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MODESTUM

Case Report **OPEN ACCESS**

Cavitating lung disease is not always due to tuberculosis! Wegener's granulomatosis with mycetoma with deep vein thrombosis lower limb: Case report with review of literature

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ABSTRACT

Pulmonary tuberculosis is most common cause for bilateral pulmonary cavities with constitutional symptoms in India being endemic and more prevalent nature of disease, irrespective of microscopy or nucleic acid amplification test abnormalities. Pulmonary manifestations of systemic vasculitis have very diverse involvement ranging from nodule, consolidation, and cavitation. In this case report, 49-year female, presented with constitutional symptoms with lung parenchymal consolidations progressed to cavitation's and started empirical anti-tuberculosis treatment without mycobacterial microscopic or genome documentation in sputum with clinical or radiological worsening. Bronchoscopy workup is inconclusive and tropical screen for bacterial, TB, and malignancy were negative and fungal yield aspergillus colonization. Vasculitis workup done in presence of clinical and radiological worsening documented PR3-ANCA positive with very highly raised titers. We have started on steroids, cyclophosphamide with antifungals and clinical response documented with near complete resolution of shadows in 24 weeks. She had developed DVT (deep vein thrombosis) lower limb during course of illness and documented excellent response to anticoagulation. DVT prophylaxis is must in all cases taking steroids with decreased daily activities to prevent fatal cardiovascular complications.

Keywords: cavitating lung disease, HRCT thorax, Wegner's granulomatosis, mycetoma, pulmonary tuberculosis

INTRODUCTION

Wegener's granulomatosis rare systemic disease first described by German pathologist Friedrich Wegener in 1936, characterized by necrotizing, granulomatous small-vessel vasculitis that affects mainly the upper airways, lungs, and kidneys, but may affect any organ system. The most frequently affected organ is the lung, with involvement seen in more than 90% of patients with WG during the course of the disease, which is a multisystemic necrotizing vasculitis first described by German pathologist Friedrich Wegener in 1936 [1]. Wegener's granulomatosis nodules may occur in a centrilobular distribution, mimicking tuberculosis, hypersensitivity pneumonitis, or an acute viral, bacterial, or fungal pneumonia [2].

CASE SUMMARY

45-year-old female, farmer by occupation, no addiction history, normotensive, non-diabetic, referred to our center by family physician for-ATT induced hepatitis with history of intermittent fever, cough and weight loss since six months of duration, received symptomatic treatment initially with antibiotics and antipyretics shown poor response to treatment, further evaluated with sputum workup as microscopy was not showing acid fast bacilli and gene Xpert MTB/RIF was negative for MTB genome, received empirical anti-tuberculosis treatment for four months, poor response to treatment and developed drug induced hepatitis and was reason for referral to our center for further workup.

Further clinical details are, as follows:

1. Jaundice-recent onset, yellowish discoloration of eyes with nails, associated with nauseas and vomiting, unable to tolerate anything by mouth, resulted in decreased urine output in the last seven days.
2. Fever-for six months, intermittent, moderate to high grade without chills and rigors associated with minimal body ache and headache.
3. Cough-for four months dry and intermittent with minimal white sputum production.
4. Loss of appetite and weight loss over period of six months.
5. Weakness and myalgia with fatigability.
6. Shortness of breath on exertion in the last two months.

