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Atypical Presentation Of Granulomatosis With Polyangiitis – A Challenge In Diagnosis Of FUO

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ABSTRACT: Fever of unknown origin (FUO) is far more often caused by an atypical presentation of a rather common disease than by a very rare disease. Most common causes of FUO are infectious, inflammatory and neoplastic. Hereby, we present a case of FUO with granulomatosis with polyangiitis as its etiology with an atypical presentation.

Key words - Fever of unknown origin, Granulomatous angitis, Infections

INTRODUCTION: Prolonged fevers have been diagnostically problematic since antiquity. Commonly, the fever resolves spontaneously or a localizing sign appears to aid in diagnosis. Petersdorf and Beeson defined *fever of unknown origin* (FUO) in 1961. This definition has been further modified over years. However, more than a half century has passed since and we are no close to a diagnostic approach, partially due to ever expanding, dynamic list of differential diagnosis and partially due to lack of standard diagnostic approach. Infectious (43%) and inflammatory (23%) form the major chunk of etiologies, while neoplasms (16%), miscellaneous and idiopathic complete the list. It is important to remember that FUO is far more often caused by an atypical presentation of a rather common disease than by a very rare disease.

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CASE PRESENTATION : A 48 year old male, with no prior systemic illnesses presented to emergency with complaints of fever for 10 days, cough for 8 days, and shortness of breath for 1 day. The fever was non-documented, associated with chills and rigors, and had no diurnal variations. The cough was productive, mucopurulent and not associated with hemoptysis. The shortness of breath was acute in onset, was present at rest. He didn't consume alcohol or tobacco. On examination, he was hemodynamically stable with oxygen saturation 88% on room air which improved to 96% on oxygen, and bilateral crepts on respiratory system auscultation. Cardiovascular, abdominal and neurological examination was normal.

His initial investigations were suggestive of leukocytosis of 14200, thrombocytopenia 93000, mild acute kidney injury with creatinine 1.4 and ABG was suggestive of Type 1 respiratory failure. His CPK, liver function tests and D-dimer were normal. ECG was suggestive of sinus tachycardia. Urine microscopy showed 1+ protein. His chest x-ray (Figure 1) was suggestive of bilateral inhomogeneous opacities. The patient's echocardiogram was normal. He was managed with high flow oxygen, antibiotics and fluids. The patient was able to maintain saturation on room air within 24 hours of admission. His dengue IgM, peripheral smear, HIV, viral markers, throat swab for H1N1, sputum for AFB, urine and blood cultures were sent. Over the course of 5 days, type 1 respiratory failure, nephropathy, leukocytosis and thrombocytopenia resolved. However, fever didn't subside.

Temperature charting showed maximum of 102°F with evening rise and night sweats.. Sputum for AFB was negative twice, peripheral smear showed no atypical cells. HIV and viral markers were non-reactive, cultures showed no growth while dengue IgM and throat swab were negative. Fever and mild cough persisted. USG abdomen was normal**.**

His ESR was 63 and repeat chest x-ray showed persistence of infiltrates on right side and clearing of left side. CECT chest (Figure 2 Panel A) suggested right lower lobe consolidation with mediastinal lymph nodes with no evidence of necrosis. A provisional diagnosis of FUO was made in view of persistent fever. Rheumatoid factor, CRP, ANA profile and tumor markers were planned. Repeat smear, cultures as well as Rheumatoid factor were negative. Bone marrow aspirate and biopsy showed cellular reactive marrow. FDG PET scan (Figure 3) revealed metabolically active enhancing mass like consolidation involving the superior segment of right lower lobe along with hypermetabolic multiple discrete and content fibronodular lesions involving both lungs, most of them along peribronchovascular distribution, there was no abnormal uptake elsewhere. Tumour markers were negative.

The persistence of proteinuria in repeat urine microscopy directed towards further evaluation. Quantification of proteinuria came out to be 1.7 g/24 hours but without evidence of any active sediments, microscopic haematuria or casts. ANA profile showed c-ANCA positivity **(42 IU/mL).** Possibility of granulomatosis with polyangiitis was considered. His x-ray of paranasal sinuses was normal. The patient showed no derangement in his kidney function tests, reason why bronchoscopy and transbronchial lung biopsy were preferred over renal biopsy for tissue diagnosis. Lung biopsy was suggestive of prominence of type II pneumocytes, islands of metaplastic epithelial cells, and focal necrosis.

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Considering inhomogenous opacities on chest radiograph, persistent fever, proteinuria and c-ANCA positivity, a diagnosis of granulomatosis with polyangiitis was made. He was stated on oral prednisolone (2 mg/kg). The fever subsided for the first time on day 34 of admission. The patient remained afebrile for next 5 days and was discharged. His prednisolone was continued. A CECT chest (Fig. 2 panel B) was repeated two months after the initiation of treatment which showed resolution of the primary lesions. The steroids were tapered over 6 months, while azathioprine was introduced at 50mg once a day and increased to 50mg twice a day. A year later, his proteinuria has decreased to insignificant with still no evidence of any active sediments. He continues to be on our follow up with no new symptoms.

