SAR Journal of Medical Case Reports

Abbreviated Key Title: *SAR J Med Case Rep*
Home page: https://sarpublication.com/journal/sarjmcr/home
DOI: 10.36346/sarjmcr.2023.v04i05.001

OPEN ACCESS

ISSN 2707-7780 (P)
ISSN 2709-6947 (O)

Case Report with Review of Literature

Cavitary Lung Disease with Constitutional Symptoms Misinterpreted & Treated as a Bronchial Asthma and Enteric Fever for a Long Period: What are Timings from Infection to Cavitation in Tuberculosis? Revisits Wallgren's timetable !

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Article History: | Received: 12.10.2023 | Accepted: 17.11.2023 | Published: 20.11.2023 |

Abstract: Pulmonary tuberculosis is the most common cause for cavitary lung disease in India due to its endemic nature and high case burden. In spite of awareness by government organizations regarding symptoms, diagnostic modalities and treatment options for disease, Pulmonary tuberculosis management is delayed in all aspects due to the large proportion of cases receiving access to the private sector where adequate training and awareness regarding tuberculosis is missing. Constitutional symptoms of tuberculosis are not severe and fatal as well and this is the most common reason for lack of timely suspicion as commonly occurred with cardiac ailments. Constitutional symptoms in tuberculosis cases are usually managed by general practitioners in line with enteric fever, jaundice, bronchitis and pneumonia and these cases were treated accordingly. In present case report, 45-year-old female, with constitutional symptoms for six months were treated in outdoor and indoor settings by general practitioners, family physicians and other healthcare professionals with antibiotics and bronchodilators in line with enteric fever, jaundice and bronchitis with asthma on many occasions with partial response to treatment and symptoms worsening. She was referred to our center after an episode of moderate hemoptysis and we have retrospectively studied the reports and noted chronic lung cavitation in chest x-rays done a few months before which is clearly demarcated and visible in posteroanterior and lateral views. Her radiological abnormalities were never evaluated as she was never examined by a pulmonologist before our center and only x-ray was done without a confirmed diagnosis. We have documented typical cavitary lesions favoring chronic infective disease with radiological features of tuberculous cavity in HRCT chest. Her induced sputum examination for CBNAAT (Cartridge based nucleic acid amplification) MTB (mycobacterium tuberculosis) positive, Rifampicin mutation (Rpo-b) Negative. Treatment initiated with anti-tuberculosis (ATT). We have recorded near complete radiological resolution, bacteriological cure after eight months of ATT with good compliance. Pulmonary tuberculosis should be suspected early in cases with cavitating lung disease with constitutional symptoms to have a successful treatment outcome.

Keywords: Pulmonary tuberculosis, Cavitary Lung disease, delayed diagnosis, AFB, Gene Xpert MTB/Rif.

INTRODUCTION

As per the Global TB Report 2021, the estimated incidence of all forms of TB in India for the year 2020 was 188 per 100,000 population (129-257 per 100,000 population). The total number of incident TB patients (new & relapse) notified during 2021 was 19,33,381 which was 19% higher than that of 2020 (16,28,161). The programme had been able to catch-up with the dip in TB notifications that was observed around the months when the two major covid waves happened

in India. Though factors such as changes in the health seeking behaviour of patients with chest symptoms (patient related) as well as diversion of the human and material resources (provider-related) were seen across the country, NTEP has been resilient in regaining the momentum of finding the missing TB patients by introducing bidirectional screening for TB-Covid, doorstep delivery of services as well as earned gains on the behaviour change of people in terms of respiratory etiquette, which in the long run is expected to have an impact on reducing the transmission of TB as well as other respiratory infections within the community The National Strategic Plan for Elimination of Tuberculosis 2017-25 was approved on the 8th of May 2017 and has been operational since then in the entire country with the goal of Ending TB by 2025 [1].

Pulmonary tuberculosis can have diverse presentations ranging from cavitation, consolidation, tumorous lesions, coin lesions, lower lung filed tuberculosis and endobronchial and miliary nodules [2-12]. Similarly, non-tuberculous pathologies can present with abnormalities such as consolidations, nodules, cavitations mimicking tuberculosis [2-14]. Bronchoscopy is a very crucial interventional pulmonology technique in evaluating these cases [2-14]. High risk factors for tuberculosis would be advanced age, malnutrition, pregnancy, steroids exposure, diabetes mellitus and immunosuppression [9-14]. Tuberculosis in advanced stage may cause cardiac dysfunction and systemic effects which will have poor outcome if timely treatment not received [15-17]. Final outcome in delayed treatment initiation may lead to destroyed lung as post tuberculosis sequel and proportionate number of cases may have lung function abnormalities irrespective of radiological outcome [18-24]. Tuberculosis may be misdiagnosed due to confusing or overlapping clinical and radiological features in high burden setting like India [25-28]. In children extrapulmonary tuberculosis can present like tuberculous meningitis and with or without mediastinal adenopathy which is usually missed due to vague presentations like bronchitis and asthma and cases with failure to thrive [29, 30].

Case Summary

45-year-old female, farmer by occupation, no addiction history, normotensive and non-diabetic with history of shortness of breath, low grade fever & chest pain for six months and hemoptysis of one day duration refereed by family physician to our center.

