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Case Report

'Stepladder Lung Cavities' with 'Starry Sky Pattern' in HRCT Thorax with Constitutional Symptoms: A Strong Predictor of Active Pulmonary Tuberculosis

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Abstract: Pulmonary Tuberculosis is most common diseases in India with significant mortality and morbidity. Tuberculosis can cause diverse thoracic presentations ranging from nodules, consolidations & cavitation, mediastinal adenopathy, pleural effusion to diffuse endobronchial disease presenting like bronchial asthma. In this case report, 29-year male, presented with constitutional symptoms for 4 months duration with partial response to medical treatment received according to their knowledge and experience towards bronchial asthma, enteric fever and jaundice. Radiological investigations documented only prominent hilum left side of thorax which was underestimated due to presence of wheeze. Recurrent, progressive and partially responding constitutional symptoms was the reason for referral to our center. We have also noted prominent hilum with inhomogeneous infiltrates left lung field and localized wheeze and crepitations on left side of thoracic cavity in mammary and interscapular region. We have further evaluated with HRCT thorax and observed thick-walled cavities in left upper lobe posterior segment. 'Stepladder Lung Cavities' in HRCT is defined as multiple cavities adjacent with each other partially communicating to noncommunicating of variable size and shape unilaterally or bilaterally in stepladder fashion. 'Starry sky pattern' in HRCT Thorax is defined as randomly placed nodular opacities presenting as discrete or conglomerated, interstitial and acinonodular opacities unilateral or bilateral adjacent to pulmonary cavities usually reported as satellite nodules. Satellite nodules are defined as nodular opacities adjacent to pulmonary primary caviatary lung disease and indicator lymphatic local spread and active pulmonary tuberculosis. We have done sputum examination and documented acid-fast bacilli in sputum smear and MTB genome with rifampicin sensitivity in cartridge based nucleic acid amplification test. Treatment initiated with anti-tuberculosis (ATT) and recorded near complete radiological resolution, bacteriological cure after six months with good compliance. High index of suspicion is must while managing these cases with constitutional symptoms with typical 'Stepladder Lung Cavities' with 'starry sky pattern' in HRCT Thorax to have successful treatment outcome.

Keywords: Pulmonary Tuberculosis, Step ladder cavities, Starry sky appearance, Gene Xpert MTB/Rif.

INTRODUCTION

Tuberculosis (TB) is one of the most ancient diseases of mankind and has co-evolved with humans for many thousands of years or perhaps for several million years [1]. WHO fact sheet on tuberculosis stated that overall; one third of the world's population (over 2 billion) is currently infected with the TB bacillus [2]. Tuberculosis is most common communicable disease in India, caused by mycobacterium tuberculosis. Pulmonary tuberculosis is leading cause of mortality due to infectious disease and is among the top 10 causes of death globally. TB is having significant impact on mortality and morbidity in in low- and middle-income countries (LMIC) where it generates a significant burden of disease [3]. Global burden of tuberculosis is considered as public health emergency since last 25 years and irrespective of efforts form health department disease remains uncontrolled in terms of incidence, prevalence, mortality and morbidity. India, China, Indonesia, South Africa and Nigeria rank first to fifth

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respectively, in terms of the incident TB cases [4]. India accounts for highest number of new cases, and total cases on treatment across the world. As per figures by WHO (during 1999 to 2020) one billion more peoples will be newly infected, 200 million will get sick and 70 million will die if aggressive control measures will not be taken and universal diagnosis and treatment options are not strengthened [5].

Cavitation is known complication of primary as well reactivation tuberculosis. Cavitation can occur in up to 40 percent of cases of reactivation tuberculosis. These cavities typically have moderately thickened walls, but fewer than 10 percent of cases have air-fluid levels. Cavities are associated with endobronchial spread of the disease [6-8]. Chest X-ray as a diagnostic tool is more sensitive but less specific with higher inter and intra reader variation. However, it should be used judiciously. It should always be preceded by a repeat sputum smear examination [9]. Similarly; the lesions of pulmonary tuberculosis can take almost any form on a radiographic picture [10].

Authors have described Tennis racket cavity in chest radiograph as active marker of tuberculosis and reported that high yield of acid-fast bacilli in sputum smear microscopy and mycobacterium tuberculosis genome in nucleic acid amplification tests [7]. We have reported 'Stepladder Lung Cavities' with 'starry sky pattern' in HRCT Thorax in patient presented with constitutional symptoms and diagnosed as case of active pulmonary tuberculosis.

CASE SUMMARY

29-year-old male, college student, no addiction history, normotensive, non-diabetic, referred to our center by family physician for recurrent waxing and waning constitutional symptoms.

Further clinical details-

1. Fever-for 4 months, intermittent, low to moderate grade without chills and rigors associated with minimal body ache and headache. He was treated as case of enteric fever for 2 months by family physician and later one month as bronchial asthma without laboratory workup documentation.
2. Cough-for 3 months dry, intermittent, with minimal white sputum production.
3. Loss of appetite and weight loss over period of 3 months
4. Weakness and myalgia with fatigability for 2 months
5. Shortness of breath on exertion in the last 2 months.

