Diagnostic dilemma of Wegener's granulomatosis and its effective management: A rare case report and update

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Abstract

Granulomatosis with Polyangiitis (GPA) is an uncommon condition belongs to the group of ANCA-associated necrotizing vasculitides. It is characterized by necrotizing granulomatosis of upper and lower respiratory system with coexisting glomerulonephritis. Its signs and symptoms are largely varied due to a wide spectrum of involvement sites. In the present case report, we describe a case of 26-year-old female presented to our centre with history of bilateral ear discharge, earache, and dry cough with a deviated mouth angle to left. Diagnostic work up was done and patient was treated with pulse methylprednisolone, plasmapheresis, and rituximab. Timely diagnosis and prompt initiation of the treatment has prevented the GPA progression and helped the patient to improve quickly. Currently, the patient is doing well and is in remission.

Introduction

Granulomatosis with Polyangiitis (GPA), formerly known as Wegener's Granulomatosis (WG) is a rare blood vessel disease.[1] It is a uncommon, multi-systemic, life threatening autoimmune inflammatory condition characterized by necrotizing granulomatous inflammation and Antineutrophil Cytoplasm Antibodies (ANCA).[2] Its systematic vasculitides involves various organs such as the sinuses, upper respiratory tract, the lungs, and the kidneys.[3] The prevalence of GPA ranges from 2.5 to 146 cases/per million, with an incidence of 0.5 to ~12 cases/per million person-years.[4] Approximately ~90% of patients with GPA present with ear, nose, and throat involvement with manifestations such as purulent/bloody nasal discharge, persistent rhinorrhea, otorrhea, earache, polychondritis, etc. Whereas, in other cases, tracheal, pulmonary, and kidney involvement is commonly seen with symptoms such as cough, dyspnea, stridor, hemoptysis, glomerulonephritis hematuria, and proteinuria, etc. The prognosis of patients is highly dependent on the spread of the PGA. In limited PGA, only upper and lower respiratory tract is involved. Whereas in generalised PGA, patients present with severe form of PGA with renal involvement with prognosis.[5] In this case report, we present a unique case of 26-year-old female presented with pulmonary and upper respiratory tract manifestations, where we discuss the differential diagnosis and treatment done in the ICU.

Case Report

A 26-year-old female was presented to our centre with complaints of earache, bilateral purulent ear discharge, dry cough, and with a deviated mouth (to the left). Initital diagnosis was done by ENT as acute suppurative otitis media. Patient was admitted and vitals were taken – Heart Rate (HR) 92bpm, Blood Pressure (BP) 130/70mmHg, Respiratory Rate (RR) 24per/min, and room air saturation 94%.

As a part of pre-operative work up, chest X- ray was done showing bilateral cavities and consolidations (Figure 1A). In view of pandemic and to rule out COVID-19 infection, a swab test was done and it turned out to be negative. Complete Blood Count (CBC) showed total White Cell Counts (WBC) – 20,700m/mm^3 with 87.2% polymorphs. Other biochemical lab parameters were within limits. The patient underwent myringotomy with grommet insertion. On post-surgery day 1, the patient had respiratory failure and ventilated invasively. The patient was having severe fever and her ear swab was tested positive for pseudomonas.

At this point the patient was referred to our centre, and her High-Resolution Computed Tomography (HRCT) was done, revealing bilateral thick walled multiple cavities in left upper lobe, right middle lobe, with consolidations in bilateral lower lobes (Figure 2A, 2B, 2C, and 2D). A connective tissue and vasculitis work-up was done, revealing positivity for Antineutrophil Cytoplasmic Antibodies (c-ANCA) on post surgery day 1. The patient was immediately given injectable steroids (methyl prednisolone 40 mg/twice a day and then once a day) along with antibiotics based on sensitivity report (injectable colistin 3 MIU/twice a day). After 2 days, she was extubated and kept on continuous Non-Invasive Ventilation (NIV) support for type-2 respiratory failure.

