A severe pleural complication associated with granulomatosis with polyangiitis

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ABSTRACT

We describe the case of a previously healthy male patient who presented to a respiratory clinic with sinusitis, pulmonary cavities, and hemoptysis. Three weeks following a diagnosis of Granulomatosis with Polyangiitis (GPA) and initiation of immunosuppressive treatment, the patient suddenly developed a large pneumothorax that was complicated by empyema. In this report we discuss and highlight the rare pleural complications associated with GPA, and alert clinicians to monitor for these important complications even after disease-modifying treatment is initiated.

1. Case presentation

A previously healthy 57-year-old gentleman presented with a 3-month history of progressive rhinosinusitis including nasal obstruction with bloody discharge, anosmia, and ageusia. He developed night sweats, a 25-pound weight loss, and a productive cough with blood streaked sputum (producing 5–15 mL of blood per day). There was no associated shortness of breath, chest pain, wheezing, rash, ocular, gastrointestinal, urinary, or neurologic symptoms. Social history revealed a 30 pack-year smoking history and previous exposure to aluminum dust and chemical sealants while working at a sheet metal company. There were no risk factors for tuberculosis infection. Initial antibiotic treatment for pneumonia and sinusitis was prescribed, with no subsequent clinical improvement. Urgent referral to respiratory medicine was requested.

On physical examination in the respiratory clinic, the patient’s heart rate was 112 beats per minute, and there was a visible ulcer in the right nare, with bloody crusting. The remainder of the physical exam was unremarkable. Laboratory investigations revealed a reduced hemoglobin of 122 g/L, elevated white blood cell count of $19.1 \times 10^9$ L$^{-1}$, and platelet count of $624 \times 10^9$ L$^{-1}$. Electrolytes, creatinine, and liver enzymes were normal. There was a positive c-Antineutrophil Cytoplasmic Antibody test (c-ANCA) with an elevated anti-PR3 antibody titre (253 CU). The anti-MPO and anti-GBM antibodies were negative. Urinalysis revealed no blood or casts, but was positive for protein (1+).

Fig. 1 presents a computed tomography (CT) scan of the chest at the time of initial presentation which showed multiple bilateral mass-like lesions measuring up to 5cm, some demonstrating central necrosis and cavitation with thick and irregular walls. Some of the lesions were pleural-based with suggestion of chest wall extension and there was no pleural effusion.

An urgent bronchoscopy was arranged and showed friable and bloody mucosa in the upper lobes bilaterally (Fig. 2a and b).

Endobronchial biopsies were taken in the upper lobe airways and sequential washings did not reveal evidence of pulmonary hemorrhage (successively bloody returns from saline bronchoalveolar lavages). Biopsies demonstrated large areas of neutrophilic necrosis (so called “basophilic necrosis”), granulomatous inflammation with multinucleated giant cells, mucosal ulceration, and squamous metaplasia (Fig. 3). There was no necrotizing vasculitis in the sample. Staining and cultures were negative for acid fast bacilli and fungus.

Given the constellation of endobronchial tissue with neutrophilic...
necrosis and granulomatous inflammation, positive c-ANCA, and clinical presentation with sino-pulmonary symptoms, the diagnosis of granulomatosis with polyangiitis (GPA) was made. Glucocorticoid treatment with prednisone 60 mg daily was promptly initiated, and after consultation with rheumatology, oral methotrexate was added.

Twenty days later, the patient returned for follow-up after an episode of sudden onset shortness of breath with right scapular chest pain that

Fig. 1. Bilateral lung lesions and central cavitation. Axial CT images with lung window settings shows multiple bilateral lung lesions, some demonstrating central cavitation.

Fig. 2a and 2b. Erythema and edema with abnormal airway mucosa. Bronchoscopy demonstrating abnormal airway mucosa with erythema and edema in the right upper lobe (A) and left mainstem bronchus (B).

Fig. 3. Basophilic necrosis of an endobronchial biopsy. Endobronchial biopsy showing multinucleated giant cell (arrow) surrounding an area of basophilic necrosis with neutrophils (arrow heads) - Hematoxilin and eosin stain.

Fig. 4. Pneumothorax with small pleural effusion from a chest radiograph. Posteroanterior chest radiograph demonstrates a large right pneumothorax with small pleural effusion. There are parenchymal abnormalities in the right upper lobe and left perihilar lesion corresponding to residual lesions seen in previous CT.
radiated anteriorly. An urgent chest radiograph revealed a large right sided loculated pneumothorax with small fluid component (Fig. 4).

