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Coexistence of Pulmonary Thromboembolism, Pulmonary Tuberculosis and Granulomatosis with Polyangiitis

A flimsy triple dribble

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Abstract

Granulomatosis with polyangiitis (GPA) is a rare autoimmune disease with multi-system involvement. It involves the upper respiratory tract, lungs and kidneys. A 36-year-old female patient presented with complaints of low-grade fever, dry cough and loss of appetite initially followed by dyspnea, purpuric skin lesions, right lower limb swelling with pain and redness. Her chest radiograph revealed right upper lobe cavitary lesion with consolidation in right lower lobe. Mycobacterium tuberculosis was detected in sputum and Broncho alveolar lavage (BAL) via Cartridge based nucleic acid amplification assay (CB-NAAT). Later, Computed Tomography Pulmonary Angiography (CTPA) revealed bilateral pulmonary artery thromboembolism. Furthermore, her C-ANCA was positive, serum creatinine was rising, urine microscopy had red cell casts and lower limb venous doppler revealed DVT. Histopathological examination of the skin lesion revealed vasculitis. Based on the above findings, diagnosis of GPA was comfortably made. Patient improved with pulse steroids, cyclophosphamide, anticoagulants and anti-tuberculous therapy (ATT).

Keywords: Granulomatosis with polyangiitis (GPA), Pulmonary Tuberculosis, Pulmonary thrombo-embolism, deep venous thrombosis, vasculitis, c-ANCA.

Introduction

Granulomatosis with polyangiitis (GPA) formerly known as Wegner's granulomatosis is a systemic vasculitis involving small vessels predominantly.[1] In countries with high prevalence of tuberculosis, the diagnosis can be challenging as the presentation of GPA is heterogenous and can mimic tuberculosis due to its clinico-radiological overlap.[2] In addition, immunosuppressive therapy, which is the main stay of treatment for GPA can also lead to an increased risk of infections like tuberculosis. We hereby present an extremely rare case of GPA which at presentation had Pulmonary Tuberculosis as well as Pulmonary thromboembolism. Whether there was an increased predisposition of one disease because of the other or an extremely rare coincidence of all three diseases occurring together remains an interesting debate and read for the authors.

Case report

A 36-year-old female, a house-wife without any obvious risk factors and comorbidities, presented with complaints of low-grade fever, dry cough and loss of appetite for one month. On evaluation by a general practitioner, she was suspected as Pulmonary Tuberculosis as her chest radiograph showed a cavity in the right upper lobe along with consolidation in right upper & lower lobes (Fig 1a). This was then confirmed by sputum examination for (Acid Fast Bacillus) AFB by CBNAAT, both of which were positive. She was hence started on ATT. However, there was not much improvement clinically even after one month of starting ATT and she developed shortness of breath, purpuric skin lesions, epistaxis and also accompanying right lower limb swelling with pain and redness. On initial examination her blood pressure was 138/88mm Hg, oxygen saturation was 88% at room air and pulse rate was 92 beats per minute. Her hemogram and serum electrolytes were normal but Urine routine and microscopy showed red cell casts, blood urea nitrogen was16.07mmol/L, plasma creatine 167.2 µmol/L (which gradually increased to 387.2 µmol/L) and elevated D-Dimer levels (2.3 FEU/L). Urine and blood cultures were found to be normal.

Because of elevated D dimer and pain in right leg, arterial and venous colour doppler of bilateral limbs was done which revealed long segment hypoechoic thrombus in right saphenous and popliteal vein with no arterial thrombus. 2D Echocardiography showed dilated Right Atrial, Right Ventricle Internal Diameter (RVID=3.23cm), with peak systolic Right Ventricular pressure of 56 mm Hg, mild Tricuspid Regurgitation with normal Right Ventricle and Left Ventricle systolic function. On further evaluation, CTPA was done. Parenchymal

window showed dense consolidation in right hemithorax with a cavity in right upper lobe and angiogram images revealed hypodense thrombus in the lumen of segmental arteries of right lower lobe and left lower lobar artery suggestive of Pulmonary Thromboembolism (Fig 2 a and 2b). Autoimmune work up revealed negative antinuclear antibodies (ANA) profile whilst c-ANCA was strongly positive (>200 RU/ml, biological reference: <20, done via Immunofluorescence). p ANCA, C4 and C3 were all negative. Punch biopsy from the purpuric skin lesions showed vasculitis consistent with GPA. (Fig 3). Flexible bronchoscopy revealed no obvious endobronchial growth as such, but BAL for AFB and CBNAAT again turned out to be positive for mycobacterium tuberculosis. Diagnosis of GPA was made based on serology, involvement of respiratory tract, hematuria and skin biopsy.