His symptoms worsened over 3 months period and presented with recurrent symptoms and treated with nonspecific workup and empirical bronchial asthma protocol. His shortness of breath worsened and family physician referred to our center for further workup and expert management.

Clinical examination documented as-

- Restless, dry oral mucosa, cyanosis, pallor, febrile.
- Heart rate-112/min Respiratory rate: 25/bpm, BP-80/60 mmhg.
- PsO2: 94% @ room air resting.
- Respiratory system examination revealed-bilateral breath sounds normal, crepitation's heard over left interscapular and mammary area.
- Nervous system examination- higher functions normal, no neurological abnormality, cranial nerves normal, recent and past memory normal recall.
- Cardiovascular and gastrointestinal systems were normal.

We have assessed past records of hospitalization as chest x-ray showing left hilar enlargement (image 1) and chest x-ray done at our centre during hospitalization documented enlarged left hilum and new nodular opacities and increased inhomogeneous opacities as in left lower zones as compared to previous (Image 2). Duration between two x- rays was 3 months and received antibiotic treatment targeting enteric fever and bronchial asthma.

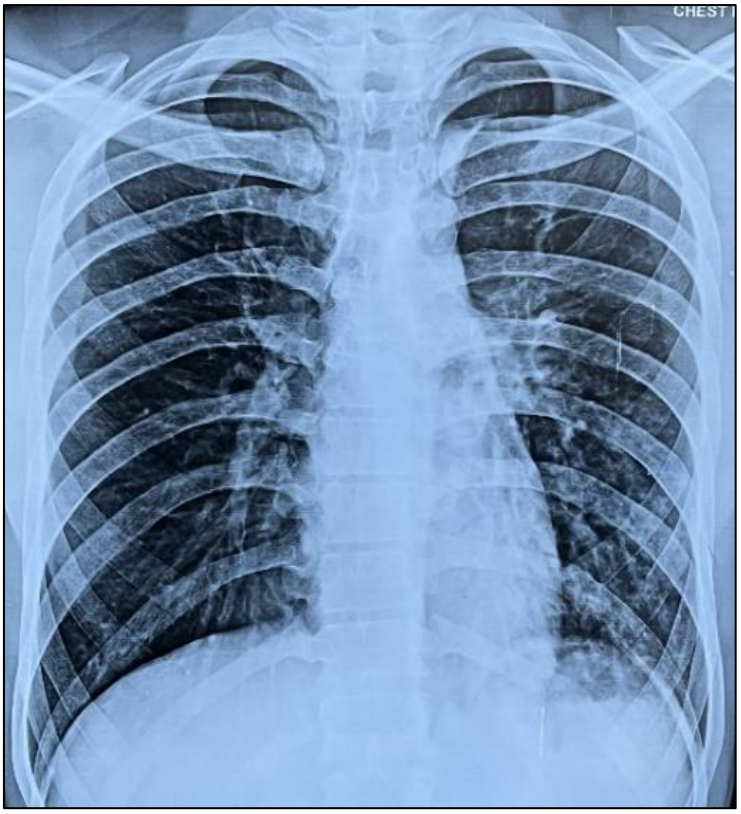

Image 1: Chest x-ray PA showing enlarged left hilum

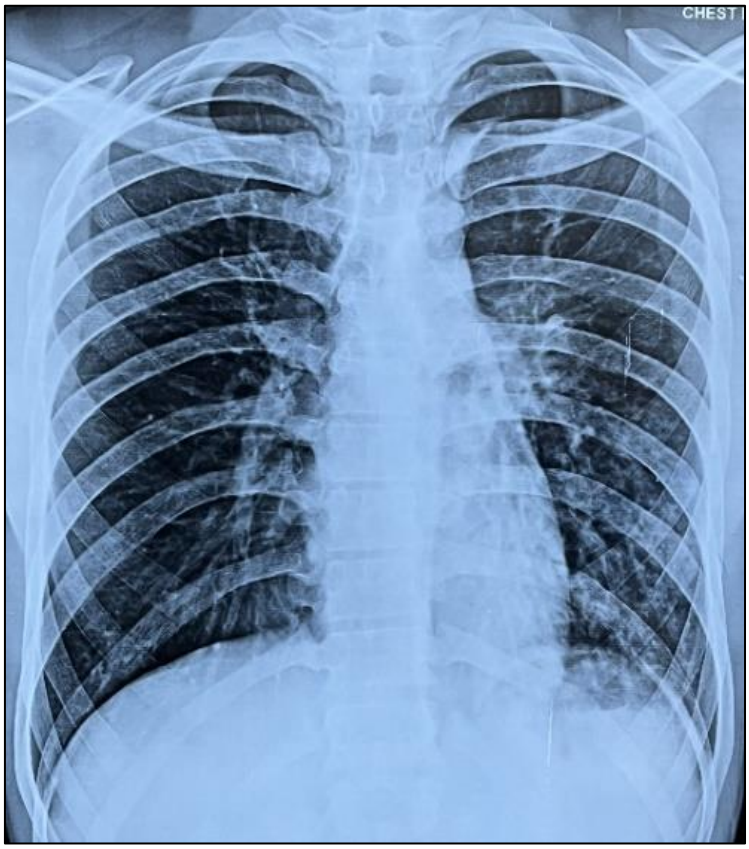

Image 2: Chest x-ray PA enlarged left hilum with infiltrates left lower zone

Laboratory Examination during hospitalization documented as-