A chest tube was inserted immediately, and pleural fluid studies revealed pH of 6.9, glucose level <0.1 mmol/L, and predominant fluid neutrophils of 89%. Pleural fluid cultures were negative for bacterial growth. A chest CT was performed, demonstrating enlargement of two pre-existing pulmonary cavities with air fluid levels, open communication with an adjacent bronchus, and hydropneumothorax (Fig. 5). The remaining pulmonary lesions demonstrated improvement when compared with previous imaging (Fig. 5). The pneumothorax and empyema resolved over time with pleural drainage and broad-spectrum intravenous antibiotic treatment.

2. Discussion

GPA is a rare necrotizing granulomatous vasculitis involving small to medium sized vessels and is typically characterized by upper and lower respiratory tract involvement and glomerulonephritis. GPA affects other organ systems less frequently, causing manifestations including arthritis, neurologic dysfunction, ophthalmic disturbances, and cutaneous lesions (purpura and ulceration) [1]. Clinical suspicion of GPA is often followed by ANCA testing, which returns positive in 82–96% of cases [2]. ANCs are considered specific, though it is suggested by experts that the diagnosis be confirmed with a tissue biopsy confirming the presence of vasculitis.

Pulmonary involvement, which is most commonly pulmonary nodules or masses that form and remit spontaneously, is present in 90% of patients with GPA [3]. The nodules can vary in number (single to multiple, but typically less than ten) and size (from millimeters to >10cm) [3]. Fifty percent of nodules cavitate, which is more commonly seen in nodules greater than 2cm, and 15% may have a ‘halo sign’ suggesting adjacent parenchymal hemorrhage [3]. Other radiographic findings associated with GPA include diffuse ground-glass opacities and consolidation (most commonly peri-bronchovascular), involvement of the tracheobronchial tree causing airway stenosis, pleural involvement, and mediastinal lymphadenopathy [3]. Each of these findings can occur in isolation or concurrently with other known pulmonary manifestations of GPA [3].

The classic pathological findings in GPA are necrotizing vasculitis, geographic “basophilic” necrosis and granulomatous inflammation [4]. The basophilic aspect of the necrosis is secondary to the karyorrhexis of necrotic neutrophils, which is not seen in infectious caseating granulomas of mycobacterial and fungal infections (the most common differential diagnoses) [4]. Also, granulomatous inflammation is not seen in bacterial abscesses, the other main differential diagnosis. Therefore, the combination of neutrophilic necrosis and granulomatous inflammation, as in our case, is characteristic of GPA and should raise the possibility of GPA in small biopsies, which are unlikely to show necrotizing vasculitis. Yet, special stains to rule out infection are always required, as well as correlation with clinical, radiological, and laboratory findings.

It is estimated that the pleura are affected in GPA in less than 10% of cases [3]. The most common pleural manifestation in GPA is pleural effusion. However, granulomatous inflammation of the pleura and/or vasculitis has been described in up to 6% of patients with GPA, and other findings including fibrinous pleuritis, pleural thickening, pleural nodularity and pneumothorax have been described [3].

Pneumothorax is a rare complication of GPA, though there have been up to 25 cases reported in the literature [5]. Multiple pathophysiologic mechanisms for pneumothorax have been postulated including pleural vasculitis or granulomas, cavity rupture, infected cavitary lesions, the formation of a bronchopulmonary fistula, increased tissue fragility due to immunosuppressant-related poor wound healing, iatrogenic following bronchoscopy, and fibrous pleural retraction after immunosuppressive treatment [5–9].

Given the low incidence of pneumothorax in GPA, it is difficult to identify the most common or likely pathogenic mechanism. In our case presentation, the most likely cause of both pneumothorax and empyema was a super-infection of two particular cavitary lesions which led to increased communication with the adjacent bronchi, and then bronchopleural fistula (Fig. 5). The infection likely progressed due to immunosuppressive treatment for 3 weeks.

While our patient eventually improved with appropriate antibiotic treatment and pleural drainage, the literature suggests that mortality with pneumothorax in patients with GPA can be up to 40% [5].

This clinical case highlights that clinicians should be highly vigilant for the potential of pneumothorax and infection in the pleural space among patients with GPA-associated large cavitary lesions in the lung parenchyma. Individuals with GPA should be monitored closely for super-infection of pulmonary cavities and pleural infection while on immunosuppressive treatment, given the severe outcomes associated with these complications.

Conflicts of interest

We confirm that there are no conflicts of interest, financial or personal, to report for all authors of this case report.

Declaration of interest

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