Since GPA with venous thrombosis and Pulmonary Tuberculosis were diagnosed almost simultaneously, a combined treatment for GPA, TB and venous thrombosis was promptly started at the same time, to avoid further worsening of patient's clinical condition. Patient was treated with pulse methylprednisolone 1 gm for three days followed by gradual tapering of steroids along with cyclophosphamide. Anti-tuberculosis treatment was started along with systemic anticoagulation (initially started with heparin gradually switched to rivaroxaban). Patient improved significantly over the next few weeks as evident in a follow up chest radiograph Figure 1 (b) and is under regular follow up. Due consent was obtained from the patient for submitting this publication for scientific purpose.

Discussion

The diagnosis of GPA is based on a combination of various clinical manifestations of a systemic disease suggestive of vasculitis; positive ANCA serology and histological evidence of necrotizing vasculitis, necrotizing glomerulonephritis or granulomatous inflammation from a relevant organ biopsy, such as the skin, lung or kidney.[2] The diagnosis of concomitant GPA and TB is challenging because firstly clinical features of TB and GPA are overlapping, secondly despite considerable specificity of c-ANCA in GPA, c-ANCA levels have occasionally been reported to be raised in patients with tuberculosis.[3] Both these etiologies coexisted in our patient as on one hand AFB was detected twice in sputum as well as BAL, and on the other hand a positive c ANCA, vasculitis on skin histopathology and dramatic response of lung consolidation to steroids confirmed the presence of GPA.

Both tuberculosis and ANCA associated vasculitis can lead to a hypercoagulable state and lead to an increased incidence of venous thromboembolic (VTE) diseases.[5] Patients appear to be particularly at risk especially during active periods of inflammation.[6] Occasional detection of ANCA in tuberculosis may also suggest triggering of an autoimmune reaction with Mycobacterium Tuberculosis as the inciting antigen. Although one can debate these manifestations being bracketed under one broad spectrum of tuberculosis but the authors would prefer to label GPA as an independent occurrence because of combined presence of c ANCA, vasculitis on skin biopsy, response to steroids and lack of drug induced lupus/ANA.

The Wegener's Clinical Occurrence of Thrombosis (WeCLOT) study recruited 180 patients during active periods of disease. The reported incidence of VTE was 7.0 per 100 person-years (95% CI 4.0–11.4).[7]In a case report published in Iran 2021, a 28 years male was diagnosed to have both TB and GPA and was hence started on both immunosuppressants and ATT. But patient eventually developed cerebral venous thrombosis in due course of time which was treated with anticoagulation. In another case published by Khilani et al in 2003, a patient was initially started with ATT based on clinico-radiological features but eventually found out to be Wegners following detection of vasculitis and c-ANCA. Our patient was also found to have both TB and GPA, but with venous thrombosis at the time of presentation which is a very rare entity.[8]

The complexity of the possible inter relationships between the disease entities makes more than one hypothesis possible here and it is virtually impossible to determine which one leads to the other. But the simultaneous detection of three entities which can otherwise exist independently also, makes this case worthwhile and intriguing for the readers.

Co-existing diagnosis of these three entities is a challenge to manage. This is because immunosuppressants like steroids and cyclophosphamide is the gold standard treatment in Wegners, while these may increase the severity of tuberculosis. However, treatment of Wegners is warranted to reduce mortality and morbidity in due course. At the same time Wegners leads to progressive renal disease which leads to change in the ATT regimen as per the renal parameters.

Conclusion

To the best of our knowledge, this is the first case report presenting a coexisting diagnosis of GPA and pulmonary tuberculosis, DVT and pulmonary thromboembolism. Therefore, clinicians should be aware of potential multiple differential diagnosis when considering diagnosis and treatment. Though immunosuppressive therapy is relatively contraindicated in patients with active TB, untreated GPA might be life threatening. Moreover, combined treatments for both vasculitis and TB shows positive patient response, according to published case reports.[9,10]

Authors' Contribution

STP and AK conceptualized the work. AK, KK and AG managed the patient. STP collected the data. KK performed the literature search. STP, AK and KK drafted the initial manuscript. AK and AG edited and finalized the manuscript. All authors approved the final version of the manuscript.