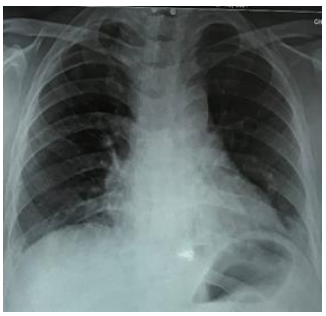

Figure 1. Chest X-ray PA-1

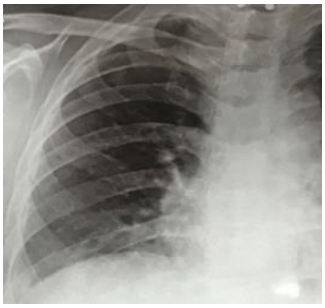

Figure 2. Chest X-ray PA-2

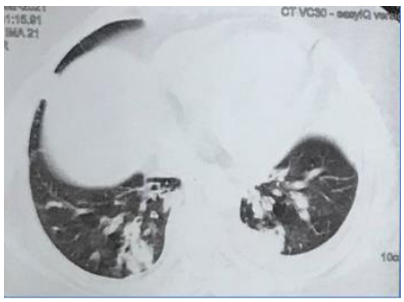

Figure 3. HRCT thorax-1

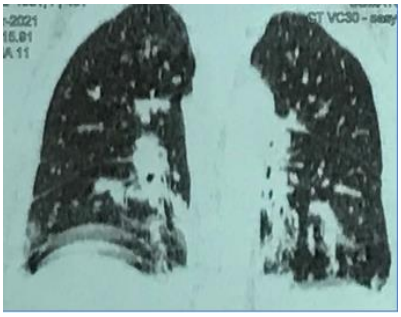

Figure 4. HRCT thorax-2

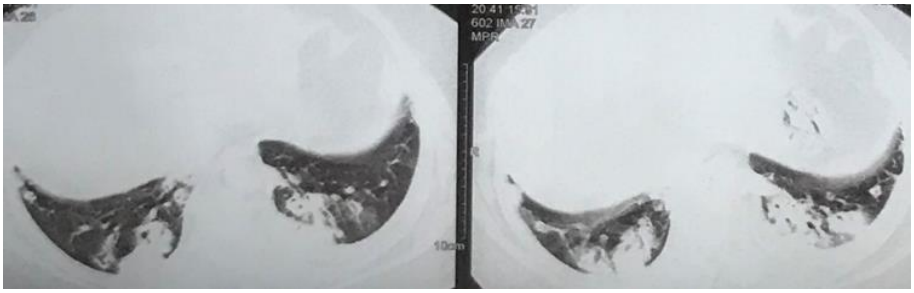

Figure 5. HRCT thorax-3

Clinical examination documented, as follows:

1. Restless, dry oral mucosa, pedal oedema-pitting type, pallor, febrile.
2. Heart rate-130/min respiratory rate: 26/bpm, BP-80/60 mmhg.
3. PsO2: 91-94% @ room air resting & 89-91% @ room air on exertion.
4. Respiratory system examination revealed-bilateral breath sounds normal, bilateral crepitation's heard on both lung fields.
5. Nervous system examination-higher functions normal, no neurological abnormality, cranial nerves normal, recent, and past memory normal recall.
6. Cardiovascular and gastrointestinal systems were normal.

We have assessed past records of hospitalization, as follows: Chest X-ray done and showing bilateral lower lobe inhomogeneous opacification (**Figure 1**) and inhomogeneous opacification with cavitation seen in right paracradiac region in lower zone (**Figure 2**).

Laboratory examination documented, as follows:

1. Hemoglobin-11.7 gm% total white blood cells-6,000/mm3 polymorphs-70%, platelet count-390,000/uL.
2. CRP-165 mg/L (0-6 mg/L), random blood sugar level-134 mg% HbA1C-5.60%.
3. LDH-880 IU/L (70-470 IU/L), uric acid-3.4 mg (3.5-7.5 mg/dL).
4. Serum electrolytes: Sodium-132 meq/L (135-145 meq/L), potassium-3.9 meq/L (3.5-5.5 meq/L), and ionic calcium-1.32 meq/L (1.09-1.36 meq/L).
5. D-dimer-560 ng/ml (<500 ng/ml).
6. IL-6-1.75 pg/ml (0.00-7.00 pg/ml).
7. Thyroid functions-normal.
8. Liver and kidney functions- normal.
9. Sputum examination for acid fast bacilli was negative and TB gene Xpert MTB/RIF were negative for MTB genome.

HRCT thorax suggestive of

1. bilateral, peripheral multifocal consolidations (**Figure 3** and **Figure 4**) involving,
2. middle and lower lobes (**Figure 5**) with,
3. consolidation with air bronchogram (**Figure 5** and **Figure 6**), and
4. consolidation with lucencies (**Figure 3**, **Figure 4**, **Figure 5**, and **Figure 6**).

