

Phrenic Nerve Paralysis as the Initial Presentation of Granulomatosis with Polyangiitis

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Introduction

Granulomatosis with PolyAngiitis (GPA) is a rare vasculitic condition best known for its predilection to involve the renal and respiratory system [1]. This disease, like many other vasculitides often presents with peripheral neurologic findings. Of these, mononeuritis multiplex, (i.e. wrist drop and foot drop) has been found to be most common [2, 3]. In our example, we present a unique case of GPA in which the initial symptom is unilateral phrenic nerve paralysis. An extensive literature review shows that this type of mononeuritis multiplex has not been reported in the United States as a presenting symptom of GPA.

Case Report

A 67-year-old man presented to the Emergency Department with a three-week history of Shortness Of Breath (SOB). Associated symptoms included, dry cough, night sweats, and a recent episode of sinusitis without epistaxis. On Physical Exam (PE), vitals were stable: HR 108, RR 18, temperature 99.2°F, BP 122/72, and oxygen saturation of 87%. HEENT was significant for frontal and maxillary sinus tenderness. No signs of crusting or ulcerations were appreciated in the nasal mucosa. Lung exam revealed dullness to percussion and decreased breath sounds at the right lung base. The rest of the PE was non

significant. Chest X-Ray (CXR) revealed right-sided hemi-diaphragm elevation with no other pulmonary findings (Figure 1). A diaphragm fluoroscopy/SNIFF test was then performed which confirmed right phrenic nerve paralysis (Figure 2) as the etiology of right sided hemi-diaphragm elevation. The patient was admitted to the medicine floor with a working diagnosis of phrenic nerve paralysis for further evaluation. His admission labs revealed renal insufficiency (BUN: 25; CR: 1.7), and microscopic hematuria. The patient however, denied any past medical history of renal disease. Therefore, his baseline renal function was unknown. Shortly after admission, the patient developed new onset lower extremity numbness and tingling, epistaxis, and fever of 102°F. EMG was done and revealed bilateral amplitude reduction of sensory and muscle action potentials without alterations of conduction velocity, changes consistent with peripheral neuropathy.

Piecing together a clinical picture of pulmonary pathology, renal insufficiency, and a new onset of peripheral neuropathy, a rheumatologic etiology was suspected. ESR and CRP were found to be 100 and 23.5 respectively. Two days into an extensive rheumatologic laboratory evaluation, this patient developed worsening SOB and hypoxia. He was intubated, placed on mechanical ventilation in the ICU. Given concern for possible GPA, the patient was empirically treated with 1 g/day of IV methylprednisolone. Forty-eight hours later, his hypoxemia and neurological symptoms improved and the patient was extubated to room air. His c-ANCA was positive at a titer of 1:60. Nasal biopsy showed evidence of granulomatous

vasculitis. Pulse dose therapy of Cyclophosphamide was administered while in the hospital. Patient showed significant improvement of clinical picture and was discharged in stable condition. He maintained outpatient follow up with Rheumatology.

Figure 1:

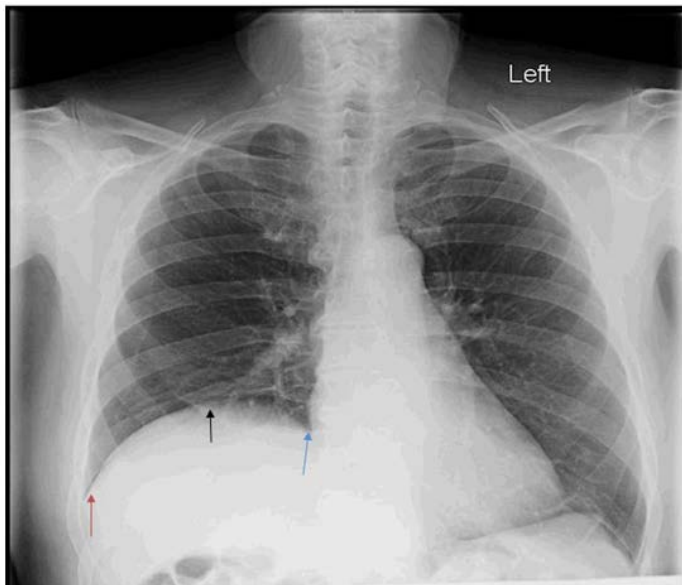


Figure 1: Chest X-ray shows elevation of right side of the diaphragm (arrows).

