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Case report

An important cause of non-resolving pneumonia

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ABSTRACT

We describe the case of a young patient with a history of non-resolving pneumonia. She was diagnosed with a limited form of Granulomatosis with Polyangiitis (GPA), by percutaneous core needle lung biopsy. In this report, we discuss the definition and clinical implications of limited GPA, treatment options, and highlight the importance of considering vasculitis in the differential diagnosis of non-resolving pneumonia.

1. Case presentation

A 48 year-old woman presented to an outpatient clinic with a two-week history of non-productive cough and general malaise. She endorsed a unilateral pruritic red palmar rash. She denied hemoptysis, fever, nasal symptoms, acid reflux, arthralgias, or constitutional symptoms. Past medical history included remote symptoms of migratory arthralgias (several months prior to her presentation), and a remote history of transient left optic neuritis. Social history revealed no tobacco, occupational, or environmental exposures.

On initial presentation, her vital signs were stable and the physical examination was unremarkable. Laboratory investigations showed normal cell counts, hemoglobin, chemistry, creatinine, and liver function tests. Urinalysis was positive for moderate red blood cells, however the patient was menstruating at the time. There was no proteinuria and no casts. Her chest radiograph showed airspace disease in the right mid lung field, and she was diagnosed with a lobar pneumonia. A ten-day course of moxifloxacin was prescribed for treatment of pneumonia.

At follow up 10 days later, her cough did not improve. A computed tomography (CT) scan showed a 6 cm mass-like area of consolidation with small cavities in the right middle lobe, and well defined solid nodules in the periphery of the left lower lobe (Fig. 1).

The differential diagnosis for the CT findings included an atypical pneumonia, possibly fungal in origin, malignancy, septic emboli, or vasculitis.

Serologies for *Histoplasma capsulatum* and *Blastomyces dermatitidis* were negative. Blood cultures grew Propionobacterium acnes but only in a single culture bottle. Anti-cytoplasmic nuclear antibodies were positive with c-ANCA at a concentration of 8 AI units.

The patient, still clinically stable, was admitted to hospital for further investigation of suspected ANCA-associated vasculitis. Erythrocyte sedimentation rate and C-reactive protein were elevated at 58 mm/hr and 18.3 mg/L, respectively. Anti-nuclear antibodies and extractable nuclear antigens were negative. Complement assays were normal and anti-PR3 antibodies were high, measuring 417 chemiluminescent units. Fluoroscopically guided percutaneous fine and core needle biopsies were obtained from the right middle lobe mass.

The core needle biopsies showed necrotizing granulomatous inflammation. The granulomas consisted mainly of giant cells and epithelioid histiocytes surrounding areas of suppurative basophilic necrosis and embedded in a polymorphous inflammatory infiltrate. The elastic stain demonstrated areas of vasculitis with fragmentation of the elastic layer. The special stains as well as tissue cultures for fungi and mycobacteria were negative. This constellation of features was diagnostic of granulomatosis with polyangiitis (GPA) (Fig. 2).

Following a negative tuberculin skin test and normal hepatitis serology, she was started on high dose prednisone (1 mg/kg), and

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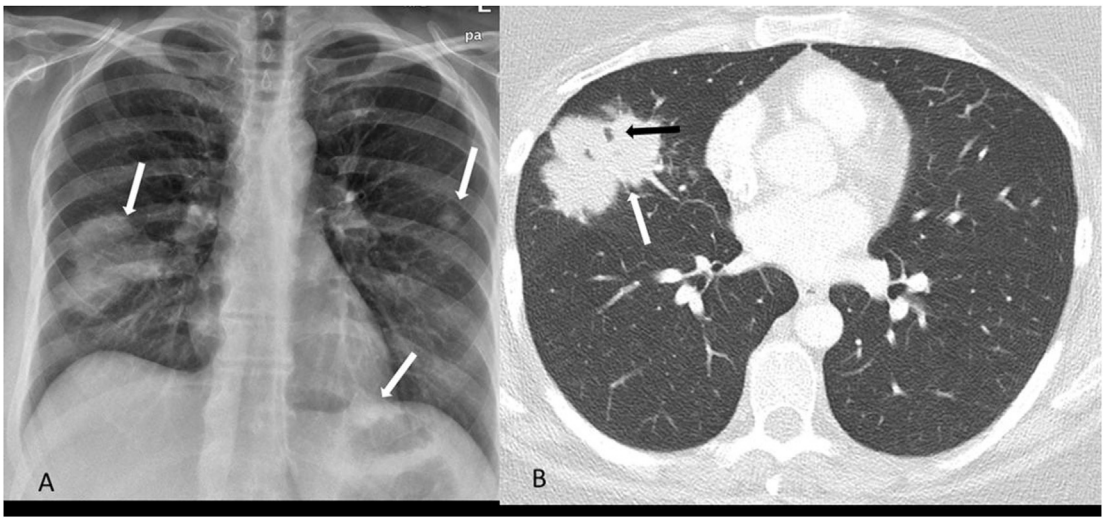