Further clinical details-

1. Shortness of breath for intermittent for six months, progressive, more during lying down position, decreased during recumbent position, and more during exertion accompanied by audible wheeze as narrated by patient. Initially, she was having grade I and progressed to grade IV one day before hospitalization.
2. Fever for six months, low grade without chills and rigors associated with bodyache, intermittent, more during evening hours, responding to antipyretics.
3. Chest pain for six months, predominantly over left side interscapular and back area, nonradiating, sharp nature sometimes and responding to analgesics.
4. Hemoptysis of one episode one day before hospitalization aggravated by cough. Hemoptysis was moderate in quantity with approximate 50 ml blood in sputum. She further narrated that she was having intermittent hemoptysis on many occasions in last six months.

We further recorded complete medical details and noted that she was treated inline with enteric fever with hospitalization for six days somewhere in private hospital and treated with antibiotics with partial response. She was also treated inline with bronchial asthma and bronchiectasis in outdoor unit by general practioners on many occasions with oral bronchodilators and steroids. She was also received treatment with analgesics for backache by orthopedician, importantly evaluated with chest x-ray lateral view and abnormality was there in retrosternal area and which was underestimated and treated as neuralgic pain with analgesics. She was sometime treated with jaundice due to anorexia with intravenous fluids and multivitamins.

Chest X-ray PA view (taken six months back by family physician) documented inhomogeneous opacities in left lung midzone, well defined round luceny in left midzone paracardiac region i.e., irregular cavity in midzone with pericavitary consolidation. [Image 1] Chest x-ray lateral view taken by orthopedic surgeon for backache showing cavitation in retrocardiac space occupying the 6^{th} to 9^{th} thoracic vertebras. Cavity is thick-walled, moderate size with pericavitary consolidation and infiltrates in retrocardiac space overlying thoracic vertebras (Image 2).

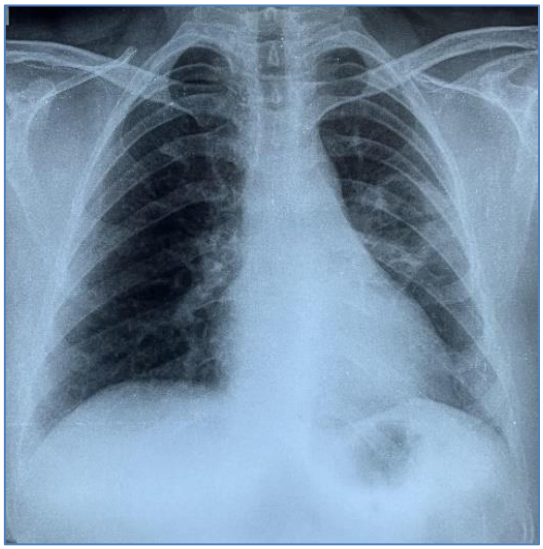

Image 1: Chest x-ray PA showing well defined cavity in left midzone with pericavitary consolidation

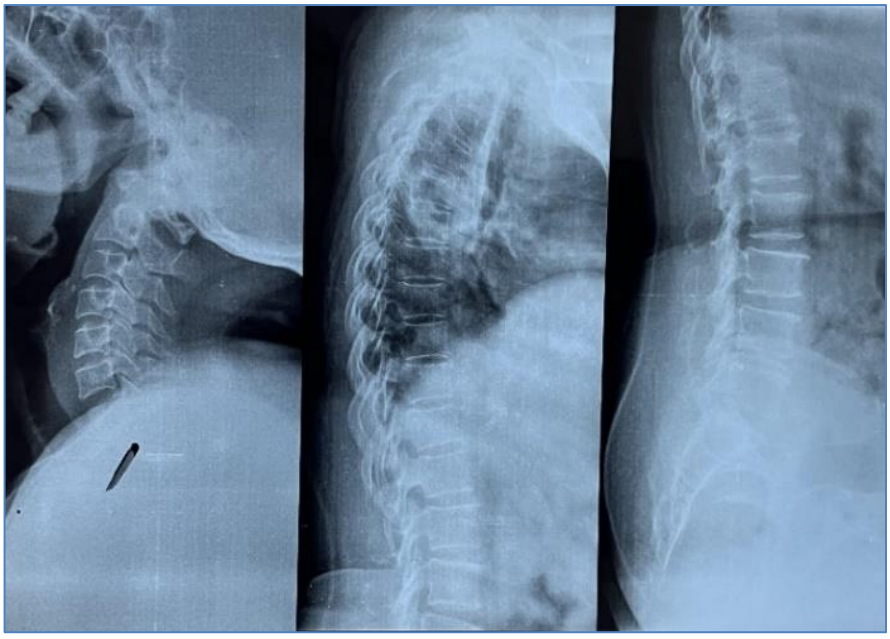

Image 2: Chest x-ray lateral view showing thick walled moderate sized caviatary lesion with pericavitary consolidation in retrocardiac space overlying thoracic vertebra

Actually, cavitary lesion was underestimated and never evaluated for etiological diagnosis. She was treated with analgesics for symptomatic pain in back and lateral aspect of chest including interscapular area. She was also evaluated by her routine family physician for respiratory discomfort with chest x-ray and treated in line with community acquired pneumonia left lung with intravenous antibiotics one month before our hospitalization. Chest x-ray was showing clear-cut, well-defined cavity in left midzone in paracardiac area with consolidation and inhomogeneous haziness in left lower zone (Image 3).

