation remain unclear, but recent animal and human studies have shed some light on this aspect of dyspnea[2]. The causes of dyspnoea are large in number. Diseases of the cardiovascular and respiratory system account for the vast majority of dyspnoea. However, conditions like anemia, thyroid disease, neuromuscular disorders, obesity etc are well known to cause dyspnoea. Although the initial assessment should look for cardiopulmonary disorders as the etiology, a broader outlook and evaluation may be needed in a minority. We share the case of a 65 year old gentleman who presented with

progressive breathlessness and no identified etiology on cardiopulmonary evaluation on multiple occasions. Careful multidisciplinary reassessment clinched him to be having multiple system atrophy, a progressive neurodegenerative disease of grave prognosis. The case highlights the importance of having a broader outlook in the evaluation of elusive dyspnoeic subjects and underscores the benefits of multidisciplinary evaluation.

Case Report

A 65 year old gentleman presented to our outpatient department with shortness of breath for last 6 months, the symptoms being slowly progressive in nature. He has been having systemic hypertension and type 2 diabetes mellitus for the last 12 years, both of which have been under good control. He was on cilnidipine and glimepiride-metformin combination for hypertension and diabetes mellitus respectively. He pursued an office job till his retirement at 60 years and denied any significant occupational exposures. He had no addictions or high risk sexual behavior. He was non atopic and denied any wheeze. The dyspnoea was not worsened with exposure to dust, humidity or temperature variations. There was no orthopnea or paroxysmal nocturnal dyspnoea. No skin or joint symptoms were noticed. He had difficulty in walking which was attributed to diabetic neuropathy by his primary physician. He was evaluated previously in two reputed centres in the last 2 months and thorough evaluation by cardiologist and pulmonologist including relevant tests (ECG, ECHO, Spirometry, HRCT of chest and CT pulmonary angiogram) failed to reveal a cause for dyspnoea.

Physical evaluation revealed a comfortable gentleman with a respiratory rate of 20 per minute and no distress. Finger oximetry revealed an oxygen saturation of 97% while breathing room air. No skin lesions were made out. The neck was supple with no venous distention or engorgement. No peripheral lymphadenopathy was made out. Chest auscultation revealed no abnormal findings. Abdomen was soft to palpation and disclosed no organomegaly. Apart from these unrewarding efforts, a generalized paucity and slowing of movements was noted along with rigidity. The gait and movements tended to suggest parkinsonism. We proceeded to re-do the investigations and get a detailed neurologist evaluation. Spirometry and diffusion capacity report was normal. (Figure 1) Blood gas analysis did not reveal carbon dioxide retention. An HRCT of the thorax along with CT pulmonary angiogram did not reveal any parenchymal, mediastinal, airway or pulmonary vascular pathology. (Figure 2) Echocardiography showed essentially a normal cardiac structure, good left ventricular systolic function, grade 1 diastolic dysfunction and no features of pulmonary hypertension. Hemoglobin, thyroid function and renal function values were normal.

A focused evaluation by neurologist suggested parkinsonian features with rigidity, bradykinesia and postural tremor. He had a broad based, short step gait. Blood pressure checking in supine and upright positions revealed severe orthostatic hypotension (Systolic BP fall of 35 mm and diastolic BP fall of 18 mm Hg).

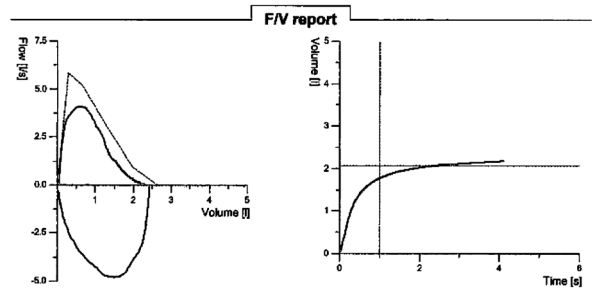

Fig. 1 : Spirometry showing normal lung function

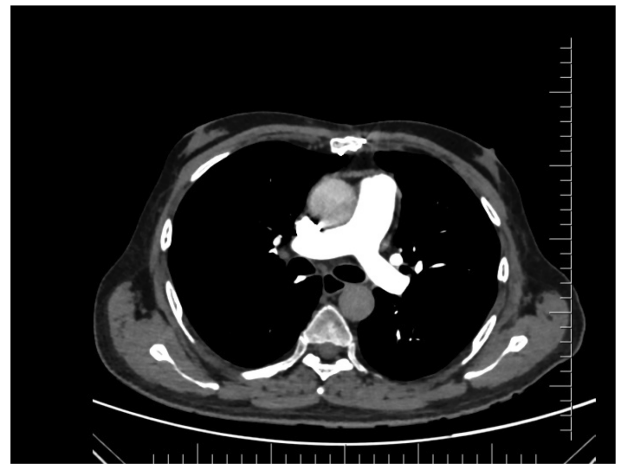

Fig. 2 : CT pulmonary angiogram with no features of pulmonary thromboembolism

Retrospective interrogation brought to light symptoms of urinary hesitancy and erectile dysfunction. USG pelvis showed significant volume of post void residual urine in the absence of bladder outlet obstruction. A probable diagnosis of multiple system atrophy was entertained and an MRI of the brain was requested. MRI brain showed decreased volume of bilateral putamen with T2 hyperintensity of the lateral putamen ('rim sign') suggestive of multiple system atrophy. (Fig 3)