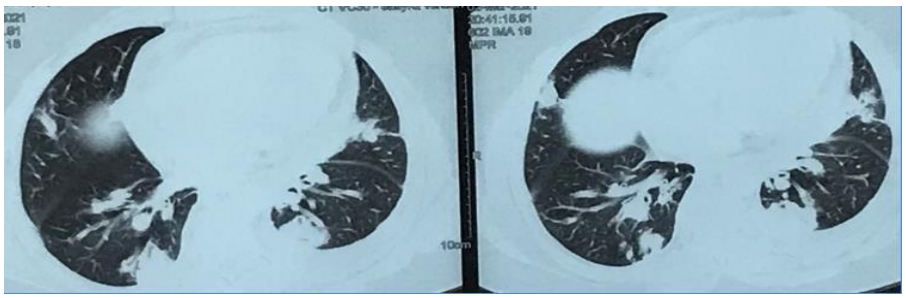

Figure 6. HRCT thorax-4

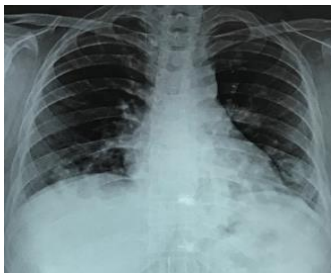

Figure 7. Chest X-ray PA-3

As she was started on empirical ATT (anti-tuberculosis treatment) for lung parenchymal opacities as per weight band with isoniazid, rifampicin, pyrazinamide, ethambutol for two months, she tolerated well and shown significant improvement on symptoms for shorter duration. After completion of intensive phase, she was shifted to continuation phase with isoniazid, rifampicin, ethambutol without steroids, she tolerated for two weeks and started on reappearance of symptoms as cough, fever, anorexia; we have evaluated for other diagnosis or ATT induced adverse drug reactions due to significant anorexia and jaundice.

Laboratory examination documented, as follows:

1. Hemoglobin-8.7 gm% total white blood cells-21,000/mm3 polymorphs-85%, platelet count-490,000/uL.
2. KFT-serum creatinine-2.8 mg/dl (0.6-1.2 mg/dl), blood urea-87 mg/dl (10-40 mg/dl).
3. Urine proteins-1+(380 mg/dl).
4. Liver function tests-Sr bilirubin-12 mg/dl (06-1.2 mg/dl) Indriect-8.4 direct-3.6.
5. Sr ALT-1681 IU/L Sr AST-1980 IU/L.
6. Sr proteins-total 6.8 gm% albumin-3.8 globulin-3.0.
7. Sr alkaline phosphatase-190 IU/L.
8. CRP-249 mg/L (0-6 mg/L), random blood sugar level-110 mg%.
9. LDH-980 IU/L (70-470 IU/L), uric acid-3.4 mg (3.5-7.5 mg/dL).
10. Pro-BNP- 96 pg/ml (<125 pg/ml).
11. Serum electrolytes: sodium-138 meq/L (135-145 meq/L), potassium-5.9 meq/L (3.5-5.5 meq/L), and ionic calcium-1.26 meq/L (1.09-1.36 meq/L).
12. D-dimer-450 ng/ml (<500 ng/ml).
13. IL-6-1.75 pg/ml (0.00-7.00 pg/ml).
14. Thyroid functions-normal.
15. COVID-19 RT PCR test and results documented negative for SARS CoV 2.
16. Chest X-ray suggestive of bilateral lung pathology predominantly cavities with inhomogeneous infiltrates in bilateral lower zones (**Figure 7**).

We further ask for more history regarding progression of disease over last three months, her husband told regarding recurrent nasal symptoms and multiple consultations for same. Patient disclosed that, she was having nasal stuffiness without nasal discharge, and she was having nasal crusting, which was increased over last three months, she also told that she was having multiple throats crusting and altered voice or dysphonia which was intermittent and spontaneously recovering with saline gargles.

We performed HRCT thorax and documented, as follows:

1. Bilateral, multiple, peripheral, and pleural based thick-walled cavities with few cavities containing radio-opaque mass inside (**Figure 8**).