- Hemoglobin-9.0 gm% total white blood cells-9000/mm3 Polymorphs-55%, Platelet count-470000/uL.
- CRP-145 mg/L (0-6 mg/L), random blood sugar level-134 mg% HbA1C-5.60 %.
- LDH-1290 IU/L (70-470 IU/L), Uric acid-3.4 mg (3.5-7.5 mg/dL).
- Serum electrolytes: Sodium-130 meq/L (135-145 meq/L) Potassium-3.7 meq/L (3.5-5.5 meq/L) Ionic calcium-1.39 meq/L (1.09-1.36 meq/L).
- D-dimer-280 ng/ml (<500 ng/ml).
- IL-6-1.75 pg/ml (0.00-7.00 pg/ml).
- Serum creatinine-1.0 mg/dL (0.7-1.4 mg/dL).
- Liver function tests- normal.
- Thyroid functions-normal.

Chest radiological examination documented enlarged left hilum with nodular infiltrates in left lower lobe with constitutional symptoms and normal D-Dimer level. We have evaluated further with HRCT Thorax.

HRCT Thorax suggestive of- [Images 3-6]

1. Thick walled 3cmx3cm cavity in left upper lobe with small cavities of less than 1 cm as stepladder pattern in left lung in sagittal section (Image 3).
2. Thick walled 3cmx3cm cavity in left upper lobe with small cavities of less than 1 cm as stepladder pattern in left lung with in-homogeneously and randomly placed nodules to give ‘starry sky appearance’ in sagittal section (Image 4).
3. Thick-walled cavity in left upper lobe posterior segment with pericavitary consolidation and satellite nodules in coronal section of lung window in HRCT Thorax (Image 5).
4. Inhomogeneous, randomly placed, enhancing pulmonary nodules in left upper lobe posterior segment with conglomeration at some point to give acinonodular opacities in coronal section of lung window in HRCT Thorax (Image 5).