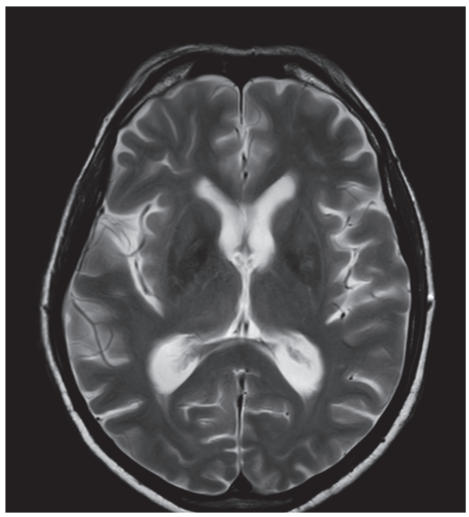

Fig. 3 : MRI brain showing mildly reduced putaminal volume with T2 hyperintensities on the lateral aspect of putamen

During the course of his hospital stay, he developed mild noisy breathing consistent with early stridor. ENT evaluation revealed sluggish abduction of vocal cords bilaterally although the glottis space was seemed adequate (no critical narrowing). Swallowing evaluation disclosed no features of aspiration. He was initiated on levodopa and was scheduled to undergo a polysomnography. He has some degree of symptomatic improvement of dyspnoea and locomotion at 2 weeks of therapy. The progressive nature of the disease, limitation in therapeutic options and guarded outcome was discussed in detail with the patient and family members. He continues to be in close follow up.

Discussion

Dyspnoea, often termed as shortness of breath or breathlessness, is an exceedingly common presenting symptom encountered by pulmonologists in their clinical practice and is often a distressing symptom reported by patients[3]. Dyspnoea accounts for nearly half of hospital admissions in respiratory unit in tertiary centres[4]. Dyspnoea is defined as an unpleasant subjective awareness of one's own breathing. As dyspnoea is a subjective symptom, the occurrence and intensity of dyspnoea varies greatly among individuals exposed to the same stimuli or with similar pathologies due to individual variations in perception threshold. Dyspnoea may be physiological, pathological or social in origin. The pathophysiology of dyspnoea is complex and involves the activation of several possible pathways either singly or in combination. The net effect of these pathway stimulation lead to increased work of breathing, stimulation of the receptors (upper or lower airway, lung parenchyma, or chest wall) and excessive stimulation of the respiratory centre by central / peripheral chemoreceptors. Although several sensory receptors located throughout the respiratory system are considered to be potentially capable for generation of dyspnoea, there is no single afferent receptor solely dedicated for the sensation of dyspnoea. Afferent information from the sensory receptors is processed at the cortex along with the respiratory motor command from the cortex and brainstem, and a mismatch between the motor command and the incoming afferent information may result in dyspnoea. This has been termed the length - tension inappropriateness theory behind the pathogenesis of dyspnoea. Excellent review and schematic representation of the dyspnoea pathway is available in medical literature[1]. Dyspnoea is not a single sensation and there are at least three distinct components including air hunger, work/effort, and chest tightness. Like pain, dyspnoea has at least two distinct separate dimensions, viz a sensory and an affective dimension.

The causes of dyspnoea are manifold and accurate differential diagnosis may be challenging to even accomplished clinicians. A focused history, targeted physical evaluation and directed battery of tests clinches the diagnosis in most, but not all situations. Dyspnoea is primarily of respiratory or cardiac origin, with almost 90% of all acute cases are accounted by asthma, heart failure, myocardial ischemia, chronic obstructive pulmonary disease (COPD), pneumonia and psychogenic disorders[5]. However it is prudent to remember that neurological, gastrointestinal and metabolic disorders, although much less frequent, can have dyspnoea as a presenting symptom. These diseases need to be considered when cardiac and pulmonary evaluations are non-contributory with regard to the cause of dyspnoea. The common non cardio-pulmonary causes of dyspnoea have been summarised in table 1.

Multiple system atrophy (MSA) is an adult-onset, sporadic, rapidly progressive, multisystem, neurodegenerative disease of undetermined etiology. The clinical features of the disease is characterized by varying severity of parkinsonian features, cerebellar as well as autonomic dysfunction. Neuropathological hallmarks of MSA are cell loss in the striatonigral and olivopontocerebellar structures of the brain and spinal cord accompanied by profuse, distinctive glial cytoplasmic inclusions (GCIs) formed by fibrillized

NON CARDIO-PULMONARY CAUSES OF DYSPNOEA

Gastrointestinal
Massive ascitis
Hepatopulmonary syndrome
Large abdominal tumor

Hematological
Anemia
Met / sulfhemoglobulinemia
Carbon monoxide poisoning

Laryngeal
Vocal cord dysfunction
Anaphylaxis with laryngeal edema

Endocrine / Metabolic
Thyroid disease
Cushing's syndrome
Metabolic acidosis

Neurological
Paralytic poliomyelitis
High spinal cord lesions
Myasthenia gravis
Motor neuron disease
Tetanus / botulism