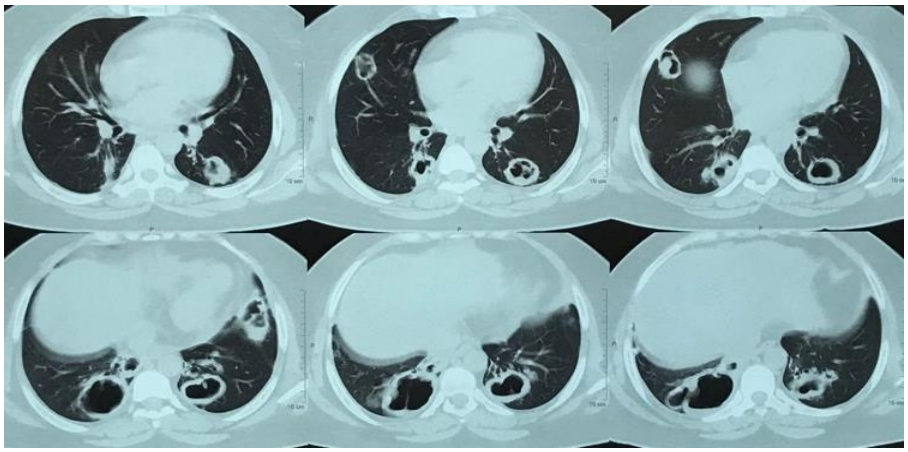

Figure 8. HRCT thorax-5

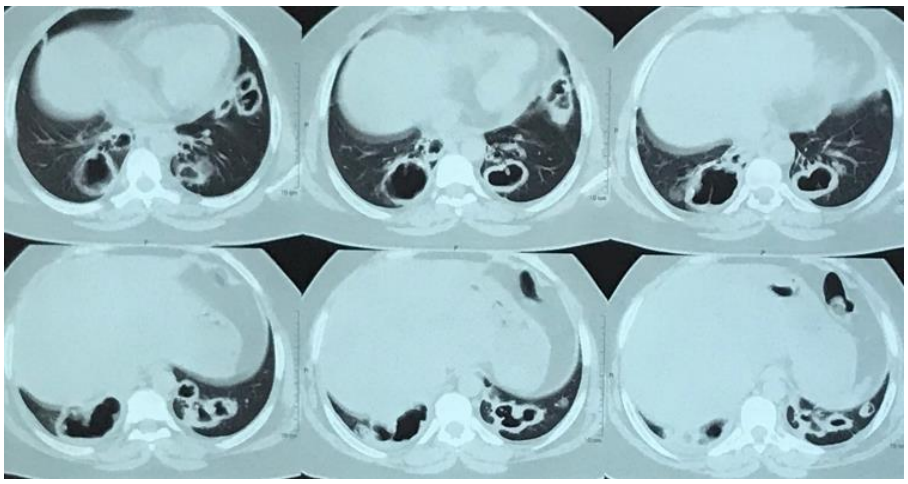

Figure 9. HRCT thorax-6

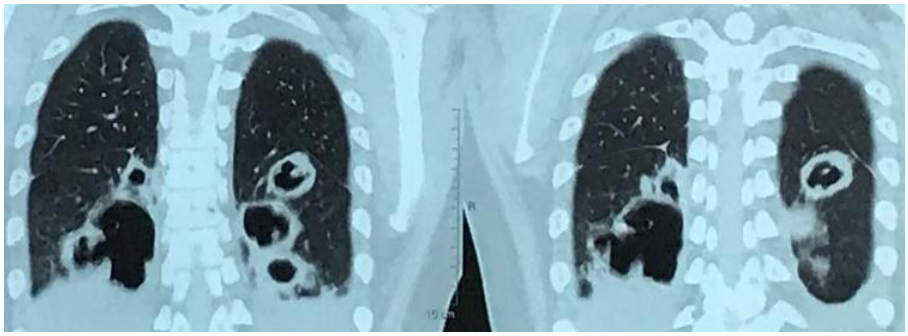

Figure 10. HRCT thorax-7

2. Bilateral, multiple, peripheral, and pleural based thick walled single and giant cavities with few cavities containing radio-opaque mass inside with variegated appearance (**Figure 9**).
3. Bilateral, multiple, peripheral, and pleural based thick walled single and giant overlapping cavities 'stepladder pattern' with few cavities containing radio-opaque mass inside with variegated appearance (**Figure 10**).