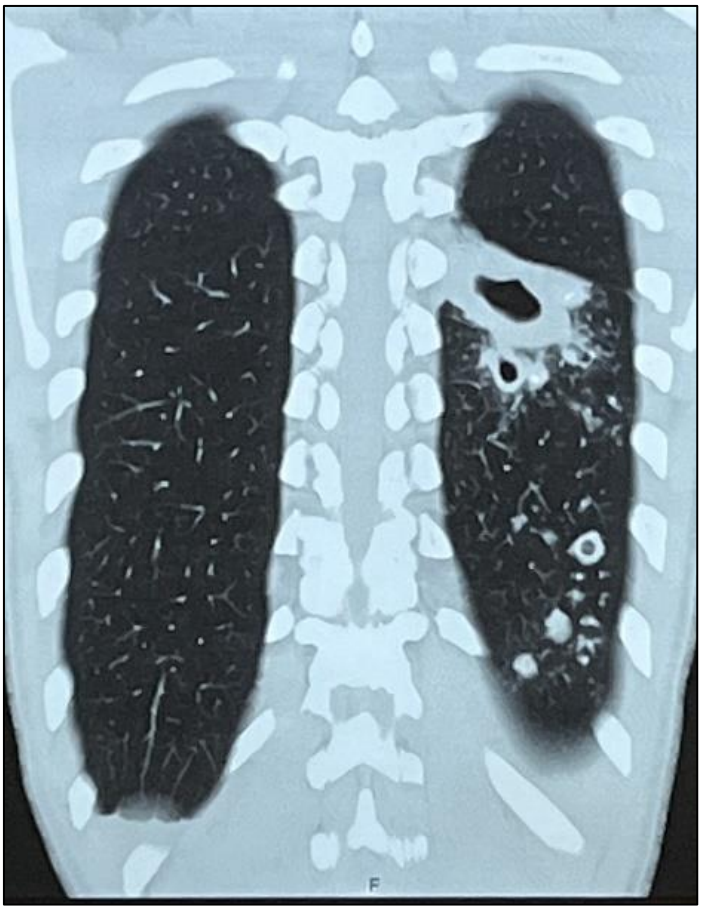

Image 3: HRCT Thorax showing step ladder pattern of lung cavities

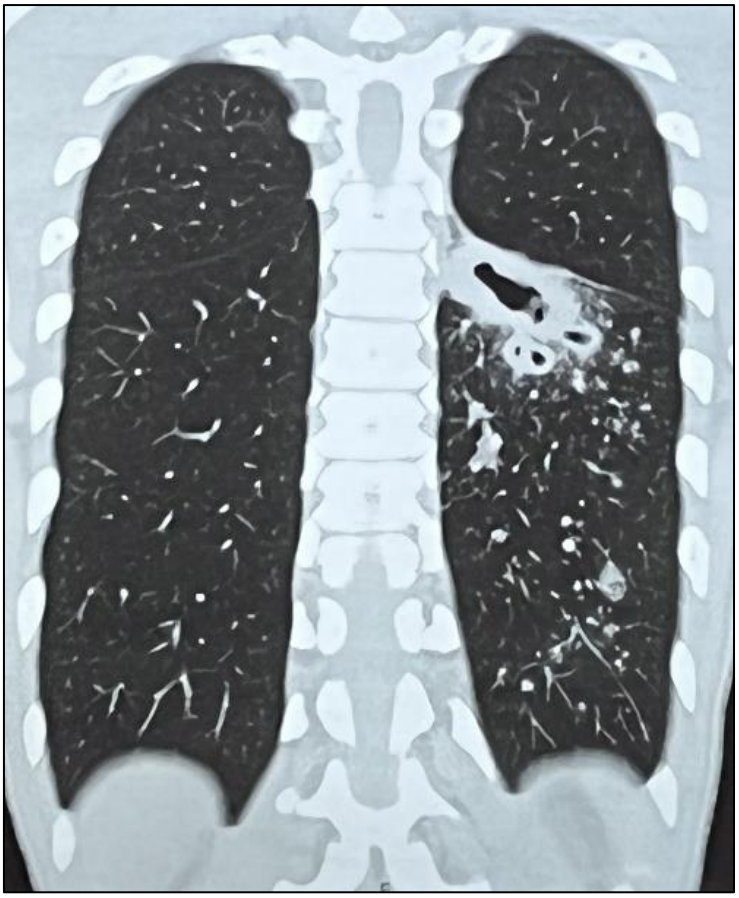

Image 4: HRCT thorax showing step ladder pattern of lung cavities with starry sky appearance of lung nodules

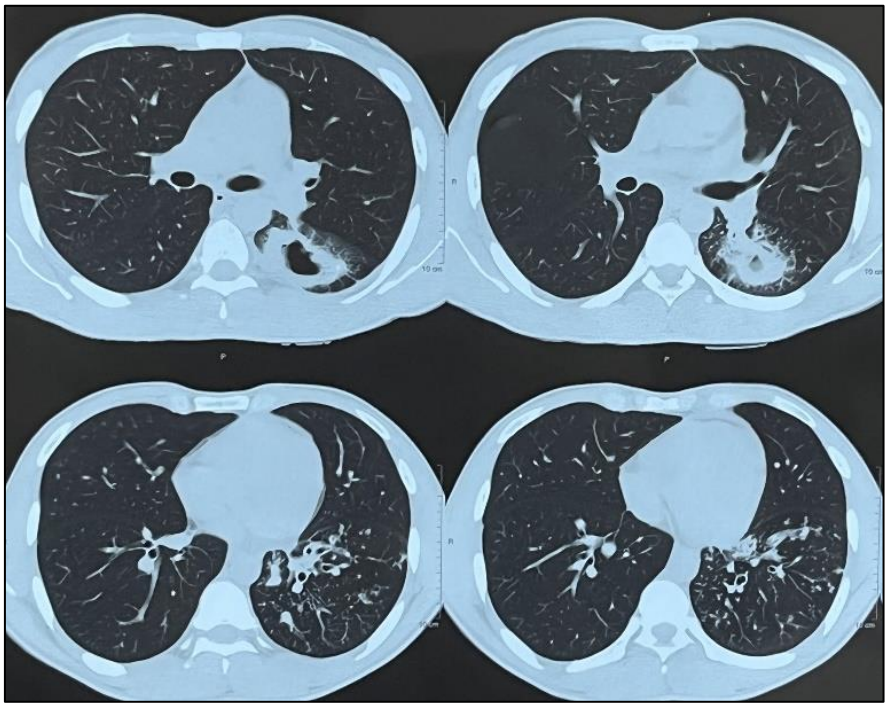

Image 5: HRCT thorax suggestive of cavity in posterior segment left upper lobe with peri-cavitary satellite nodules

As HRCT thorax was showing cavitary lung disease, we have further evaluated with induced sputum examination of early morning sample on two consecutive days. Induced sputum was thin, white and mainly salivary as per laboratory technician evaluation, and still we have advised to evaluate and workup for

sputum microscopy and Gene Xpert MTB/RIF or CBNAAT test (cartridge based nucleic acid amplification test) as per NTEP (National tuberculosis elimination program).