Psychogenic dyspnoea

Table 1 : Common non cardiopulmonary causes of dyspnoea

alpha-synuclein proteins[6]. These pathologic hallmarks are seldom demonstrable ante-mortem. The probable early cases of MSA were described as olivoponto cerebellar atrophy (OPCA) about a century ago. The Shy-Drager syndrome with features of parkinsonism and autonomic failure with orthostatic hypotension was described in 1960. A consensus statement by the American Autonomic Society and American Academy of Neurology has categorized MSA into MSA with predominant parkinsonism features (MSA-P) and MSA with dominant cerebellar features (MSA-C)[7].

The diagnosis of MSA is challenging. 87% of patients have features of parkinsonism like rigidity, tremor, bradykinesia and postural instability, but are poorly responsive to levodopa. More than half have features of cerebellar disease like gait or limb ataxia. The presence of autonomic dysfunction prompts the diagnosis of MSA. Orthostatic hypotension is the hallmark of autonomic dysfunction and is defined as blood pressure fall by at least 30 mm Hg systolic as well as 15mm Hg diastolic within 3 minutes of standing from a previous 3-minute interval in the recumbent position. The patient complaints of dizziness or light-headedness on getting up from recumbent position. Urogenital dysfunction like incomplete bladder emptying (in the absence of bladder outlet obstruction), urinary incontinence and erectile dysfunction are common in MSA. A diagnosis of probable MSA may be made on the consensus statement mentioned previously. A complete discussion of MSA is beyond the scope of this case report, but some of the salient distinguishing features of MSA as opposed to Parkinsonism in listed in Table 2.

FEATURE	MULTIPLE SYSTEM ATROPHY	PARKINSONISM
Progression of symptoms	Fast (usually over weeks to months)	Relatively slow (Months to years)
Postural instability and falling	Early and more common	Late and less common
Speech	Severe be severely affected	Less severe affection
Respiration	Inspiratory gasps and stridor in upto 60% subjects	Much less common
Peripheral temperature	Cold hands; slow warm up	Normal
Orthostatic hypotension	Very common	Distinctly uncommon
MRI brain	Hyperintensity of the lateral margin of the putamen on T2-weighted images	Putaminal atrophy and hypointensity
Dopamine uptake on PET scan (Caudate – putamen index)	Decreased uptake in putamen and caudate nucleus	Decreased in putamen; smaller increase in caudate nucleus
Lewy bodies	Absent	Present (substantianigra)
Cytoplasmic inclusion	Glial inclusions; argyrophilic cellular inclusions in oligodendrocytes	Absent
Response to levodopa	Poor and ill sustained	Good and sustained

Table 2 : Distinguishing features of Parkinsonism Versus Multiple System Atrophy

Neuroimaging may be corroborative in the diagnosis of MSA, but the imaging features are in no way diagnostic. MRI brain is the most frequent imaging modality requested and may be particularly helpful in ruling out alternate diagnoses. Brain images may be normal in MSA. However, olivopontocerebellar atrophy (OPCA), cerebellar atrophy, and the putaminal lesions of striatonigral degeneration are often detected using MRI techniques. The slight hyperintensity of the lateral margin of the putamen on T2-weighted MRI is a characteristic finding in patients with MSA involving the extrapyramidal system[8]. The absence of vascular damage, absence of multi-infarct pattern in brain or other structural lesions may be helpful. In patients with parkinsonian MSA (MSA-P), MRI of the brain shows putaminal atrophy, hypointensity of putaminal body, and markedly hyperintense putaminal rim. Putaminal rim sign, also known as the putaminal slit sign, is a relatively specific sign of multiple system atrophy - parkinsonism (MSA-P), and refers to a linear region of high signal surrounding the lateral aspect of the putamen[9].

Respiratory involvement in MSA has been described. Laryngeal stridor due to vocal cord paralysis, central / mixed sleep apneas (with excessive daytime somnolence, pulmonary hypertension and cor pulmonale), swallowing disturbances leading to recurrent aspiration pneumonias and respiratory muscle weakness with

restrictive ventilatory defect can occur. Respiratory insufficiency can rarely be the primary presenting symptom of MSA[10]. Sleep- disordered breathing, especially central sleep apnea is commonly encountered which could explain why patients with MSA may die of respiratory insufficiency despite tracheostomy. Central sleep apnea occurs mainly due to involvement of the respiratory center and impaired hypoxemic ventilatory response. Pulmonary function tests, formal evaluation of vocal cord function and swallowing by ENT specialist as well as polysomnography is indicated even in the absence of overt pulmonary involvement. Aspiration pneumonia is a common terminal event in MSA and feeding might have to be undertaken via nasogastric tube / percutaneous gastrostomy tube in the presence of overt aspiration. The prognosis in MSA is poor as this is a progressive disease and therapy is mainly supportive. Initial response to levodopa has been described with improvement in vocal cord function and amelioration of stridor, but secondary failure of pharmacotherapy is the rule in MSA. Delineation between central and obstructive sleep apnea is crucial in the management of respiratory insufficiency. Management of laryngeal stridor may necessitate surgical plasty of the vocal cords. Vocal cord lateral fixation, Laser arytenoidectomy, intralaryngeal injections of botulinum toxin into adductors, tracheostomy etc are some of the modalities attempted[11]. Additionally, the use of non-invasive ventilation with continuous positive airway pressure (CPAP) or bilevel positive airway pressure therapy while sleeping is used to prevent sudden nocturnal death. If respiratory stridor is present during wakefulness and the patient doesn't tolerate the C-PAP and refuses a possible tracheotomy, it is possible to perform a CO2 laser subtotal arytenoidectomy to restore an adequate airflow through the glottis[11].