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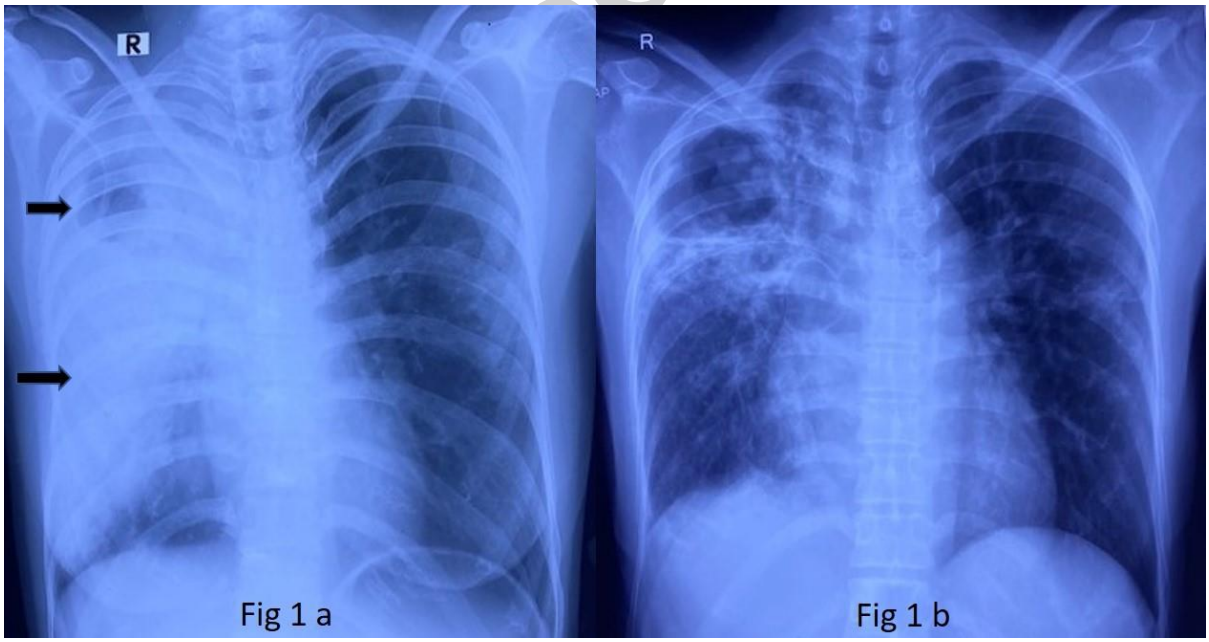

Figure 1: A: Chest radiograph shows a cavity in the right upper lobe (upper arrow) along with consolidation in right upper & lower lobes (lower arrow). **B:** Follow up chest radiograph shows significant resolution of the consolidation seen as compared to the previous radiograph.