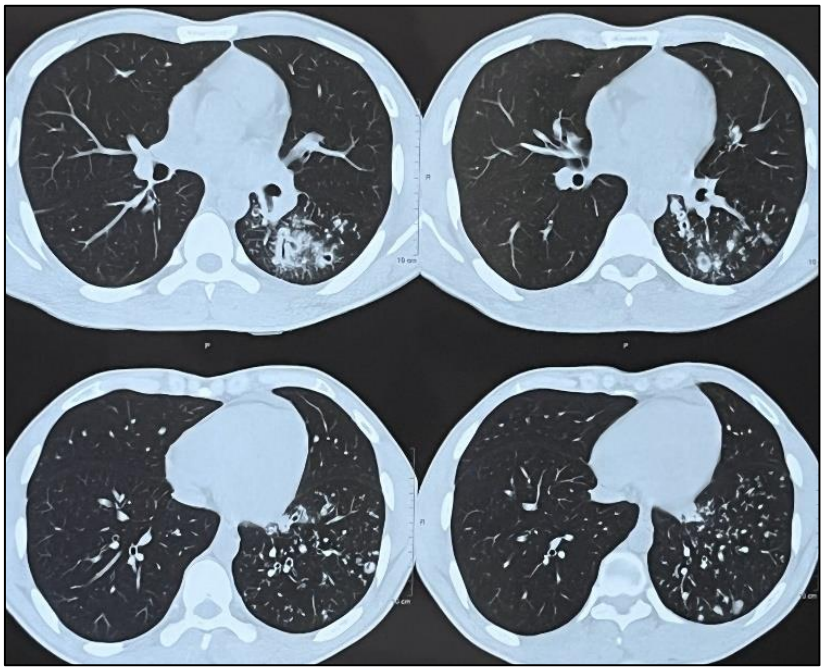

Image 6: HRCT thorax showing in-homogeneously enhancing random nodules left upper lobe posterior segment

Sputum examination documented acid fast bacilli and TB Gene Xpert MTB/RIF test shown MTB genome (mycobacterium tuberculosis genome) and rpo-b (rifampicin-beta) mutation negative.

During hospitalization, we have started supportive care till final reports came with intravenous fluids and beta- lactum antibiotics. We have stopped antibiotics after sputum examination documented as tuberculosis and started ATT (Anti-tuberculosis treatment) as per weight band with Isoniazid, Rifampicin, Pyrazinamide, Ethambutol. He was tolerating antituberculosis treatment without any liver or renal dysfunctions. He was discharged to home after one week of treatment with four drug ATT. After 2 months of treatment, radiological response documented with clearance of radiological abnormalities. Radiological response documented as significant decrease in hilum enlargement and nodular infiltrates left lower zone (Image 7).

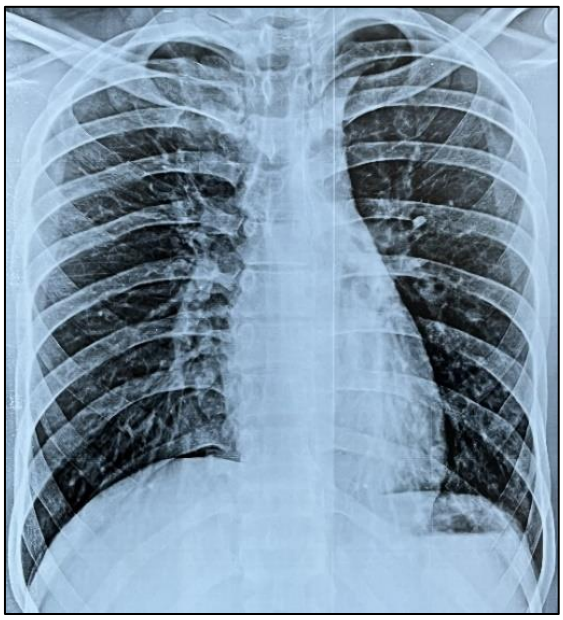

Image 7: Chest x-ray PA at 2 months showing near complete resolution of enlargement of left hilum with infiltrates in left lower zone