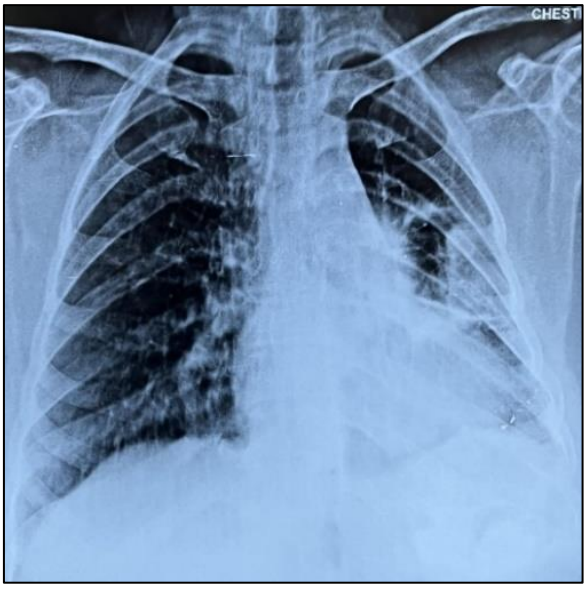

Image 3: Chest x-ray PA showing cavity in left midzone paracardiac region with pericavitary consolidation and left lower zone inhomogeneous infiltrates with obliteration of left costophrenic angle

Clinical examination documented as-

Thin built, afebrile, no pallor or cyanosis or clubbing.

Heart rate-100/min Respiratory rate: 26/bpm, BP-100/60 mmhg

PsO2: 88% resting & 84% on routine walk @ room air

Respiratory system examination revealed normal vesicular breathing with bilateral wheezing heard in all areas and crepitations in left interscapular and axillary area during auscultation.

Cardiovascular, gastrointestinal & nervous system examination were normal.

Laboratory Examination during hospitalization documented as-

Hemoglobin-10.0 gm% total white blood cells-19000/mm3 Polymorphs-85%, Platelet count-270000/uL

CRP-290 mg/L (0-6 mg/L), random blood sugar level-124 mg% HbA1C-5.60 %

LDH-785 IU/L (70-470 IU/L)

Serum electrolytes: Sodium-135 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-412 ng/ml (<500 ng/ml)

Serum creatinine-1.0 mg/dL (0.7-1.4 mg/dL)

Liver function tests- normal

Thyroid functions-normal

ECG was showing sinus tachycardia.

Pro-BNP- 90 pg/ml (<125 pg/ml)

CPK-MB- 10.33 IU/L (0-25 IU/L)

Trop-I- (cardiac troponin)-12 ng/L (0-19 ng/L)

COVID-19 RT PCR test and results documented Negative for SARS-CoV-2

Viral markers such as HIV-II and HIV-II antibody negative and Australia antigen negative We have further evaluated with HRCT thorax for cavitary lesion with consolidation with inhomogeneous infiltrates in left mid zone.

HRCT Thorax suggestive of- (Images 4-6)

1. Thick-walled cavity in posterior segment of left upper lobe with pericavitary consolidation. Cavity is 3 cmx 2cm in size without fluid, margins are smooth and regular with consolidation rim surrounding cavity.
2. Cavity with pericavitary consolidation and satellite nodules in left upper lobe posterior segment
3. Large thick-walled cavity with consolidation and GGO in left upper lobe posterior segment.
4. Left lung volume is decreased with pull of mediastinum towards left side and showing rib crowding and pleural based consolidation with cavitation in left lung posterior segment.
5. Satellite nodules are marker of random and perilymphatic nodules due to miliary, bronchogenic and lymphohematogenous spread of tuberculosis in left lower zone which makes haziness and misinterpretation as consolidation in routine chest x-ray.

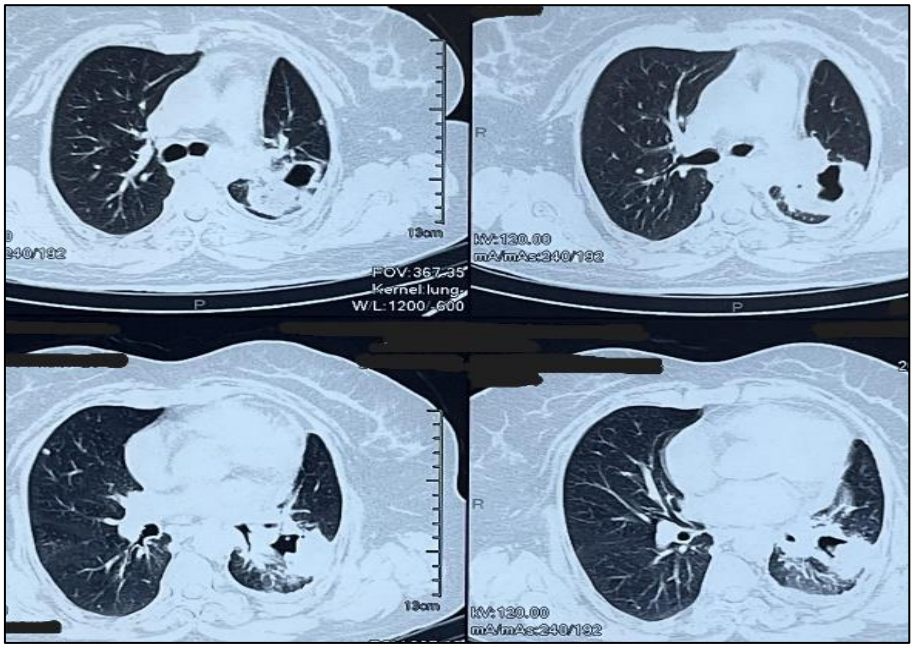

Image 4: HRCT Thorax showing thick-walled cavity in left upper lobe posterior segment