Fig. 1. (A) Chest radiograph (posteroanterior view) reveals right mid lung zone mass (arrow) and multiple pulmonary nodules (arrows) in left lung. (B) Chest computed tomography in axial plane, in lung window, confirms presence of right middle lobe mass (white arrow), with well defined borders, lobulated outline and cavitation (black arrow).

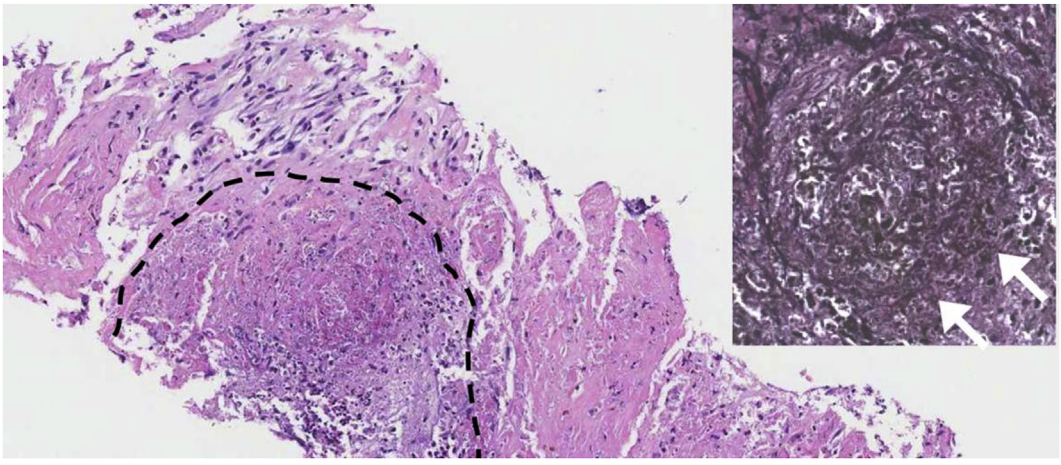

Fig. 2. The image shows extensive mixed type necrosis with a focal rounded area of suppurative necrosis on the left side (dashed line) (H&E stain, 100×). The elastic stain in the inset highlights, in black, the elastic layer of the blood vessel wall, which is partially destroyed (arrows) by the inflammation (Verhoeff stain, 200×).

Methotrexate (15 mg/week). Within 4 weeks her cough and malaise improved. Further investigation with bloodwork, urinalysis, and nasal examination showed no evidence of multi- organ involvement. On repeat chest radiograph four weeks after treatment, there was interval improvement in the airspace disease density (Fig. 3).

2. Discussion

GPA, formerly known as 'Wegener's Granulomatosis', is a systemic necrotizing granulomatous small and medium vessel vasculitis commonly affecting the upper and lower respiratory tracts, and kidneys. Early recognition, diagnosis, and treatment of GPA is imperative, as the mortality rate is >80% if left untreated [1,2].

Like other vasculitides, the clinical presentation of GPA is diverse and can involve any organ system. Most commonly, otolanryngeal involvement occurs (76% of cases), and manifests as bloody nasal discharge, nasal crusting or ulceration, and conductive hearing loss [1]. Approximately half of patients with GPA also endorse constitutional symptoms (fever, malaise, anorexia, weight loss) and renal involvement including hematuria, red blood cell casts, and renal failure [1]. Pulmonary involvement occurs in 60% of cases, most commonly presenting as cough, dyspnea, and hemoptysis from cavitating nodules, nonspecific airspace infiltrates, and alveolar hemorrhage [1]. However, isolated pulmonary involvement from GPA is rare [3]. In a study of 77 patients with GPA, isolated pulmonary involvement occurred in only 9% (7/77) [3]. Mucosal, cutaneous, cardiovascular, gastrointestinal, and nervous system involvement have also been reported, but occur much less commonly [1].