We have stopped anti-tuberculosis treatment, supportive treatment for liver dysfunctions, with intravenous fluids for dehydration and shock and as per nephrologist opinion for 'pre-renal' treatment protocol and her general condition improved, liver dysfunction recovered, and kidney functions improved. After clinical stability, we have decided for bronchoscopy to rule out tropical etiology.

Bronchoscopy examination revealed hyperemic mucosa at lower trachea, carina and purulent secretions coming out from bilateral main stem bronchial lumens, increased rugosity in segmental bronchial openings, No evidence of endobronchial growth, gross visible abnormality also no evidence of submucosal or peribronchial abnormality. BAL was collected after 100 ml saline instillation and four aliquots were sent for cytology, gene Xpert, bacterial, and fungal culture.

1. BAL cytology suggestive of acute inflammation, negative for malignant cell.
2. BAL AFB-negative, gene Xpert MTB/RIF-negative.
3. BAL bacterial culture-no growth.

Fungal culture-aspergillus species, are as follows:

1. As tropical workup negative and no evidence of malignancy as probable etiology for bronchus sign, we sent blood sample for vasculitis workup.
2. MPO-ANCA (P-ANCA)-0.86 RU/ml (normal range 0-20 RU/ml).
3. PR3-ANACA (C-ANCA): >200 RU/ml (normal range 0-20 RU/ml).

Nephrologist consultation taken for renal involvement and decided for wait and watch for renal functions, and plan for biopsy in follow up. We have done renal biopsy at three month follow up and microscopy shown normal histology.

We have started injection methylprednisolone 40 mg IV TDS, Cyclophosphamide at dose of 50 mg OD, increased to 100 mg in second week and 150 mg OD in third week and continued for 12 weeks, antipyretics for fever control, adequate oral liquids with intravenous fluids and maintained hydration with Kidney functions and liver functions tests monitoring. Tab Voriconazole was started at 200 mg BD for 12 weeks and documented significant improvement in lung cavities. After one-week, Injectable methylprednisolone has been shifted to oral and dose decrease from 40 mg TDS to oral 48 mg and tapered over 24 weeks.

During course of treatment, she developed swelling of left lower limb with painful movements of left thigh and calf with exaggerated symptoms on dorsiflexion of left foot. Lower limb doppler documented deep vein thrombosis in left saphenous vein in mid-thigh region extending up to the popliteal region, anterior and posterior tibial veins appeared to be partially thrombosed (**Figure 11**, **Figure 12**, **Figure 13**, and **Figure 14**).