She was unable to produce sputum and we have induced sputum with saline nebulization. Pathologist labeled sputum sample as inadequate due to very few epithelial cells and her microbiological examination was negative for acid fast bacilli. We have sent same sample for CBNAAT analysis. Her induced sputum examination for CBNAAT (Cartridge based nucleic acid amplification) MTB (mycobacterium tuberculosis) positive, Rifampicin mutation (Rpo-b) Negative.

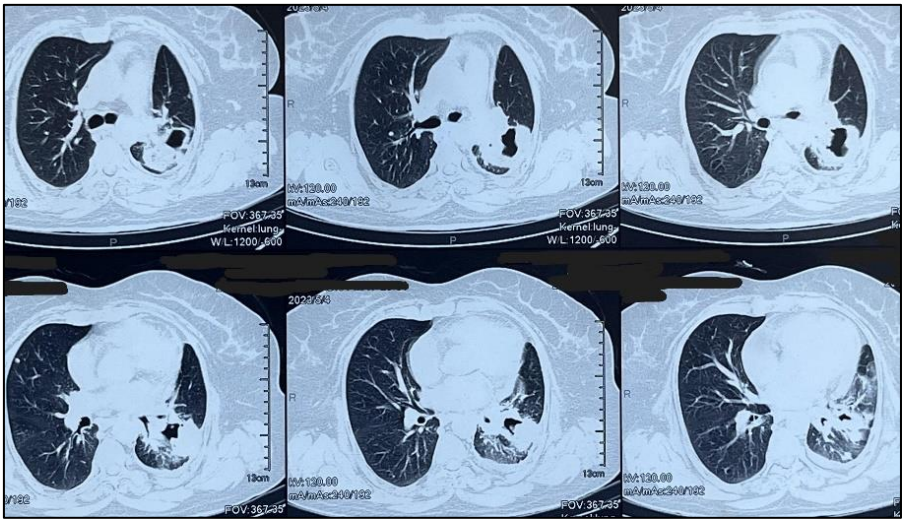

Image 5: HRCT Thorax showing thick-walled pleural based cavity in left upper lobe posterior segment

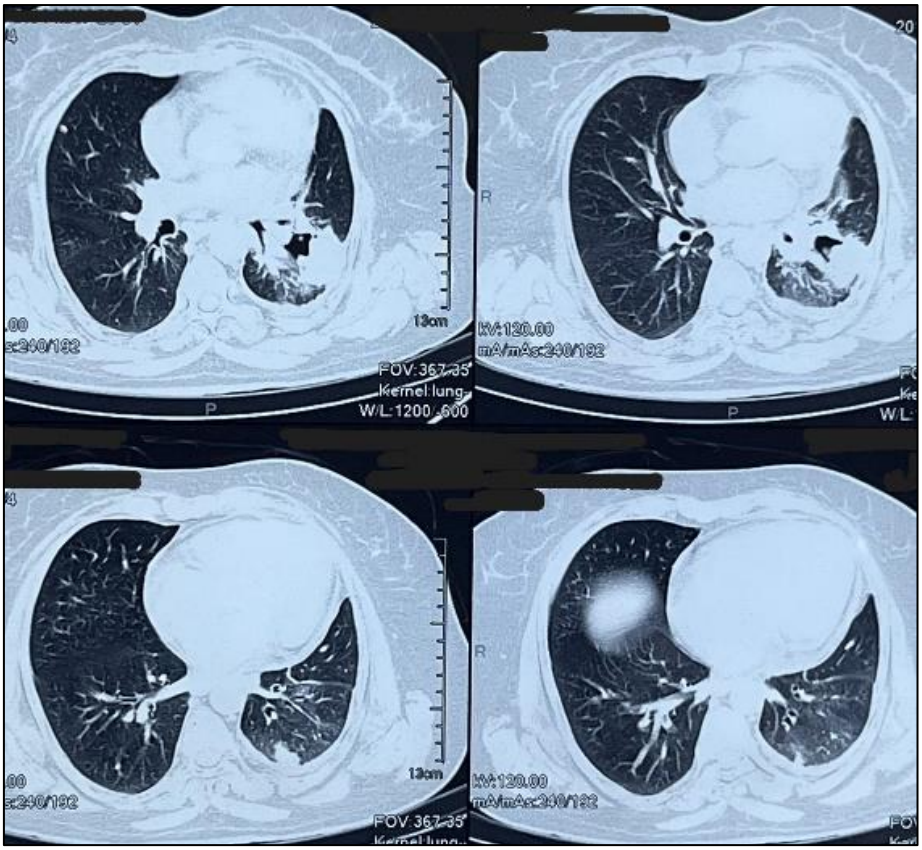

Image 6: HRCT Thorax showing thick-walled cavity in left lung posterior segment with pericavitary consolidation and decreased left lung volume