Summary

The causes of progressive breathlessness in clinical practice are manifold. Although diseases of the cardiovascular and respiratory system account for the vast majority of cases, neurological and metabolic diseases need to be considered in the absence of cardio-pulmonary involvement. Multiple system atrophy is an uncommon progressive neurodegenerative disease which can indirectly involve the respiratory system in multiple ways. The diagnosis of MSA may be challenging, but poorly responsive parkinsonism with autonomic involvement is a strong pointer towards the possibility. Vocal cord paralysis with stridor, recurrent aspirations, central / mixed sleep apneas, restrictive ventilatory defect etc can occur and need to be looked for as well as therapeutically targeted. The case is an eye opener and urges us to look beyond the heart and lungs in subjects without an etiological clue for dyspnoea.

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Case Report

Pulmonary Arterio - Venous Malformations Presenting as Hemothorax

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Abstract

Pulmonary arteriovenous malformation is a rare anomaly that presents in several different ways. PAVM are usually asymptomatic in presentation. Pulmonary haemorrhage in patients with pulmonary arterio - venous malformation is very rare. Pulmonary haemorrhage is a very lethal complication of pulmonary arteriovenous malformation and it should be treated aggressively. We report a case of 73 year old female who was evaluated for spontaneous haemothorax on the right side and detected to have large PAVM. She was successfully treated by embolization with platinum coils and vascular plugs

Key Words

Pulmonary arteriovenous malformation, spontaneous hemothorax, pleural effusion.

Introduction

Pulmonary arterio-venous malformations (PAVM) are characterized by direct communication between pulmonary artery and pulmonary vein causing right to left shunt[1]. PAVM has various clinical presentations from an asymptomatic incidentally discovered lesion to potentially life threatening haemothorax. Haemothorax is a very rare complication of PAVM and it is usually due to rupture of subpleural PAVM[1]. There is a strong association with Osler-RenduWeber disease[2]. Although most patients are asymptomatic, dyspnoea may occur due to right to left shunt[3]. Because of paradoxical emboli, various central nervous system complications have been described including stroke, and brain abscess[4]. Pulmonary angiography is diagnostic[5]. Therapeutic options include angiographic embolisation with metal coils or balloon occlusion, and surgical excision[3]. Pulmonary haemorrhage due to spontaneous rupture of the PAVMs is a rare but a potentially life-threatening complication that should be treated aggressively with embolotherapy[6].

A case of pulmonary arteriovenous malformation producing right-sided haemothorax as its initial presentation in a 73 year-old female is reported here. 73 year old female presented with right sided catching type of chest pain which increased with inspiration. Pain was non radiating, associated with increased breathlessness for 5 days duration. Breathlessness increased from MRC grade 2 to grade 3. She preferred lying right lateral position.

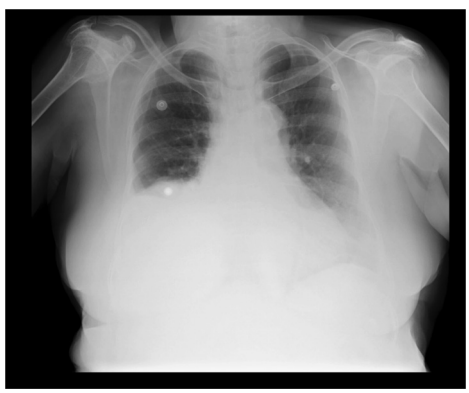
She also gave history of on and off episodes of fever since 2-3 month; last episode being one week prior. It was usually a low grade evening rise of temperature associated with chills and rigor. She also complained of loss of weight (unquantified) since 6 months. There was no history of abdominal distension, pedal edema or diaphoresis. Patient was admitted in a nearby hospital & evaluated and pleural aspiration was attempted. The procedure was deferred since the fluid aspirated was hemorrhagic.

She was diabetic and hypertensive, for which she was on metformin and amlodipine respectively for last 4 years. She had been having dyspnoea on exertion since 10 years which progressed from grade 1 to 2 since 3 years.She had no addictions besides pan chewing which she stopped 5 years back. She also gave a significant history of exposure to indoor air pollution. Two of her two brothers had Type 2 DM and CKD.

On examination, she was pale. However, there was no icterus, cyanosis, clubbing, lymphadenopathy or edema. She was tachypnoeic with a respiratory rate of 34/min. Her other vital signs were within normal limits. Head to foot examination was normal.