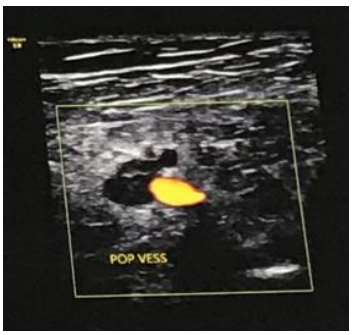

Figure 11. Venous doppler-1

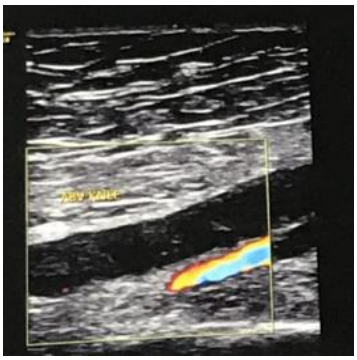

Figure 12. Venous doppler-2

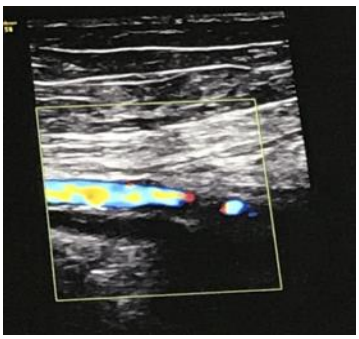

Figure 13. Venous doppler-3

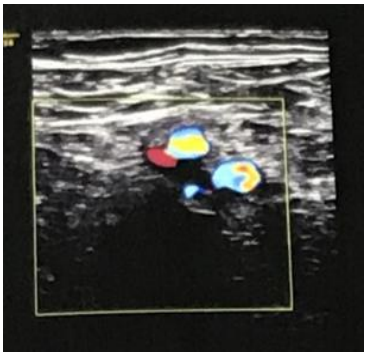

Figure 14. Venous doppler-4

She has been treated with low molecular weight heparin subcutaneous injection for five days followed by oral Rivaroxaban 20 mg one time daily for 12 weeks and after documentation of resolution of deep vein thrombosis, tapered to 2.5 mg one time daily and advised for continuation till two years.

We have added trimethoprim sulphomethaxazole (160/800) two times for one month then one time daily for one month and ones in week for 48 weeks. Strict monitoring of hemogram, renal, and liver function tests were done as weekly for first month and then monthly till 12 months, till near complete resolution of lung cavities and lung parenchymal abnormalities (**Figure 15**, **Figure 16**, **Figure 17**, **Figure 18**) were documented with satisfactory clinical response.

After six months, we have continued oral disease modifying agents as methylprednisolone four mg daily with cyclophosphamide 100 mg daily were continued for additional 24 weeks and then methylprednisolone alternate day for one year and cyclophosphamide stopped after one year. Methylprednisolone four mg one tablet per week with trimethoprim sulphomethaxazole (160/800) one tablet per week continued for additional 24 weeks. We have documented complete remission of lung manifestation after three months and maintained with disease modifying agents till 18 months.

DISCUSSION

Wegener's granulomatosis (WG) was first described by German pathologist Friedrich Wegener as rhinogenic granulomatosis in 1936 and is an uncommon vasculitis of small and medium-sized arteries. WG, which is an angiogenic and multiple system necrotizing disease involving the upper and lower respiratory tract and kidneys, is affected by a number of factors, including heredity, infection, the immune system and the environment, and diagnosis is typically confirmed via clinic and laboratory examinations [3].

Pulmonary involvement ranges from subclinical changes evidenced by chest CT or bronchoalveolar lavage fluid to devastating haemoptysis [4]. The most common respiratory symptoms include cough, mild dyspnoea, haemoptysis, and pleuritic chest pain [4].

Lung nodules are the most common manifestation of Wegener's granulomatosis and occur in approximately 40-70% of patients. Nodules are usually multiple and bilateral and occur without a zonal predilection. The size of Wegener's granulomatosis nodules varies, most commonly measuring between two and four cm but ranging from a few millimetres to 10 cm [5].

Cavitation occurs in approximately 25% of nodules larger than two cm; the walls of the cavities may be thin or thick and nodular. Wegener's granulomatosis nodules and cavities may be easily mistaken for metastases, lung abscesses, or septic infarcts. As with any lung cavity, those occurring in Wegener's granulomatosis may become secondarily infected, in which case gas-liquid levels may develop. Haemorrhage may occur around nodules and manifests on high-resolution CT as ground-glass opacity surrounding the consolidated nodule, referred to as the halo sign [6, 7].

Lung consolidation and ground-glass opacity often occur in approximately 30% of patients with active Wegener's granulomatosis and are usually the result of haemorrhage. When present in isolation, lung consolidation is often initially attributed to pneumonia, and Wegener's granulomatosis may be diagnosed when consolidation persists despite appropriate treatment. Arteriolar involvement with Wegener's granulomatosis may present as mosaic attenuation or tree-in-bud opacities [7, 8].