During hospitalization, we have started supportive care till final reports came with intravenous fluids, intravenous hemostatic (tranexamic acid and botropause) 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. She was tolerating antituberculosis treatment without any liver or renal dysfunctions. She was also offered salmeterol plus fluticasone inhaler with oral acebrophylline tablet for her shortness of breath with wheezing and showed satisfactory clinical response in terms of relieving her breathlessness. She was discharged to home after one week of treatment with four drug ATT. After completion of intensive phase, she was shifted to continuation phase with Isoniazid, Rifampicin, Ethambutol. Radiological follow-up examination done at 6 months shown near complete resolution of large thick-walled cavity with infiltrates in left mid zone with normal lung parenchyma in both lung fields [Image 7]. She 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.

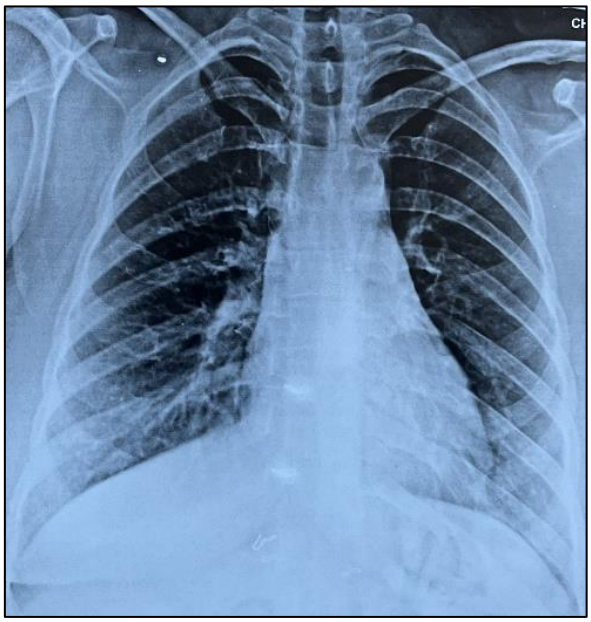

Image 7: Chest x-ray PA showing complete resolution of left lung cavity with near normal parenchyma left lung and clear costophrenic angle left side with normal right lung fields

DISCUSSION

According to the World Health Organization (WHO), one-third of the world's population is estimated to be infected with Mycobacterium tuberculosis. India has more new cases annually than any other country. The

Revised National Tuberculosis Control Programme (RNTCP), based on the internationally recommended directly observed treatment short-course (DOTS) strategy, was launched in 1997 and expanded across the country in a phased manner. A full nationwide coverage was achieved in March 2006. In spite of its impressive performance in terms of case detection and cure rates, the programme has many challenges due to inadequate infrastructure and the different health-seeking behavior pattern and the TB–diabetes comorbidity [31]. Early diagnosis of TB and prompt initiation of treatment are essential for the effective TB control programme. Patients with undiagnosed pulmonary TB predominantly act as reservoirs for transmission, and delay in the diagnosis may worsen the disease, increases the risk of death and the chances of transmission of TB in the community, as each infectious case will result in 10–15 of the secondary infections [32]. It also increases the patient expenditure on the disease.

Early case detection and treatment is critical for controlling tuberculosis (TB), but national TB programs are heavily dependent on passive case finding. Studies suggest that diagnosis of TB is often delayed and one major reason is repeated visits at the same healthcare level and non-specific antibiotic therapies. Overall diagnostic delay has been attributed to both patients and the health system [33]. Delayed diagnosis of TB can enhance the transmission of infection, worsen the disease, increase the risk of death, and may be a reason why TB incidence has not declined substantially, despite the global scale-up of DOTS [34]. India has a complex and highly heterogeneous health care delivery system, with both public sector and private sector (both formal and informal) health care providers (HCPs). Private and informal HCPs are often the first source of care for any illness and also TB. There is evidence, albeit limited, that patients with TB symptoms often begin seeking advice in the informal private sector (chemists and unqualified practitioners), then seek care from qualified practitioners, and eventually end up in the public sector for free treatment. Patients move from one provider to another, before they are finally diagnosed and started on anti-TB treatment [35-37]. The main factor contributed to diagnostic delay was inadequate knowledge about TB. Patients had a longer diagnostic delay if they had consulted a private health-care provider; this may be because of the easy accessibility of government health-care providers to diagnostic microscopy center and greater awareness regarding RNTCP when compared to private providers. Private health-care providers do not have strong linkages with the government health system. Lack of training of health-care providers in the private sector contributes to delay in diagnosis. Therefore, linkage of private practitioners in RNTCP needs to be stepped up.

Timetable for Pediatric TB- Wallgren's timetable [38] (Figure 1 & 2)

Manifestation of TB in children can be predicted based on the Wallgren Timetable highlighted below: Pulmonary tuberculosis – within a few months of primary infection. Miliary and meningeal tuberculosis – 2-6 months. TB adenitis - 3-9 months. Bones and joints – several years. Renal and genital tuberculosis – may take over a decade. Pulmonary lesions occurring as a result of reactivation of a dormant focus previously established in the body takes a number of years after primary infection.