Figure 2:

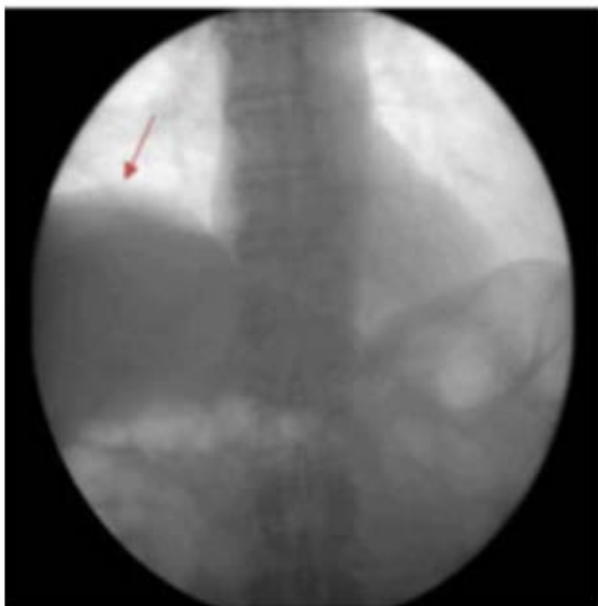


Figure 2: Diaphragm fluoroscopy shows the paralysis of the right diaphragm (arrow).

Discussion

GPA, formerly Wegener's granulomatosis, is a rare disease with a prevalence of 3 per million in the USA. There are four diagnostic criteria: abnormal urinary sediment (red cell casts or micro-hematuria), abnormal findings on CXR (nodules, cavities, or fixed infiltrates), oral/nasal ulcers; and granulomatous inflammation on biopsy. GPA has a spectrum of clinical presentations that includes ear, nose, mouth, throat, and lung complaints in over 90% of the cases [4]. Patients, however, may also present with peripheral neuropathy, amongst the most common; mononeuritis multiplex, i.e. foot drop or wrist drop. Our case is unique in that our patient presented with phrenic nerve paralysis, an extraordinarily rare occurrence in GPA. In fact, a thorough literature search shows that there has been no documented case in the US thus far.

Our patient's initial finding of phrenic nerve paralysis, a form of mononeuritis multiplex, serves to highlight an important clinical pearl. Vasculitis may present with a variety of CNS or peripheral nervous system manifestations, mononeuritis multiplex, in any form, should alert the physician to investigate the possibility of a rheumatologic process [5, 6].

Early recognition and treatment of a vasculitic syndrome is crucial and life sparing. GPA should be suspected in the presence of elevated ESR, CRP, signs and symptoms of vasculitis, and with at least one organ system involvement. Although a positive c-ANCA is highly suggestive of GPA [7], definitive diagnosis is made by histologically upon biopsy of affected tissue [8].

The induction treatment of GPA starts with glucocorticoids at a high initial dose of 0.75–1mg/kg/day for 4 weeks after which this can be tapered. Pulse therapy with Solumedrol 500-1000mg/day is indicated for organ or life threatening manifestations. Cyclophosphamide as high dose intermittent pulses of 15mg/kg/dose on 6–10 occasions, 2–3 weeks apart is the mainstay of therapy. Recent studies have shown that Rituximab can be used as an alternative for patients with ANCA vasculitis who have failed cyclophosphamide or in whom cyclophosphamide is contraindicated. Following successful induction therapy with either cyclophosphamide or

rituximab, azathioprine is used as a maintenance immunosuppressive agent, usually given as 2mg/kg/day. For non-organ or non-life threatening ANCA vasculitis Methotrexate can be used as effective induction and maintenance therapy [9, 10].

It is important to mention, that although our patient had typical features of GPA such as respiratory and renal pathology, he did not present classically. One may argue, that his previous history of sinusitis could be considered the inaugural sign of GPA, however, the patient did not have the classical vasculitic features with nasal ulcerations/crusting.

Phrenic nerve paralysis as initial presentation of GPA has not been previously documented or presented in the US. In fact, as stated earlier, a thorough literature review revealed only 2 cases worldwide that demonstrated an association with phrenic nerve paralysis and GPA.

In the journal, *Annals of Rheumatic Disease* [11], 2005, a case was published in which a patient presented with the chief complaint of a mediastinal mass. Upon work up, an incidental finding of an elevated hemi-diaphragm was noted. Later biopsy of the mass revealed necrotizing granulomatous inflammation indicative of GPA. The hemi-diaphragm elevation was assumed to be due to phrenic nerve paralysis secondary to neuropathy in the context of GPA. This case differs primarily in the fact that the presenting symptom was not phrenic nerve paralysis, rather a later finding attributed to the disease process.

Similarly, in the second case report [12] (published in *Rheumatology International* 2003) the phrenic nerve paralysis causing the hemi-diaphragm elevation occurred in the late stages of GPA and not in the initial presentation of the disease. Additionally, the authors stated that the phrenic nerve paralysis was found to be completely independent of the disease flare.

Pearls

Granulomatosis with Polyangiitis (formerly Wegener's Granulomatosis) is an autoimmune disorder characterized by inflammation of blood vessels and often presents with non-specific symptoms.

The classic clinical pattern is a triad involving the upper airway, lungs and the kidney but peripheral nerves can also be affected. If GPA is clinically suspected, intravenous glucocorticoids and or immunosuppressive agents must be started immediately to prevent potentially fatal complications.

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