During this period, patient was having persistent tachycardia and hypoxemia with clinical Well's score of 6 [pulmonary embolism (PE) probability, intermediate]. To rule out PE, HRCT with CT Pulmonary Angiogram (CTPA) was done on day 3 and no evidence of embolisms was detected. However, interval increase in cavitating lesions (Figure 1B) with tracheal involvement and bilateral diffuse alveolar haemorrhage (Figure 1C) were noted (Figure 2E and 2F). Due to continuous haemoglobin drop, blood transfusion was done every alternate day (one pint packed red cells) explaining the Diffuse Alveolar Haemorrhage (DAH). To overcome the situation, pulse methyl prednisolone therapy

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(500 mg/once a day for 3 days followed by 40 mg/twice a day and then once a day) was given. Patient got re-intubated in view of NIV failure on day 5. Bedside bronchoscopy was done on day 6 to rule out DAH and the extent of tracheal involvement. To surprise, a near complete obstruction of left main bronchus with lots of slough was identified. Increase in haemorrhagic Bronchoalveolar Lavage (BAL) sample was also in suggestive of DAH. Biopsy was taken and histopathology showed necrosed artery, and inflammatory cells (acute and chronic) infiltrating the necrosed bronchial cartilage with giant cells suggesting vasculitis. Other conditions such as proteinuria and microscopic hematuria were identified pointing towards the renal involvement secondary to vasculitis. A diagnosis of GPA was made, based on the patient's history, histopathological findings, and diagnostic workup.

Due to multiple organ involvement (airways, lung parenchyma, and renal system), treatment was monitored by a multidisciplinary team involving intensivist, pulmonologist, rheumatologist, and nephrologist. After GPA confirmation, patient underwent 9 cycles of plasmapheresis (40 mL/kg) from day 8. Based on the reports and rheumatologists advise, 5 doses of pulse methylprednisolone (125 mg/once a day for 3 days) with rituximab (2g induction dose followed by 500 mg weekly once) was given. Patient made a good recovery and shifted from ventilator to continuous NIV support on day 12. After pulse steroids and 2 doses of rituximab, patients' symptoms improved and she felt a lot better (Figure 1D). Patient was shifted from NIV to nasal oxygen by day 16 and discharged. On follow-up, another 5 doses of rituximab was given on a weekly basis and patient was discharged home with saturation maintaining on room air. The patient is currently doing well and in remission.

Discussion

GPA is an uncommon, rapidly progressive, systemic disease characterized by triad of necrotizing granuloma of upper respiratory tract, systemic vasculitis and necrotizing glomerulonephritis. Differential diagnosis and timely treatment is the key to avoid multi organ failure. Its exact aetiology remains unclear. Although the age range extends to both extremes, most of the patients are in their fifth decade. The disease is a slightly predominant in males over females, and it is rare among children.[6,7] The clinical presentation of GPA patients can be so diverse that the list of differential diagnoses is vast, ranging from infections to other vasculitides. Unexplained constitutional symptoms are often part of the initial presentation but symptoms related to upper respiratory tract involvement are the cardinal features of GPA. Such symptoms are seen in patients on presentation (~45%) and during the course (~87%), if left untreated.[8] In the present report, even our patient was