Stage	Duration	Features
1	3–8 weeks	The primary complex develops. Conversion to tuberculin positivity occurs
2	About 3 months	Life-threatening forms of disease due to haematogenous dissemination occur, i.e. tuberculous meningitis and miliary tuberculosis
3	3–4 months	Tuberculous pleurisy may be the result of either haematogenous spread or direct spread from an enlarging primary focus
4	Up to 3 years	This stage lasts until the primary complex resolves. More slowly developing extrapulmonary lesions, particularly in the bones and joints, may appear
5	Up to 12 years	Genitourinary tuberculosis may occur as a late manifestation of primary tuberculosis

Figure 1: Showing Wallgrens timetable of primary tuberculosis

Tuberculosis (TB) is an airborne infection transmitted between humans. Its natural history begins with the exposure of a susceptible host to an infectious case of pulmonary TB. Yet, only 30% of contacts will develop a TB infection. Indeed, most infections remain clinically latent carrying a risk for disease reactivation; it is widely accepted that approximately 10% of infected individuals will progress to TB whereas the rest will likely harbour the organism for the rest of their life [39].

Close contacts with Latent Tuberculosis Infection (LTBI) are at particularly high risk of reactivation. Their level of risk of progression differs according to age group: in those aged < 14 years, the risk accrues within 150 days whereas in those aged ≥ 15 years, the risk is more evenly distributed, with approximately one-half of the total risk accruing within the first 227 days [40].

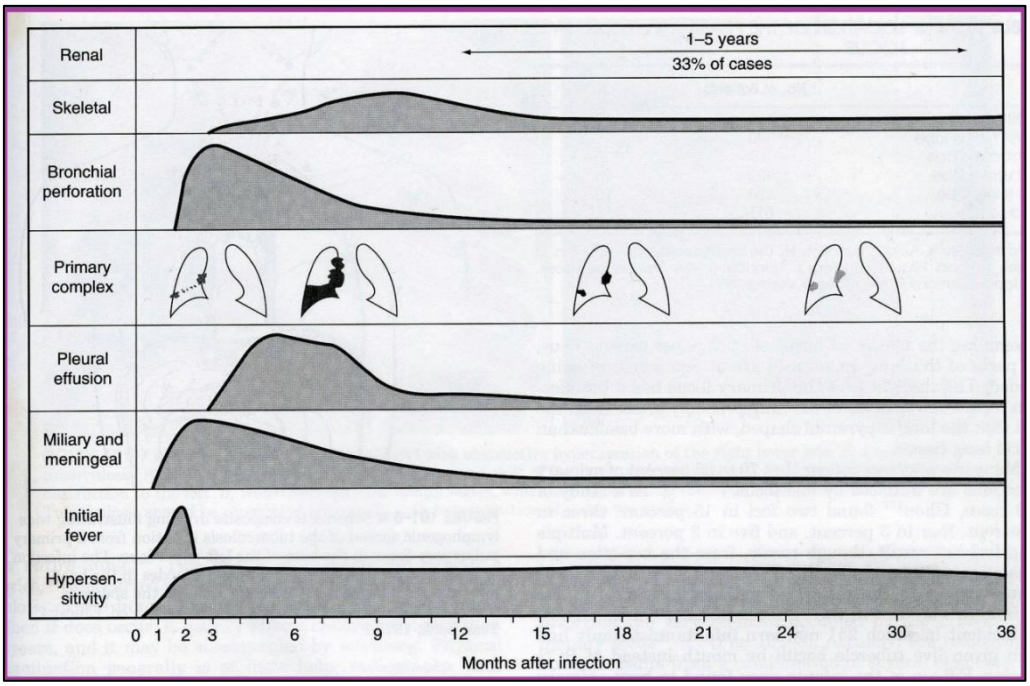

Figure 2: Chart showing Wallgrens timetable of primary tuberculosis

The largest study to evaluate Interferon Gamma Release Assays (IGRAs) and Tuberculin Skin Tests (TSTs), the UK PREDICT TB cohort study, recently showed that in a low-incidence setting among TB contacts and migrants from high TB risk countries positive predictive values are only 3-4% [41]. It means that only 3-4% of those positive progresses to active TB after infection. The PREDICT study also indicated that IGRAs were more sensitive and specific than TST 10 mm. Partially in contrast to this result, Auguste has lately documented among recent arrivals from high-endemic countries that TST 10 mm and 15 mm had lower sensitivity, but higher specificity compared to IGRAs and TST 5 mm in predicting future progression. In any case, no test globally outperformed the other [42].

TB patients with pulmonary cavity, which contains up to 1.000.000.000 of mycobacteria, are the principal source of disease transmission compared with those with noncavitary disease. Also, Endobronchial TB (EBTB) is a highly infectious disease even if the yield of sputum positivity for Mtb is not as high as in parenchymal involvement. More in detail, mycobacteria are isolated in 16-53% of EBTB patients in relation to which one of the seven categories of EBTB [43] the patient shows, being the granular forms more often positive to acid fast bacilli in sputum examination while the fibrostenotic forms regularly negative [44]. The granuloma is a pauci-bacillary lesion. Actually, much of the literature assumes that mycobacteria reside within granulomas. However, multiple studies found that granulomas are sterile after 5 years [45]. Owing to the paucity of data on the evolution of parenchymal lesion in humans, the time elapsed since infection and the exact mechanisms resulting in pulmonary cavitation are poorly understood. So that, our current knowledge of natural history of TB and pathogenesis of cavitation stems also from animal models, microbiology and mathematical models [46].