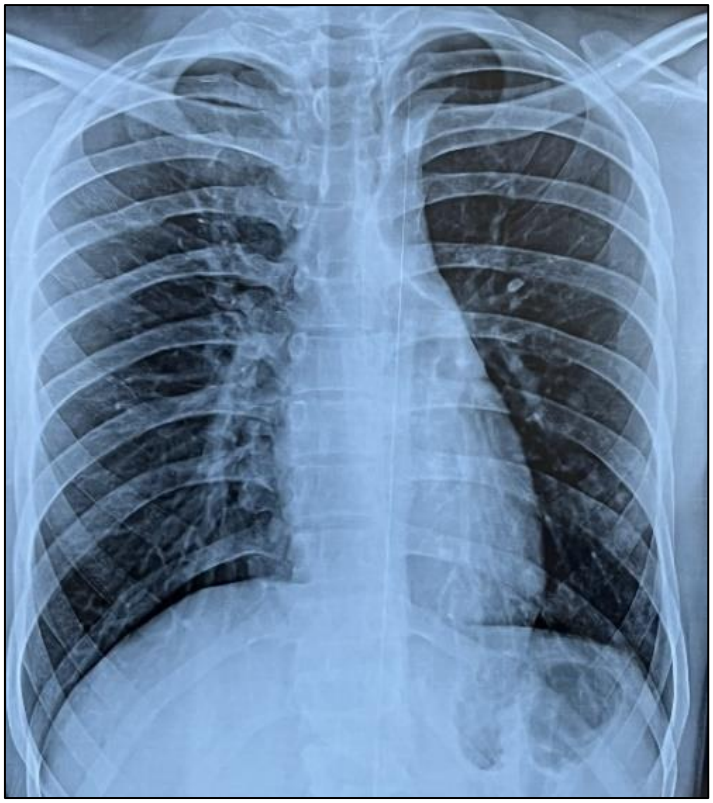

Image 8: Chest x-ray PA at 6 months showing normal hilum and lung parenchyma both sides

After completion of intensive phase, she was shifted to continuation phase with Isoniazid, Rifampicin, Ethambutol without steroids. Radiological follow-up examination done at 6 months shown near complete resolution of infiltrates left lower zone and both hlia were normal with normal lung parenchyma both lung fields (Image 8). He tolerated complete course of ATT for six months as per National guidelines and documented 'cure' of tuberculosis. Sputum smear microscopy done at 2 months and six months documented absence of acid-fast bacilli and we confirmed as cure from disease. Clinical and radiological response documented after completion of ATT with complete resolution of radiological abnormalities in chest X-ray.

DISCUSSION

A cavity has been defined in the radiology literature as (pathologically) "a gas-filled space within a zone of pulmonary consolidation or within a mass or nodule, produced by the expulsion of a necrotic part of the lesion via the bronchial tree" and (radiographically) "a lucency within a zone of pulmonary consolidation, a mass, or a nodule; hence, a lucent area within the lung that may or may not contain a fluid level and that is surrounded by a wall, usually of varied thickness" [11] In theory, one would like to distinguish a cavity from other air- or fluid-filled lung structures with different pathophysiologies, but in practice, this is not always possible. Some have tried to make this distinction by defining cysts as being air-containing spaces surrounded by a thin (4 mm or less) wall and cavities as being as air- containing spaces with walls that are at least 5 mm thick. Unfortunately, considerable overlap in etiology and pathophysiology exists between these two categories [12].

A cavity is the result of any of a number of pathological processes including suppurative necrosis (e.g., pyogenic lung abscess), caseous necrosis (e.g., tuberculosis), ischemic necrosis (e.g., pulmonary infarction), cystic dilatation of lung structures (e.g., ball valve obstruction and Pneumocystis pneumonia), or displacement of lung tissue by cystic structures (e.g., Echinococcus) [13]. In addition, malignant processes may cavitate because of treatment-related necrosis, internal cyst formation, or internal desquamation of tumor cells with subsequent liquefaction [14-16]. The likelihood that a given process will cavitate depends upon both host factors and the nature of the underlying pathogenic process. The prevalence of cavities among persons with a given process varies widely. In general, certain processes tend to form cavities more commonly than others. For example, Mycobacterium tuberculosis generally has the highest prevalence of cavities among persons with pulmonary disease of any infection, probably because this pathogen causes extensive caseous necrosis. In the case of M. tuberculosis, the tendency to form cavities is clearly advantageous to the propagation of the organism because cavities contain large numbers of organisms, which can then be efficiently aerosolized and transmitted to other susceptible hosts [17, 18]. Other pathogens, such as Klebsiella pneumoniae, are associated with extensive

pyogenic lung necrosis and frequent cavitation [19]. This organism is also disproportionately represented among cases of pulmonary gangrene, in which there is extensive pulmonary necrosis and infarction, suggesting that the organism possesses pathogenic determinants that are more likely to lead to pulmonary necrosis and cavitation than other common causes of pulmonary infection, such as Streptococcus pneumoniae [20]. The predilection to form necrotic cavities may be due to the priming of the inflammatory response by the concurrent aspiration of stomach acid [21] or factors specific to the organism, such as endotoxin [22]. Unfortunately, there is no single common factor that differentiates organisms that are frequently associated with pulmonary cavitation from organisms that are rarely associated with pulmonary cavitation. However, as a general rule, organisms that cause subacute or chronic pulmonary infections (e.g., mycobacteria and fungi) seem to be more frequently associated with cavities than organisms that cause acute pulmonary infections (e.g., viruses and S. pneumoniae). This rule has many exceptions (e.g., necrotizing pneumonias associated with Staphylococcus aureus and K. pneumoniae).