A high degree of clinical suspicion is imperative in order to make an early diagnosis. Although GPA is associated with a constellation of pathological features, a definite diagnosis requires demonstration of necrotizing vasculitis in an affected organ [4]. When there is lung involvement, the choice of biopsy technique is based on the balance of the invasiveness of the procedure and the histological yield of the obtained specimen. Surgical lung biopsy has an established high diagnostic yield, but has appreciable associated morbidity, including pain and prolonged recovery times [3,5,6]. The efficacy of transbronchial biopsy is less; in one series only 12% (2/17) alveolar, and 33% (7/21) lower respiratory tract biopsies had sufficient pathologic characteristics which led to a diagnosis [7]. In

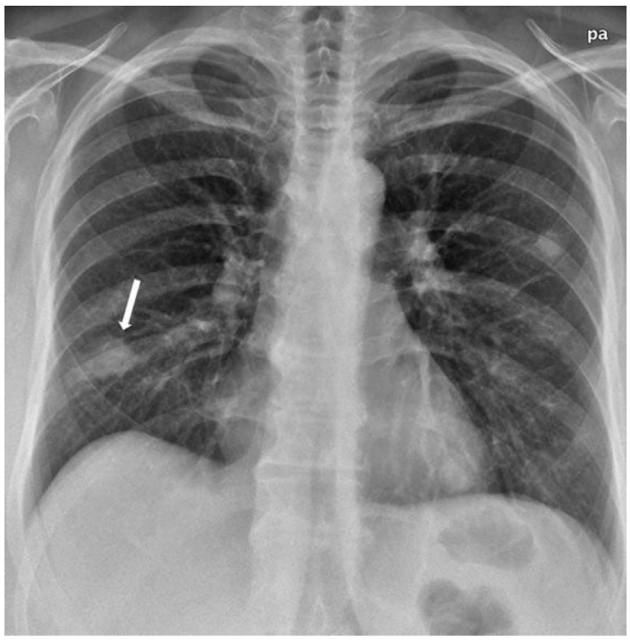

Fig. 3. Follow up chest radiograph (posteroanterior view) performed following treatment, demonstrates significant decrease in size of largest lesion in mid lung zone (white arrow).

general, histological features from transbronchial biopsies might raise the possibility of GPA in the appropriate clinical context, but are usually not helpful in confirming the diagnosis [7]. Core needle biopsy, such as the one used in our case, has been shown to provide a definitive diagnosis in a proportion of cases, but the data regarding the yield of the procedure is limited and not specific for limited pulmonary vasculitis [8]. Overall, core needle biopsies are superior to fine needle aspiration for non-neoplastic inflammatory lung conditions [9]. Fine-needle aspiration biopsies are helpful in ruling out malignancy and obtaining tissue for culture, but cannot confirm the diagnosis of GPA [9].

At least two phenotypes can be distinguished in GPA; limited disease (less severe), and diffuse disease (more severe) [1]. The current expert consensus defines limited disease as manifestations that are neither organ nor life threatening, in contrast to diffuse disease which is organ or life threatening [1]. Approximately one quarter of cases present as limited disease, and limited disease is more common in young females [1]. Otolaryngeal involvement is also more prevalent in subset of patients with limited disease, while renal involvement occurs much less commonly. Rates of pulmonary involvement are equivalent between limited and diffuse disease, however limited disease does not present with alveolar hemorrhage [1]. Further, the sensitivity of ANCA testing lacks in limited disease compared to diffuse disease (67% vs 91%) [1].

Earlier reports hypothesized that limited and diffuse GPA were entities along the same disease spectrum; suggesting that limited disease would eventually evolve to severe disease if allowed to develop in the absence of treatment [10]. However, pathological patterns have emerged illustrating that the presence of vasculitis may characterize more diffuse disease, while granulomatous inflammation is more prevalent in the limited subset [1]. At the cellular immune level, a Th1 mediated process predominates in granulomatous inflammation in contrast to a Th2 pattern in the vasculitic subset [11]. This could suggest that limited and diffuse disease are distinct entities, and limited disease may not always progress to severe life-threatening disease.