Pathological definitions of granuloma and cavitation [47]:

The granuloma, hallmark of TB infection, is: "a highly organized structure consisting of many immune cell types (e.g., macrophages, neutrophils, natural killer cells and T- and B-cells) that surround a caseous necrotic core of Mtb-infected alveolar macrophages. The granuloma is traditionally thought to be host-protective by sequestering and preventing dissemination of Mtb proliferation and spread"

The pulmonary cavitation, hallmark of TB disease, is: "a process by which normal pulmonary tissue is obliterated, becoming gas-filled spaces or cavities in the lung. This process initially involves caseous necrosis of lipid pneumonia lesions, producing caseous pneumonia. During caseation, alveolar cells and septa are destroyed along with neighbouring vessels and bronchi. Cavities form when these regions of caseous pneumonia liquefy, fragment and are released upon coughing".

Hypotheses on granuloma and cavity formation [48]

***Granuloma formation* [49-51]**

The results of in vitro experiments and data from animal and mathematical models suggested that inhaled mycobacteria are first phagocytosed by resting (i.e. inactivated) alveolar macrophages which are unable to clear them because Mtb has evolved mechanisms for evading killing by its host macrophages. Thus, the maturation of the mycobacterial phagosome is blocked, Mtb replicates in an intracellular niche within macrophages, so evading detection by humoral immunity, with a doubling time of 24/96 hours.

At this point, macrophages, which are now defined "infected", start producing and secreting antimicrobial peptides, cytokines (like tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-12, and IL-6) and chemokines, able to create, all around the site, a gravitational field that direct other cells, particularly T lymphocytes, to areas of greater cytokines concentration so leading to the formation of granuloma. The concentration gradient of cytokines is not achieved correctly if macrophages do not secrete TNF-α. When the bacteria inside the macrophage reach the number of 20, the macrophage can explode, and the escaping bacteria are taken up by other alveolar macrophages and by dendritic cells. Dendritic cells are mobile cells whose task is to migrate to the nearest lymph nodes where they present Mtb antigens to the T naïve cells so transforming them in activated CD4+ which produce cytokines, principally interferon-γ (IFN-γ), the main activator of macrophages, that in conjunction with TNF-α and IL-12 drive the host immune responses into Th1 polarization.

At this point, Mantoux test is still negative. Mathematical models had showed that, in the granuloma formation, the fastest process is diffusion of chemokine, then T cell movement (2 μm/ min) and macrophage movement (1 μm/min). It means that T cell speed should be about 0.12 mm/ hour, that is 2.88 mm/die. For this reason, Mtb specific T-cells can reach the lung only 14-21 days after the infection starts depending on how far the nearest lymph nodes are from the site of granuloma formation. Production of TNFα and IFN-γ by T-CD4+ stimulates killing activities by macrophages. T-cells complete granuloma formation by forming the lymphocytic cuff surrounding it. Only after their arrival to the parenchyma the Mantoux test become positive. Once formed, the granuloma contains the mycobacteria and prevents spreading, but at the same time serves as a site of replication and persistence for Mtb. In non-human primates, the typical time frame for the entire process of the development of a granuloma is from 14 to 100 days.

***Cavity formation* [52-54]**

Mtb generally has the highest prevalence of cavities among people with pulmonary disease of any infection. The established paradigm of cavity formation was developed by Dannenberg in the late 20th century. He considered the caseating granuloma as the characteristic TB lesion which encounters liquefactive necrosis, leaving behind a cavity during active disease. However, this paradigm principally derives from classical experiments in the rabbit model of Mycobacterium bovis infection, in which large tubercles develop and then rupture into the airways [52]. Hunter, instead, pointed out that pre-antibiotic era researchers had documented that all human Mtb granulomas, once formed, did not undergo erosion and necrosis and that human studies had suggested that cavities originate, rather, from lipid pneumonia. After he directly examined the slides from autopsies of adults who died of untreated pulmonary TB during the preantibiotic era, he developed a different paradigm according to which, during the post primary TB, the lesions progress as an endogenous lipid pneumonia, not as a caseating granuloma, that undergo caseous necrosis whose necrotic tissue may either soften, fissure and coughed up leaving a cavity or harden producing fibrocaseous TB [53].

Although the precise immune mechanisms underlying cavities formation are not fully understood, normal immunity should play a significant role. In fact, as underlined above, humans suffering from AIDS develop cavities when their CD4 count is > 350 cells/μl while they usually do not when their CD4 count is 200 cells/ μl; reports about cases presenting the tuberculosis associated Immune Reconstitution Inflammatory Syndrome (IRIS) have described patients with advanced HIV/TB and minimal initial radiographic lung involvement who develop massive pulmonary infiltrates or lung cavitations after the Antiretroviral Therapy (ART) had restored their immunity [54] (the IRIS typically occurs within the first few weeks and up to 3 months after ART is initiated). Nevertheless, diverse autoimmune phenomena occur in human TB (for example, autoantibodies are detected in 40% of TB patients); erythema nodosum occurs in TB and autoimmune diseases; sarcoidosis, an autoimmune disease, resembles TB (their histologies characterized by well-organized granulomas formed from activated macrophages are similar, also the location of lesions in the upper lobes and the tendency to affect other organs are similar). Based on the above-mentioned characteristics of HIV/TB coinfection and similarities between autoimmunity and TB, Elkington, in 2016, has hypothesized that the cavity could be the result of an autoimmune inflammation due to inappropriate host responses to self-antigens induced by mycobacteria [55].