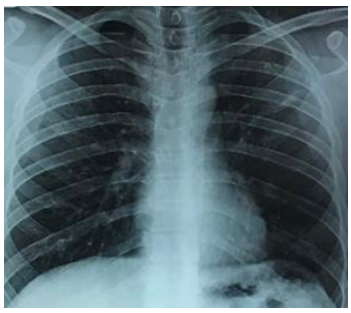

Figure 15. Chest X-ray

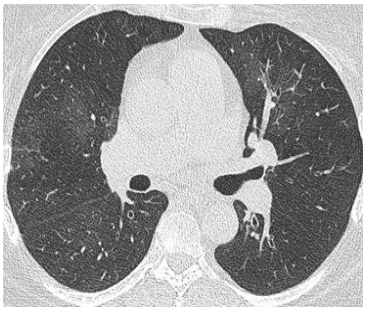

Figure 16. HRCT thorax-8

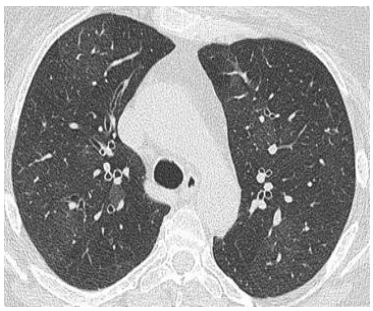

Figure 17. HRCT thorax-9

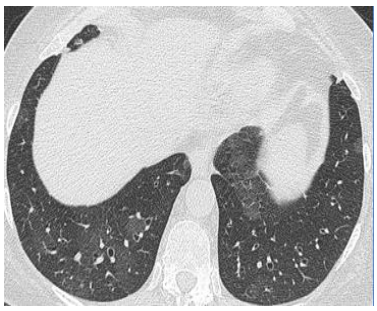

Figure 18. HRCT thorax-10

Aspergillomas have been most frequently documented as occurring in residual tuberculous cavities. Aspergillomas are also a common accompaniment to advanced fibrotic disease in sarcoidosis, with up to 53% of such patients having radiographic evidence of aspergillomas. Indeed, any cavity within the lung is a potential focus for the development of aspergilloma, and predisposing conditions include bulla in emphysematous lung, cystic spaces from end-stage fibrosis, pneumatocoeles caused by pneumocystis carinii, miscellaneous cavitatory infections (e.g., histoplasmosis), bronchogenic/congenital lung cysts, Wegener's granulomatosis, cavitary pulmonary infarction and lung fibrosis from radiotherapy [9].

In present case report, clinical scenario mimicked with pulmonary tuberculosis with partial response to ATT, and clinical and radiological worsening with empirical ATT, tropical workup was ruled out tuberculosis, and further workup established vasculitis as cause for presentation. We have treated as per standard protocol and documented satisfactory treatment outcome.

Key Learning Points from This Case Report

1. Pulmonary tuberculosis is most common cause for bilateral pulmonary cavities with constitutional symptoms in India being endemic and more prevalent nature of disease.
2. Although bilateral pulmonary cavities with constitutional symptoms is well described in Pulmonary tuberculosis, other etiological reasons for similar findings are lung other tropical infections like fungal and vasculitis with lung involvement.
3. Persistent symptoms and poor response to anti-tuberculosis treatment is clinical clue towards to rule out other etiological factors for similar syndromic presentation. Upper airway symptoms like nasal crusting and dysphonia were important defining pointers towards Wegner's granulomatosis workup.
4. Constitutional symptoms like cough, fever, and weight loss with lung abnormality on HRTC thorax may mislead towards empirical treatment without documentation on microscopy and nucleic acid amplification tests.
5. Steroids are cornerstone of treatment of Wegner's granulomatosis with lung involvement shown excellent response to steroids with cyclophosphamide and renal workup should be actively sought in all cases before initiation of treatment as many cases may document abnormality during course of treatment.
6. Patients taking long term steroids and less routine activity mandates DVT prophylaxis to prevent fatal cardiovascular complications.
7. We recommend, all cases constitutional symptoms with negative workup for tropical diseases screen including tuberculosis should undergo prompt evaluation to rule out underlying systemic vasculitis as etiological factor.
8. Wegner's granulomatosis is treatable condition irrespective of lung involvement and having good prognosis if renal function tests are normal.
9. Pulmonary manifestations of Wegner's disease are rare, underestimated, and early pickup of entity in course of illness will have good outcome with excellent prognosis.

Author contributions: All authors have sufficiently contributed to the study and agreed with the results and conclusions.

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Ethical statement: The authors stated that the study was approved by the Institutional Review Board/Ethics Committee of MIMSR Medical college, Venkatesh chest Hospital and Critical Care Center, Latur, India. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal

Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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