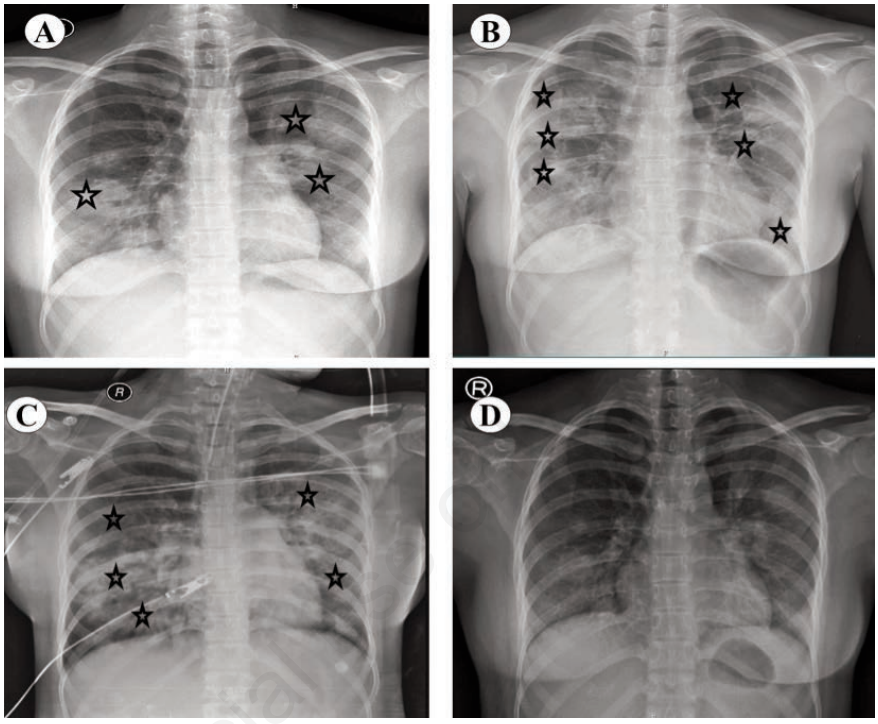

Figure 1. Chest radiograph images at various stages. A) Multiple cavities bilaterally on day 1; B) Cavitary lesions increased on post-surgery day 1; C) Bilateral alveolar shadows suggesting DAH; D) Chest radiograph post-treatment which shows near total regression of DAH and some cavitating nodules.

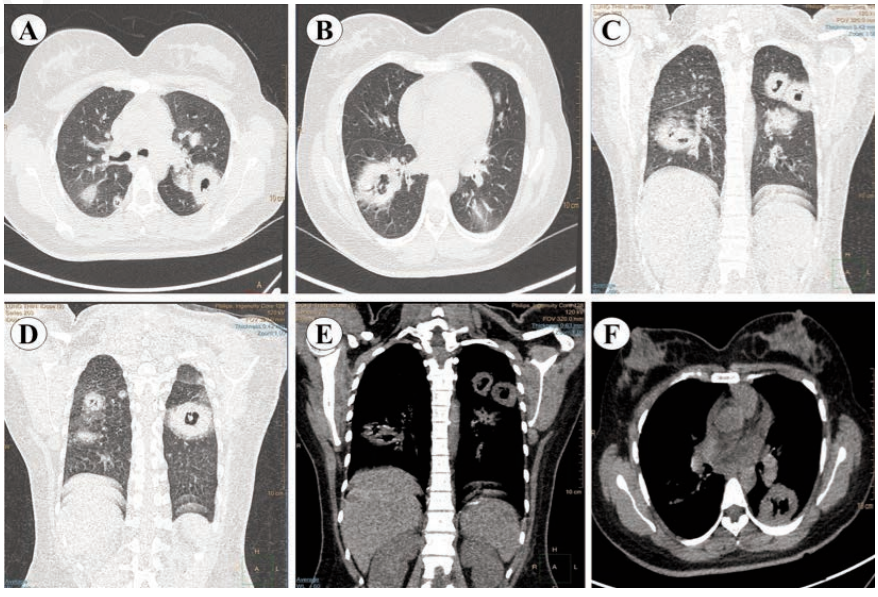

Figure 2. A, B, C, D) Cavitary lesions in bilateral lung fields on day 1 post-surgery. E, F) CT thorax on day 3 post-surgery done along with pulmonary angiogram showing increase in cavitary lesions.

presented with typical symptoms of GPA involving ear, nose, and throat as reported in previous case reports and reviews.[1,3,6,8–10] However, establishing the disease initially based on typical symptoms as GPA was a challenge without a proper diagnostic workup. An event of tests was performed one after the other as per patient symptoms. In our case, ear problem was solved by performing myringotomy with grommet insertion. Based on the pre-operative x-ray reports and post-surgical respiratory failure, HRCT of lungs was performed showing consolidations and multiple cavities in the lung lobes. Followed by connective tissue and vasculitis workup was done confirming GPA.