According to historical and microbiological studies and mathematical simulations, the estimate "TB timing" ranges, from several months to 1-2 years or more. Hunter has hypothesized that mycobacteria need a time of 1 to 2 years to asymptomatically obstruct bronchioles to physically isolate a lobule of lung and then accumulate within its alveoli mycobacterial antigens and host lipids in preparation for a sudden necrotizing reaction to produce a cavity of sufficient size to mediate transmission of infection to new hosts [45] At the TC examination, this obstructive lobular pneumonia is visible as a characteristic centrilobular tree-in-bud which has histopathologically interpreted as a result of obstruction of the terminal or respiratory bronchioles where the "buds" are foci of pneumonia in the alveoli of the obstructed ducts.

CONCLUSION

In the present case report, we have reported a case of cavitary lung disease with constitutional symptoms managed as nonspecific general health ailment without doing workup towards tuberculosis in spite of chest radiological investigations done early during course which were underestimated either due to lack of suspicions by treating general physician or never done reporting of that chest x-rays form trained radiologists. She was referred to specialist's center after moderate hemoptysis where she was thoroughly evaluated including HRCT thorax and confirmed as pulmonary tuberculosis by documenting cavitary disease in left lung and performing induced sputum examination for CBNAAT (Cartridge based nucleic acid amplification) MTB (mycobacterium tuberculosis) positive, Rifampicin mutation (Rpo-b) Negative. She was treated as per NTEP schedule and weight band with four drug ATT for four months and three drugs for four months with clinical and radiological cure.

Learning points:

1. Chronic constitutional symptoms such as weight loss, anorexia and low-grade fever, cough and shortness of breath with or without hemoptysis is commonly described in active pulmonary tuberculosis and rarely documented in other ailments including bronchitis, asthma, jaundice and community acquired pneumonia. These nonspecific conditions as suspected by general practitioners were reasons for significant delay in confirming pulmonary tuberculosis.
2. Thick-walled cavities with pericavitary consolidation with constitutional symptoms were commonly documented in active pulmonary tuberculosis. Other reasons for the similar picture are lung malignancy and community acquired pneumonia and Wegener's granulomatosis where constitutional symptoms are not very common.
3. Conventional chest radiograph is a less sensitive technique and all cases with doubtful cavitary lesions with constitutional symptoms should undergo HRCT thorax to investigate further. This will have additional advantage of documenting the extent and nature of parenchymal abnormalities with pleural, vascular and mediastinal abnormalities.
4. Tuberculous cavity has very typical characteristics and is described as a soft cavity with minimal air fluid level, usually single large and solitary to multiple in number. These cavities are classically associated with pericavitary consolidations and satellite nodules.
5. Sputum production and its yield in cavitary lung disease associated with pulmonary tuberculosis depends on size of cavity, anatomical location, bronchus communication of cavity and quantity of sputum production.
6. Induced sputum has a very significant impact on diagnostic yield and the most cost-effective technique in ruling out active pulmonary tuberculosis. It is a sensitive technique when smear examination is considered and its specificity increased with cartridge based nucleic acid amplification of Gene Xpert MTB/RIF test in cases with cavitary lung disease.
7. Induced sputum looks like salivary or less mucoid due to its methodology. We recommend it as routine and it will decrease the need for more invasive tests such as bronchoscopy. Bronchoscopy guided sampling such as BAL has significant yield in sputum negative cavitary lung diseases. Induced sputum is cost effective, easily performed technique and its sensitivity is comparable with bronchoscopy in cavitary lung disease. In the absence of cavitary lung disease, bronchoscopy is superior to conventional microscopy in smear after induced sputum examination.
8. Delay in diagnosis of tuberculosis occurs for two reasons: patient and physician. Fromer one is commonly due to lack of knowledge of tuberculosis disease and poor knowledge regarding health professional selection by patients. Sometimes patients are not willing to investigate due to financial constraint and with financial ability not willing to undergo due to fear of disease. These patients are labelled as difficult patients.
9. Second most common reason for delay in diagnosis is treatment provider or physician factor. Lack of disease knowledge including signs and symptoms, unavailability of resources required for diagnosis, lack of chest radiology training, lack of suspicion of disease, many physicians feel that patients will be lost form their center if they will ask them to investigate further or seek other professionals if they

suspect tuberculosis. This category is called a difficult doctor.

10. Pulmonary tuberculosis should be suspected early in cases with cavitating consolidations with constitutional symptoms to have a successful treatment outcome. Proper training of peripheral or rural or primary health care sector professionals regarding complete knowledge about signs, symptoms, investigations and treatment options regarding tuberculosis should be done regularly and repeatedly to prevent delay in diagnosis and adverse disease outcome.
11. Health awareness campaigns regarding tuberculosis should be made by government agencies including free treatment available as per NTEP guidelines to prevent mortality and morbidity due to this easily treatable disease of the millennium.

Conflicts of Interest: Nil

Research Funding: Nil

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