The distinction between diffuse and limited disease is very important because of the implications for therapy [1]. Severe GPA requires prompt use of aggressive induction agents, including high dose glucocorticioids and cyclophosphamide, while limited disease responds well to less toxic agents such as methotrexate plus prednisone [12]. In either limited or diffuse disease, clinical remission is usually achieved within three to six months after induction treatment, and patients can be transitioned to maintenance therapy regimens [12]. Maintenance therapy regimens are less immunosuppressive than induction therapy, and generally use tapering doses of glucocorticoids and a less potent immunosuppressive agent such as azathioprine (or continuation of methotrexate in the context of limited disease).

Close follow up during induction and maintenance therapy is important to monitor for drug toxicities, infections, and disease relapses [12]. The rate of disease relapse occurs in 18%–40% within 24 months, and occurs more often in patients with limited disease [1,12].

In summary, this case highlights the importance of considering GPA as a differential diagnosis in the course of non-resolving airspace disease seen on chest imaging. Core needle biopsy (for pathology and culture analysis) is a legitimate means to confirm the diagnosis when there is lung involvement, and can be performed in a minimally-invasive fashion. Isolated lung involvement is rare, and it is important to search for other systemic manifestations of GPA at the time of diagnosis, and during follow up. Recognizing the difference between limited and diffuse disease is important, as this affects the type of treatment, prognosis, and relapse rate.

Patient consent

Obtained.

References

[1] J.H. Stone, Wegener's Granulomatosis Etanercept Trial Research Group. Limited versus severe Wegener's granulomatosis: baseline data on patients in the Wegener's granulomatosis etanercept trial, Arthritis Rheum. 48 (8) (2003 Aug) 2299–2309.
[2] E.W. Walton, Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis), Br. Med. J. 2 (5091) (1958 Aug 2) 265–270.
[3] J.F. Cordier, D. Valeyre, L. Guillevin, R. Loire, J.M. Brechot, Pulmonary Wegener's granulomatosis. a clinical and imaging study of 77 cases, Chest 97 (4) (1990 Apr) 906–912.
[4] J.C. Jennette, R.J. Falk, P.A. Bacon, N. Basu, M.C. Cid, F. Ferrario, et al., 2012 revised international chapel hill consensus conference nomenclature of vasculitides, Arthritis Rheum. 65 (1) (2013 Jan) 1–11.
[5] W.D. Travis, G.S. Hoffman, R.Y. Leavitt, H.I. Pass, A.S. Fauci, Surgical pathology of the lung in Wegener's granulomatosis. review of 87 open lung biopsies from 67 patients, Am. J. Surg. Pathol. 15 (4) (1991 Apr) 315–333.
[6] G.S. Hoffman, G.S. Kerr, R.Y. Leavitt, C.W. Hallahan, R.S. Lebovics, W.D. Travis, et al., Wegener granulomatosis: an analysis of 158 patients, Ann. Intern Med. 116 (6) (1992 Mar 15) 488–498.
[7] A. Schnabel, K. Holl-Ulrich, K. Dalhoff, M. Reuter, W.L. Gross, Efficacy of transbronchial biopsy in pulmonary vaculitides, Eur. Respir. J. 10 (12) (1997 Dec) 2738–2743.
[8] D.M. Carruthers, S. Connor, A.J. Howie, A.R. Exley, K. Raza, P.A. Bacon, et al., Percutaneous image-guided biopsy of lung nodules in the assessment of disease activity in Wegener's granulomatosis, Rheumatol. Oxf. 39 (7) (2000 Jul) 776–782.
[9] X. Yao, M.M. Gomes, M.S. Tsao, C.J. Allen, W. Geddie, H. Sekhon, Fine-needle aspiration biopsy versus core-needle biopsy in diagnosing lung cancer: a systematic review, Curr. Oncol. 19 (1) (2012 Feb) e16–27.
[10] R.A. DeRemee, T.J. McDonald, E.G. Harrison, D.T. Coles, Wegener's granulomatosis. Anatomic correlates, a proposed classification, Mayo Clin. Proc. 51 (12) (1976 Dec) 777–781.
[11] E. Csernok, A. Trabandt, A. Müller, G.C. Wang, F. Moosig, J. Paulsen, et al., Cytokine profiles in Wegener's granulomatosis: predominance of type 1 (Th1) in the granulomatous inflammation, Arthritis Rheum. 42 (4) (1999 Apr) 742–750.
[12] S.K. Frankel, G.P. Cosgrove, A. Fischer, R.T. Meehan, K.K. Brown, Update in the diagnosis and management of pulmonary vasculitis, Chest 129 (2) (2006 Feb) 452–465.