The radiographic appearance of cavitary lesions can sometimes be useful to differentiate among a broad spectrum of etiologies but should be combined with clinical and laboratory data to obtain an accurate diagnosis. One traditional method used to classify cavitary lesions is wall thickness. Cavitary lesions associated with specific diseases are frequently described as being “thick walled” or “thin walled,” but exact definitions for these terms are often lacking. Of course, measured wall thickness will depend on the imaging technique used (plain radiography or computed tomography) [23].

A perfect storm of factors combines within the cavity to drive increased transmission, morbidity, and mortality [figure 1] [24].

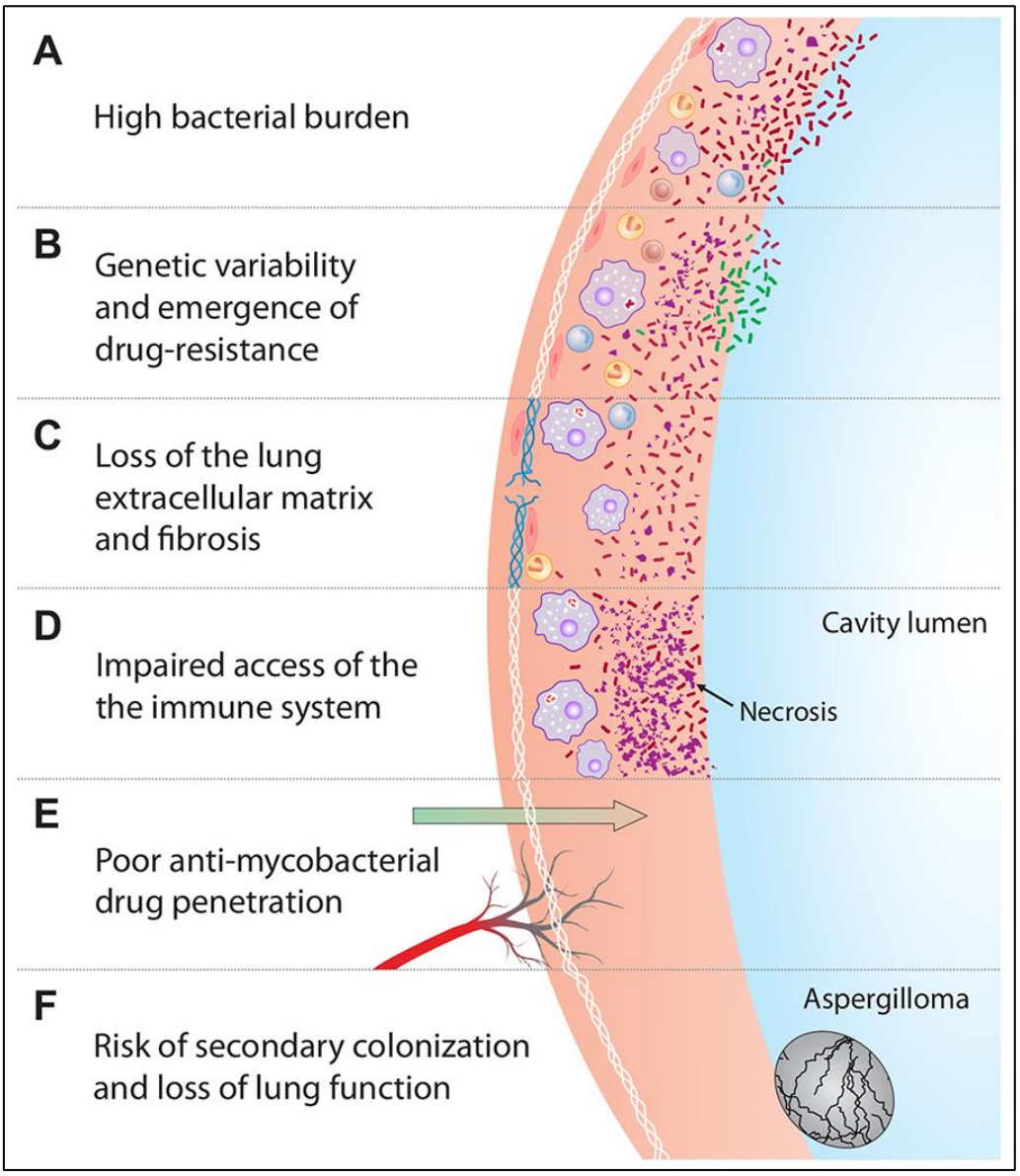

Figure 1

In the most accepted model for TB cavity formation, the necrotic center of a granulomatous lung abscess erodes into an airway while some necrotic debris remains inside the newly formed cavity [25]. Phagocytes and granulocytes penetrate poorly into these necrotic areas creating an immune-sheltered zone of bacterial growth. High oxygen levels within the cavity also provide a rich environment with high rates of bacterial replication leading to a large bacillary burden at the inner edge of the cavity (107-109 bacilli), estimated to be a hundred thousand times higher than in necrotic TB lesions [26-28]. Rapid bacterial proliferation increases the frequency of replication-induced mutations and the likelihood of developing drug resistance [29-32]. These concentrated bacilli are poised to be expelled out of the lungs through the bronchial tree during transmission events. Finally, the inner contents of cavities are also poorly vascularized which limits the penetration of anti-mycobacterial drugs and may further promote selection for drug-resistant mutants [33-36].