Airway involvement and presence of lung consolidations as identified in our patient are often seen in 15-30% of patients with active GPA. Such symptoms are usually the result of haemorrhages and late complications. The distribution is focal or diffuse and consolidations may be secondary to organizing pneumonia or pulmonary infarcts. These findings may mimic bronchioloalveolar carcinoma, acute respiratory distress syndrome, pulmonary edema, tuberculosis, or infections related to viral, fungal, and bacterial. In these patients, concentric wall thickening is prominently reported, which may be irregular or circumferential. In such cases, bronchoscopy is a useful tool to further characterize bronchial stenoses, particularly in the central airways.[11]

ANCA activity is detected in all form of vasculitides and GPA is characterised as one of the ANCA-associated small vessel vasculitides. Detection of c-ANCA is not a GPA conformational test. However, literature supports it as an important aid in diagnosing atypical or limited forms of GPA; where c-ANCA have a sensitivity of 90% and specificity of 97%, respectively. c-ANCA is predominantly associated with active GPA in contrast to p-ANCA, which has been frequently associated with crescentic glomerulonephritis, idiopathic necrotizing, microscopic polyangiitis, and other vasculitides/diseases. The sensitivity and specificity of c-ANCA is also largely dependent on the disease severity. Where, positivity of c-ANCA decreases as the disease enters remission. Therefore, monitoring c-ANCA levels can be highly useful in identifying and differentiating the disease relapses from intercurrent infections. Other major dilemma in patients with GPA is development of ANCA due to other ailments such as rheumatologic diseases, sclerosing cholangitis, inflammatory bowel disease, neoplasms, and infections. In such patients, the only differentiating factor are predominant perinuclear ANCAs or exhibition of atypical staining pattern.

HRCT-CTPA confirmed no pulmonary embolisms but constant decrease in haemoglobin continuous suggesting DAH, an initial and rare manifestation of the disease. Immediate and aggressive treatment with pulse steroids is recommended and same protocol was followed in our patient.[9] In these cases, renal involvement is severe and fatal.[9] Symptoms our patient such as hematuria and proteinuria were also suggestive of GPA-associated glomerulonephritis, similar to a previous reports.[12,13]

As per previous reports, later on we decided to add plasmapheresis with existing regimen to quickly decrease the load of pathogenic ANCA.[9,14,15] As on date, no much clinical data and large multi-modal trials are present to support the treatment. However, some studies suggested that utilisation of this plasmapheresis in severe renal failure scenarios have showed a reduction of dialysis from 60% to 40% post 1 year followed by treatment.[14,16]

To keep symptoms under control and to avoid relapse, rituximab was introduced to the existing pulse steroids regimen. Rituximab (2 doses) has showed some positive results by clearing the circulating B cells from the circulation and by targeting the CD20 antigen on B cells, without affecting plasma cells which may be important in disease relapse.[14,17] Another 5 doses were of rituximab were given and patient symptoms improved dramatically. Patient was discharged once stabilised and saturation reached normal at room air.

Conclusions

As reported in the present case, GPA presents with atypical manifestations affecting various organ systems. Although GPA is an uncommon disease, recognition of its typical initial signs and symptoms such as airway and pulmonary manifestations can play a vital role during differential diagnosis. In determining and identifying such typical cases, a clinician and his multi specialist team should remain vigilant to identify the other disease specific subtle signs. Knowledge of these variants in GPA will also help the clinical team in recognising the condition at an early stage preventing delay in accurate diagnosis. It will also further help the patients to get a timely treatment with excellent prognosis by preventing any progression of the disease.

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