Respiratory system examination revealed trachea deviation to the left with a lateral shift of cardiac apical impulse. Chest movements were decreased on the right hemithorax. A stony dull note was percussed anteriorly from right 4th ICS and also in the infrascapular, infraaxillary, lower interscapular areas. Breath sounds and vocal resonance was also decreased in the aforementioned areas.

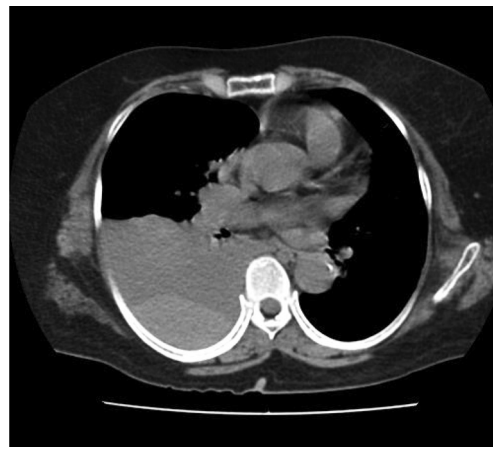
Chest xray showed a homogenous opacity in the right lower zone which silhouetted the cardiac border and diaphragm. Upperborder of the opacity was convex and ill-defined. There was no air bronchogram and the costophrenic and cardiophrenic angles were obliterated. All these features were suggestive of a pleural and underlying parenchymal pathology.

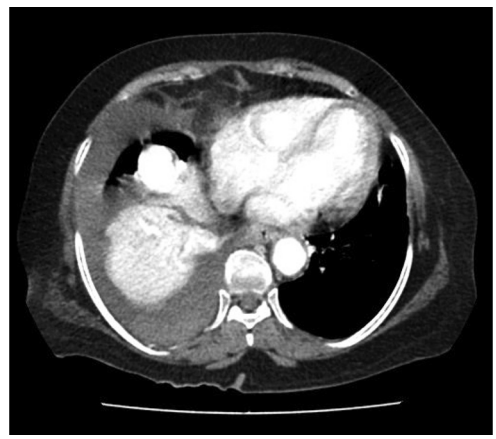


Blood investigation showed anemia; haemoglobin of 8.8gm% and PCV 26.3. Coagulation profile was normal.

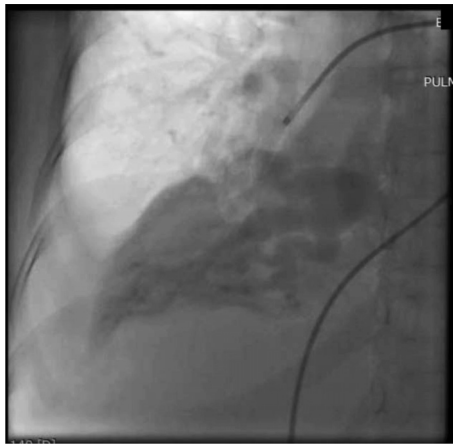
USG thorax showed approximately 500ml of fluid in the right pleural space with collapsed lung underneath. 50 ml of hemorrhagic pleural fluid was aspirated and analysed. Procedure was stopped due to dry tap.Pleural fluid analysis showed a total leukocyte count of 11500 predominatly neutrophils (80%). Pleural fluid LDH was 1137 and protein was4.6gm%. Pleural fluid PCV was18 suggesting hemothorax. Pleural fluid cytology was negative for malignant cells.

A CECT thorax was then done which showed moderate right sided pleural effusion with hyperdense area in the dependant portion, most likely representing a clot. There was also a homogenous, well-circumscribed, brightly enhancing lesion measuring 2.4 cms with enahancement similar to that of the pulmonary artery, in the right middle lobe. Both lobes and isthmus of the thyroid gland were bulky. Diffuse hypoattenuation of the liver was also noted - suggestive of fatty liver. Most likely diagnoses were pulmonary artery aneurysm or pulmonary arteriovenous malformations.





We then proceeded by performing a pulmonary angiogram by our interventional cardiologist. It showed pulmonary AV malformation with saccular venous aneurysm with feeding fistula from right lower pulmonary artery.



In order to confirm the degree of shunt, we obtained blood from main pulmonary artery and left ventricle which demonstrated inadequate oxygenation. The result was as follows:

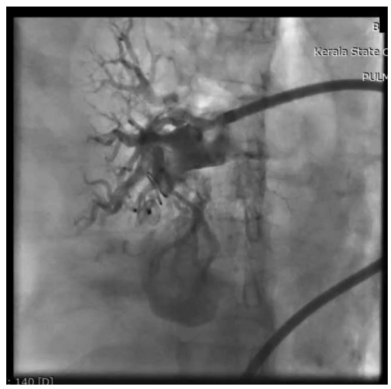
Main Pulmonary Artery ABG

pH - 7.417
PO2 - 25.7
PCO2 - 46.5
HCO3 - 29.3

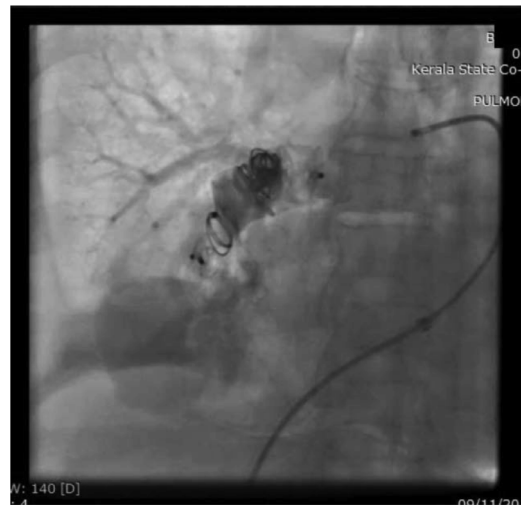
Left Ventricle ABG

pH - 7.436
PO2 - 40.9
PCO2 - 42.3
HCO3 - 27.9

We then decided to embolize the pulmonary artery with platinum coils (Cooks embolization coils) and vascular plugs (amplatzer vascular plug II) in order to reduce the shunting of blood.



Post procedure, there was no shunting of blood and the malformation was not visible.



Patient improved significantly following the procedure. We were able to aspirate another 300ml of blood and following that she was discharged home.

Discussion

PAVM are rare congenital vascular malformations of the lung. PAVMs can be due to congenital or acquired causes, more than 80% being congenital[7,8,9,10]. The Secondary or acquired PAVMs may be due to chest trauma, thoracic surgery, hepatic cirrhosis, metastatic carcinoma, mitral stenosis, infections like actinomycosis and schistosomiasis, and systemic amyloidosis[11,12,13,14,15,16]. Females are more frequently affected. PAVMs may be single or multiple. Solitary PAVMs are commonly seen in bilateral lower lobes, the most common site being left lower lobe[8,17,18]. Pleural involvement is seen in most cases. Usually the feeding artery is one or more branches of pulmonary artery and the efferent limb draining in to the pulmonary vein. In rare cases feeding arteries of PAVM can arise from the systemic arteries and also drain in to the inferior vena cava.

The fundamental defect is right-to-left shunt, the degree of shunt determines the clinical effects on the patient[10,11]. In minimal shunt, the symptoms will be subacute or even absent. In case of shunts greater than 20% of the cardiac output and if haemoglobin levels are more than 50g/l then there will be cyanosis, clubbing, and polycythaemia. In some cases lesions will be discovered by chance on chest radiography or

during evaluation of Osler-Rendu-Weber disease (found in 60-90% cases)[2] Symptoms like dyspnoea, haemoptysis, cyanosis and clubbing develop between the fourth and sixth decade[3]. Orthostatic hypoxaemia (orthodeoxia) may occur as most of the lesions are situated at lung bases[3,19]. Platypnoea is due to decreased blood flow through PAVMs in the supine position[3]. Neurological complications include strokes (18%), transient ischaemic attacks (37%), cerebral abscess (9%), migraine (43%), and seizures (8%)[4] Usual diagnostic modalites like Inhalation of 100% oxygen method, contrast echocardiography, radionuclide imaging and Contrast enhanced Computed tomogram are very useful tool in evaluation of patients with PAVM[3,20]. Pulmonary angiography remains the gold standard method. It also helps to plan therapeutic strategy[21]. 25% of patients show, progressive enlargement of lesion over a period of time[22]. The most common complication in PAVM, are neurological due to paradoxical embolization[23].

A very rare and lethal complication is Pulmonary haemorrhage. It can occur either in thepulmonary parenchyma causing hemoptysis or into the pleural cavity causing haemothorax. Haemoptysis is usually due to intra parenchymal rupture or due to endobronchial rupture of PAVM. Ferrance et al reported 8% incidence of haemothorax in his study and it was mostly due to rupture of sub pleural PAVM[24].

Symptomatic PAVM should be treated either using a transcatheter approach or by surgical management. Recently White and co-workers concluded that even asymptomatic PAVM with feeding vessels 3 mm or greater need to be treated[25]. Embolization therapy is the standard treatment of PAVM. Remy etal in their study found that embolotherapy using various coils, detachable balloons have been found to be very effective in 90-95% of patients[26]. Surgical resection is only indicated in cases of failure of embolotherapy, serious bleeding despite embolotherapy and intrapleural rupture of PAVM causing massive haemothorax. Our patient was treated with embolotherapy.

This case is presented in view of its rarity, with a rare complication and successful management.

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Interactive Case Discussion

Chronic Cough in a Diabetic

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Abstract

Cough is a common symptom. A variety of intra thoracic as well as extra thoracic diseases can cause cough. We discuss the differential diagnosis and clinical approach to chronic cough in this case based discussion.

Key words

Chronic cough; Causes for cough; Cavity in lung.

A 47 year old male patient, known diabetic on oral hypoglycemic drug since 5 years presented with persistent cough for last 6 months. Cough was insidious in onset with scanty mucoid sputum. There was no aggravating or relieving factors for cough. He had no other associated respiratory symptoms. There was no history of fever, weight loss or anorexia. He had no symptoms referable to other systems. He was not on any other medications except metformin for diabetes mellitus. He had no other illness in past. He was a non smoker. He had no addictions. There was no psychiatric symptoms or behavioral disturbances.