Why is cavitary TB so hard to treat? [24] [Figure 1]

(A) High concentrations of extracellular bacteria grow in the loose necrotic debris at the interior surface of the cavity [27].

(B) The bacterial proliferation leads to replication induced mutations at drug-resistance determining loci and a high probability of mutants with acquired drug resistance [29, 30].

(C) Extracellular collagen matrix is depleted within caseous lesions and in the cavity wall. Depletion of extracellular collagen matrix facilitates the formation and growth of cavities since the remaining necrotic debris is easily evacuated through an adjoining bronchus. Once depleted, the healing response is unable to regenerate the basement membrane or lung tissue. Individuals face lifelong pulmonary deficits and a high-risk for opportunistic infections within persistent lung cavities.

(D) The inner layer of the cavity wall is composed of necrotic debris. Few immune cells penetrate this region to aid in control over M. tuberculosis replication, and this contributes to the high bacterial burden.

(E) Vascular necrosis around the cavity and strong drug-binding properties of caseum result in poor anti-mycobacterial drug penetration which also contributes to the high bacterial burden [37-39]. The effects of sub-optimal drug penetration may also drive selection for drug-resistant mutants [40].

(F) Cavities often persist even after they are sterilized of mycobacteria and are replaced with scar tissue (closed healing). Therefore, cavitation can lead to loss of lung volume and chronic pulmonary deficits [41].

Cases with pulmonary tuberculosis especially Lower lung field tuberculosis (LLF TB) is usually underdiagnosed because of diverse clinical and radiological presentation, less diagnostic yield of conventional diagnostic modalities, and these modalities used routinely and universally. Bronchoscopy-guided diagnostic techniques are superior, sensitive, and reliable to confirm LLF TB. Gene Xpert MTB/ RIF in bronchial wash samples is found to be best diagnostic modality in evaluating LLF TB and should be used routinely to have successful treatment outcome. A proportionate number of NRP cases are having LLF TB and a high index of suspicion is a must while evaluating these cases [42].

Authors have documented that allergic bronchopulmonary aspergillosis (ABPA) has diverse clinical presentation ranging from typical bronchial asthma to tropical infectious pulmonary diseases such as pneumonia and TB. A high index of suspicion is must while managing these cases, especially in tropical countries like India where burden of TB is high. All possible measures should be taken to rule out TB [43].

CONCLUSION

In our study we have documented very unusual pattern of cavitations in lung parenchyma in patient suffering from tuberculosis. We labelled this typical ‘Stepladder Lung Cavities’ with ‘Starry sky pattern’ in active pulmonary tuberculosis. Patient presented and treated as bronchial asthma by family physician before final diagnosis at our center. Probable rational would-be endobronchial spread of tuberculosis and diffuse endobronchitis secondary to inflammatory response could have wheezing in this patient. High index of suspicion is must while managing these cases with constitutional symptoms with typical ‘Stepladder Lung Cavities’ with ‘starry sky pattern’ in HRCT Thorax to have successful treatment outcome. Usually, these cases may be missed due to nonspecific symptoms initially and as disease progresses and significant anorexia or weight loss helps in suspecting further workup to rule out active pulmonary tuberculosis.

Key learning points from this case report are:

1. ‘Stepladder Lung Cavities’ in HRCT is defined as multiple cavities adjacent with each other partially communicating to noncommunicating of variable size and shape unilaterally or bilaterally in stepladder fashion.
2. ‘Starry sky pattern’ in HRCT Thorax is defined as randomly placed nodular opacities presenting as discrete or conglomerated, interstitial and acino nodular opacities unilateral or bilateral adjacent to pulmonary cavities usually reported as satellite nodules.
3. Satellite nodules are defined as nodular opacities adjacent to pulmonary primary cavitary lung disease and indicator lymphatic

local spread and active pulmonary tuberculosis.

4. Although tuberculosis is the leading cause of 'cavity' on chest radiograph globally, no radiological pattern is specific for tuberculosis.
5. Proportionate number of tuberculosis cases in India is having cavities on chest radiographs, especially reactivation cases.
6. 'Stepladder Lung Cavities' is not very commonly described in literature as a predictor of active pulmonary tuberculosis. We confirmed higher grades of bacteriological yields in AFB smear examination in cases with 'Stepladder Lung Cavities'
7. Hence, important clinical lesson is all the cases with 'Stepladder Lung Cavities' on chest radiograph should be analyzed thoroughly for underlying active pulmonary tuberculosis, as it indicates underlying active disease process due to Mycobacterium tuberculosis

Conflicts of Interest: Nil.
Research Funding: Nil.

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