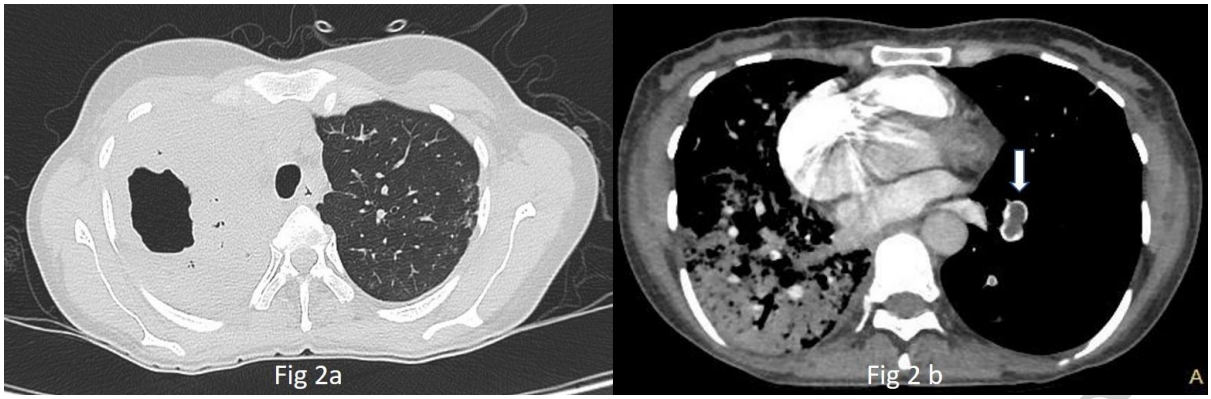

Figure 2: A: Parenchymal window of CT thorax shows dense consolidation in right hemithorax with a cavity in right upper lobe. **B:** CTPA images revealed hypodense thrombus in the arterial branch of left lower lobe (vertical arrow) highly suggestive of Pulmonary thromboembolism.

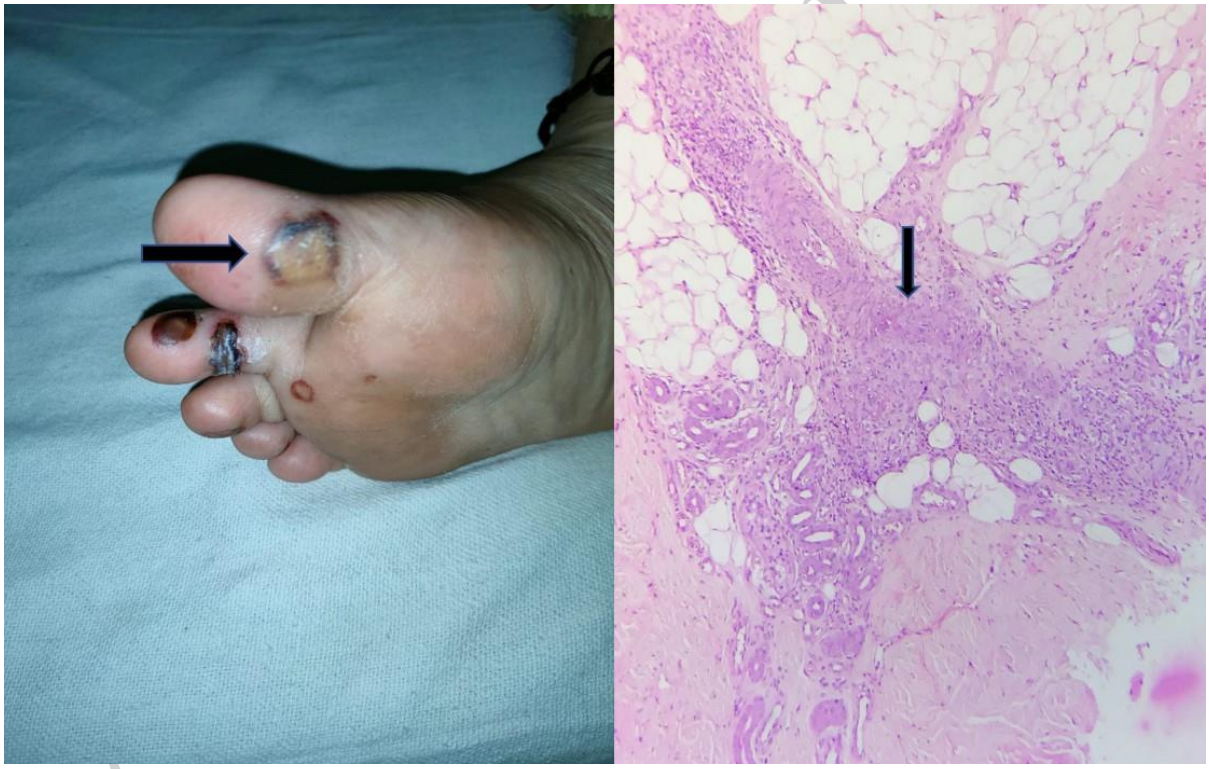

Figure 3: A: Hemorrhagic vesicles with perilesional purpura and erythema over the sole region. (Horizontal arrow). **B:** Subcutaneous tissue showing medium-sized vessels infiltrated by histiocytes in aggregates, lymphocytes and a few neutrophils. The vessel wall shows focal fibrinoid necrosis. (Vertical arrow) (HE, 100x)