Question : 1

Which of the following is LEAST LIKELY to cause chronic cough in this patient?

1. Hyper reactive airway disease
2. Gastro esophageal reflux disease (GERD)
3. Tropical pulmonary eosinophilia
4. Cough variant asthma
5. Psychogenic cough

Answer : 5

Psychogenic cough is least likely in middle age. It usually occurs in children who cannot express themselves. Psychogenic cough is usually due to underlying psychological stress. It occurs only when the patient is with others and being observed. It does not occur at night or during sleep. This patient had no history of psychiatric symptoms or behavioral disturbances[1].

Rarely cough can be the sole or prominent symptom in some extra thoracic diseases and systemic diseases.

Question : 2

Which of the following condition is LEAST

LIKELY to cause chronic cough?

1. Chronic liver abscess/sub phrenic abscess
2. Iliocecal tuberculosis
3. Autoimmune/connective tissue diseases
4. Hematopoietic and lymphoid malignancies
5. Tuberculous pericarditis

Answer : 2

Iliocecal tuberculosis is least likely to cause as there are no cough receptors in this region. Sub diaphragmatic lesions like liver abscess/sub phrenic abscess can irritate the diaphragm to cause cough. Pericardium also has cough receptors. Hence pericarditis can lead to cough[2]. Autoimmune/connective tissue diseases and hematopoietic and lymphoid malignancies can involve lungs/ mediastinum and can lead to cough.

History of medications is important as some drugs can cause cough.

Question : 3

Which of the following groups of drugs is LEAST LIKELY to cause chronic cough?

1. Tricyclic antidepressants
2. Angiotensin-converting enzyme (ACE) inhibitors
3. Beta blockers
4. Non-steroidal anti-inflammatory drugs (NSAIDs)
5. Calcium channel blockers and nitrates

Answer : 1

Tricyclic antidepressants are least likely to cause chronic cough[3].

Cough is a protective reflex which occurs due to the stimulation of a complex reflex arc. Cough is initiated by the irritation of cough receptors. Cough receptors are present mainly in the upper and lower airways. Apart from airways some cough receptors are present in other sites also, stimulation of which can lead to cough.

Question : 4

Which one of the following sites DOES NOT have cough receptor?

1. Diaphragm
2. Pericardium
3. Esophagus
4. Stomach
5. Peritoneum

Answer : 5

Cough receptors are present in pleura, upper airways, external and internal ear, diaphragm, pericardium, esophagus and stomach[4]. Any lesion in these areas can lead to cough as a symptom.

Question : 5

Which of the following is LEAST LIKELY to cause chronic dry cough without any other obvious symptoms or signs?

1. Hyper reactive airway disease
2. Chronic obstructive pulmonary disease (COPD)
3. Gastro-esophageal reflux disease
4. Small intrathoracic tumors
5. Endobronchial lesion

Answer : 2

In COPD predominant symptom is breathlessness.

Question : 6

In this patient who is a diabetic with chronic cough, scanty sputum and no other symptoms, what could be the possible causes for chronic cough?

Answer :

Hyper reactive airway diseases

Gastro esophageal reflux disease (GERD)

Tropical pulmonary eosinophelia

Cough variant asthma

Intra thoracic secondaries

Endobronchial lesion

Cardiac causes

Extra thoracic lesions

Rarely cough can occur as a para neoplastic manifestation in renal cell carcinoma[5].

Physical findings

General physical examination was unremarkable. Upper respiratory tract and systemic examination were normal.

Question : 7

What is the next investigation in this patient?

Answer :

Chest x-ray PA view

In any patient with chronic cough without sputum production, after physical examination next investigation of choice is chest x ray[6].

Investigations

Total and differential leukocyte counts were normal. ESR was 32 mm/hr. Sputum AFB smear 2 samples were negative. Sputum gene Xpert - MTB was not detected. Sputum culture yielded no growth. USG abdomen was normal.

Question : 8

What is the next investigation?

Answer :

High resolution CT scan of thorax (HRCT) [6].

Question : 9

In which of the following condition CT scan thorax is NOT essential for diagnosis in chronic cough with normal chest x-ray and no obvious cause for cough?

1. Occasional hemoptysis in an elderly smoker
2. Progressive dyspnea
3. Significant weight loss
4. Fever on and off
5. Symptoms suggestive of allergic rhinitis

Answer : 5

If there is allergic rhinitis then most likely the cause for cough is allergic rhinitis. In such a case allergic rhinitis needs to be properly treated first which may relive cough. Further evaluation may be done if cough persists despite treating allergic rhinitis[6].

HRCT thorax was done which showed a cavity in the right lower lobe.