DISCUSSION: Granulomatosis with polyangiitis (GPA) is a rare autoimmune disease characterized by a pauci-immune necrotizing vasculitis of small and medium sized vessels. It is usually seen between 4th to 6thdecade of life, with a predilection for Caucasians. The myriad presentation makes its diagnosis difficult. Most patients are diagnosed within 3–12 months from the onset of symptomatology, and on average two organ systems are involved at time of diagnosis. Common complaints and signs of GPA include fatigue, fever, weight loss, arthralgias, rhinosinusitis, cough and dyspnea, urinary abnormalities (an active urine sediment) with or without renal insufficiency, purpura, and neurological dysfunction.[1]

Presentation with fever with a suspicion of infectious aetiology is uncommon in GPA. Sipahi et al in a series of 857 cases of FUO, found that connective tissue disorders were the etiology in 15% cases amongst which systemic vasculitis contributed barely 3%. Several case reports describe fever and pulmonary symptoms with abnormal chest imaging studies (often initially interpreted to be pneumonia). [2] Similarly suspecting tuberculosis in such patients in countries with high prevalence like ours is not unwarranted.

The lack of renal involvement is bound to raise few eyebrows but studies from the National Institutes of Health (NIH) in the United States showed that evident glomerulonephritis was present in only 18 percent of patients at presentation. However, glomerulonephritis subsequently developed in 77 to 85 percent of patients, usually within the first two years of disease onset. [3] Our case is on regular vigilance for the same as “Limited” disease (without glomerulonephritis) and unusual presentations can lead to delay in diagnosis and, therefore, treatment. A consequence of delay in diagnosis is that severe renal failure may develop before treatment is started.

In 1966 Carrington and Liebow described a limited form of the disease, in which involvement of primarily affected the upper and lower respiratory tracts. The clinical course of these patients was relatively benign compared with the generalized form.[4]It may be, however, that the limited form is an early manifestation of the disorder that will eventually involve the kidneys. Perry et al described a series of Wegener’s limited to upper and/or lower respiratory tract involvement.[5]

The gold standard for diagnosis is tissue diagnosis. Prompt diagnosis of granulomatosis with polyangiitis (GPA) is important to permit initiation of therapy that may be life-saving. A positive ANCA test strongly suggests the diagnosis but histologic examination of tissue

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obtained by biopsy of an affected organ (generally, skin, kidney, or lung) remains the most definitive method to establish a diagnosis. Lung biopsy is usually required in cases with no renal involvement, as in our case. It may show capillaritis with granulomatous inflammation. However, in a study only 2 out of 19 ANCA positive patients showed consistent biopsy results.[6] Thus, TBLB is seldom positive unless taken from grossly abnormal areas. It is not uncommon for malignancy to mimick as Wegener's and vice versa.

Serology aids in diagnosis with positivity for c-ANCA differentiating GPA from Microscopic polyangiitis (p-ANCA). ANCA may be negative in 10% cases.[7] Positive c-ANCA with tissue diagnosis by lung biopsy in our case led to early diagnosis and prompt management. Once remission is induced (usually occurs within three to six months), patients are switched to maintenance therapy with less toxic immunosuppressive modalities like azathioprine or mycophenolate mofetil (MMF).[8]

This case report highlights the importance of high clinical suspicion of granulomatous angitis and supportive investigations in case of FUO to make the diagnosis and prompt management.

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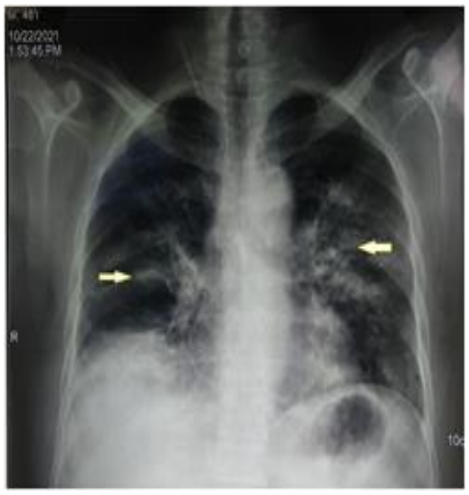
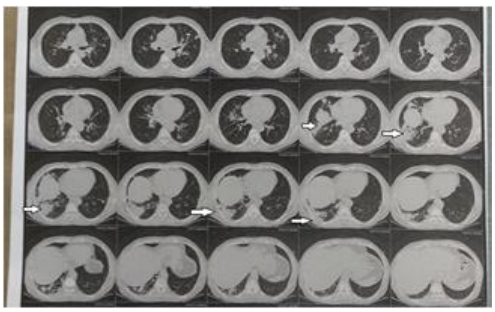


Figure 1: X Ray Chest Showing bilateral inhomogeneous opacities (Arrows)



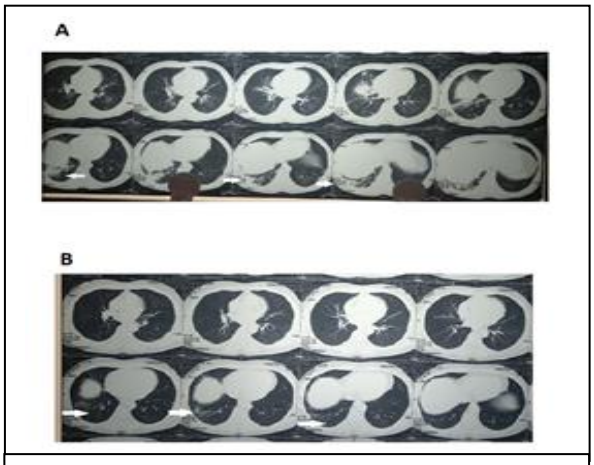


Figure 2: Panel A - CECT Chest Showing right lower lobe consolidation with mediastinal lymph nodes with no evidence of necrosis (Arrows). Panel B - CECT Chest done after 2 months with treatment showing resolution of the primary lesions as compared with panel A lesions (Arrows)

Figure 3: FDG PET Scan suggestive of metabolically active enhancing mass like consolidation involving the superior segment of right lower lobe with hypermetabolic lesions in both lung fields (Arrows)