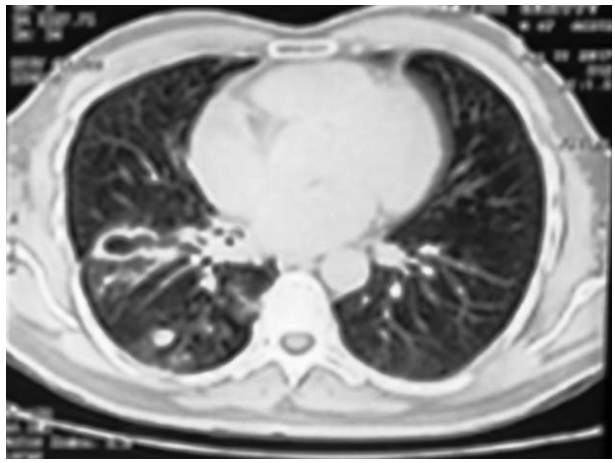

Fig 1 : CT scan showing cavity

Question : 10

Which is the most common cause for cavity in the lungs?

1. Squamous cell carcinoma
2. Fungal infection
3. Tuberculosis
4. Klebsiella pneumonia
5. Melioidosis

Answer : 3

Most common cause for cavity in the lung is pulmonary tuberculosis[7].

Question : 11

Which of the following is a NOT common radiological characteristic of tubercular cavity?

1. Upper lobe predominance
2. Infiltrates surrounding the cavity
3. Prominent air fluid level
4. May be thick or thin walled
5. Can be Single/Multiple

Answer : 3

Tubercular cavity is usually devoid of air-fluid level[7].

Question : 12

What are the causes for sputum AFB smear negativity in a case with cavity in lung?

Answer :

1. Improper collection of sputum
2. Improper sputum examination
3. Patient on Anti tuberculosis treatment/ Completed treatment
4. Other causes for cavity in lung like - other infections/ sequelae of infections, systemic auto immune diseases[8].

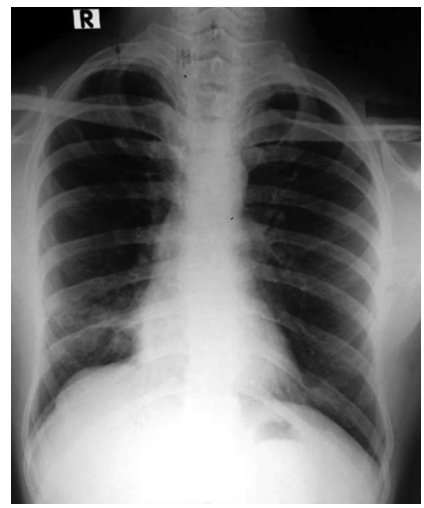

Fig 2 : Initial Chest x ray

Bronchoscopy was done as CT showed cavity.

Bronchoscopic washings for AFB smear was 2+

Bronchoscopic washings gene X pert MTB detected - High. No rifampicin resistance.

AFB culture MTB grown

Question : 13

Which of the following is the MOST COMMON indication for bronchoscopy in suspected tuberculosis?

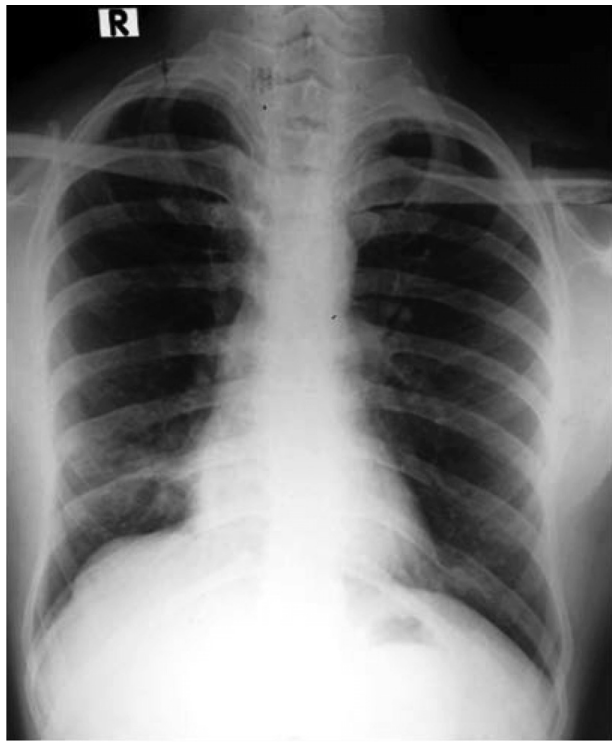

Fig 3 : Chest x ray after completion of 6 months ATT

1. To rule out other diseases which mimic TB
2. Symptoms and chest x ray not typical
3. Sputum AFB smear negative
4. Gene Xpert negative
5. Cavitating lesion in chest x ray

Answer : 1

Many other diseases can mimic TB clinically and radiologically. When diagnosis is not certain bronchoscopy is indicated in such cases[8].

Final diagnosis : Pulmonary tuberculosis.

Question : 14

Which of the following is LEAST LIKELY to cause cavity in the lungs?

1. Pulmonary Tuberculosis
2. Klebsiella pneumonia
3. Viral Pneumonia
4. Squamous cell carcinoma
5. Fungal infection

Answer : 3

Viral infection per se is least likely to cause cavity in the lungs[9].

Treatment

Patient was started on ATT, category 1 under RNTCP. Cough reduced in 2 weeks, and subsided completely after 6weeks. After 6 months of regular ATT there was uneventful recovery.

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