Weakness in an Elderly Woman With Asthma and Chronic Sinusitis

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Abstract

Weakness and sensory changes are common complaints in both the inpatient and the outpatient setting. However, this presentation remains a diagnostic challenge to clinicians due to the many possible underlying etiologies. The initial evaluation of weakness and sensory changes starts a thorough history and physical examination to guide the diagnostic process. In this article, we present the case of an elderly woman with complaints of weakness and sensory changes to highlight a step-wise approach to diagnosis and management.

A 69-year-old female presented to the emergency department (ED) with weakness and numbness of her extremities. Her symptoms began 2 months earlier with abrupt onset of pain followed by progressive numbness, dysesthesias, and weakness of her right hand and forearm. After a month, she developed similar symptoms on the left. Two weeks later, she noted numbness in her legs and frequent tripping. She started using a cane for gait stability; 1 week later, she transitioned to a walker and ultimately presented to the ED in a wheelchair. Neurological review of systems was positive for loss of muscle mass but negative for back or neck pain, stiffness, dysphagia, or dysarthria. She denied headaches, behavior or memory changes, changes in auditory or visual acuity, vertiginous symptoms, tinnitus, or double vision. She denied any autonomic symptoms including lightheadedness, bowel or bladder symptoms, and dry mouth or eyes.

The evaluation of weakness and sensory changes begins with a thorough history and physical examination, both of which are essential for initial localization. Her lack of cortical or cranial nerve symptoms suggests involvement outside of the cerebrum and brainstem. Loss of muscle mass, absence of bowel and bladder symptoms, and lack of stiffness suggest localization outside of the spinal cord, making a peripheral nervous system lesion more likely. Furthermore, the presence of both sensory and motor symptoms suggests radiculopathy, plexopathy, or neuropathy rather than primary muscle or neuromuscular junction pathology. The distribution of her symptoms extends beyond 1 root, plexus or nerve, further narrowing the possibilities to a polyradiculopathy, polyneuropathy, or mononeuritis multiplex. Notably, she described an abrupt onset of a painful, sequential, asymmetric pattern of motor, and prominent sensory symptoms. This pattern favors mononeuritis multiplex over

a polyradiculopathy or polyneuropathy. In this case, a more precise localization largely relies on the physical examination.

She described a 20-year history of recurrent asthma exacerbations and sinus infections, as well as a 3-month history of intermittent low-grade fevers, loss of appetite, malaise, and fatigue. She denied eye pain or redness, oral ulcers, cough, hemoptysis, or new rash. She denied use of alcohol, tobacco, or illicit substances and denied travel from her home in urban Atlanta. Her medications included fluticasone-salmeterol and amlodipine.

Her history of low-grade fevers, malaise, fatigue, and anorexia suggests a systemic process. Asthma and sinusitis raise the possibility of conditions affecting both pulmonary and nervous systems. The differential diagnosis is expansive, broadly including inflammatory/rheumatologic, iatrogenic/medication-induced, infectious, neoplastic/paraneoplastic, or toxic-metabolic disorders. Given several possible etiologies, careful general and neurologic examinations play a large role in developing a focused differential diagnosis.

She was found to be a thin, tired-appearing female with normal vital signs; she was not orthostatic. She had no lymphadenopathy, rashes, or oral ulcers. She had full range of motion of her joints without tenderness, nodules, or effusions. Her pulmonary, cardiac, and abdominal examinations were normal. On neurologic examination, her mental status and cranial nerves were normal. She had wasting and decreased tone of her distal muscles

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Table 1. Nerve Conduction Studies and Electromyography Results.

Sensory Nerve Conduction Studies					
Nerve		Peak Latency, ms (Normal)		Amplitude, μV (Normal)	
Right radial		2.45 (<3.1)		11.4 (>9.0)	
Left sural		NR (<4.4)		NR (>3.0)	
Motor Nerve Conduction Studies					
Nerve, Muscle		Distal Latency, ms (Normal)		Amplitude, μV (Normal)	
Right ulnar, abductor digiti minimi		Wrist 3.35 (<3.3)		Wrist 0.8 (>6.0)	
Left ulnar, abductor digiti minimi		Wrist 2.9 (<3.3)		Wrist 11.9 (>6.0)	
Right peroneal, extensor digitorum brevis		Ankle NR (<6.5)		Ankle NR (>2.0)	
Left peroneal, extensor digitorum brevis		Ankle 5.0 (<6.5)		Ankle 0.3 (>2.0)	
Electromyography					
Muscle	Fibrillations	Sharp Waves	Amplitude	Duration	Recruitment
Right abductor pollicis brevis	3+	3+	Normal	Normal	Severely reduced
Right first dorsal interosseous	4+	4+	None	None	No activity
Right extensor indicis propius	None	None	Normal	Normal	Normal
Right tibialis anterior	1+	1+	None	None	No activity
Right vastus lateralis	1+	None	None	None	No activity

bilaterally. She had proximal and distal weakness in the upper and lower extremities, namely in median, ulnar, femoral, and fibular innervated muscles and sparing radial-innervated muscles. She had decreased sensation to pinprick in the posterolateral aspect of both lower extremities and the palmar surface of the right hand. She had absent vibration and impaired proprioception in both upper and lower extremities, with the right worse than left. She had absent patellar and ankle reflexes and hypoactive biceps, triceps, and brachioradialis reflexes bilaterally.

Weakness in the setting of atrophy, impaired sensation, and diminished or absent reflexes is indicative of a sensorimotor peripheral neuropathy. Significant atrophy suggests an axonal process, rather than a demyelinating one. Although a diffuse polyneuropathy or polyradiculopathy can behave similarly, the sequential involvement of individual nerves spanning different roots, trunks, and plexi is most suggestive of mononeuritis multiplex. In this case, neurophysiologic testing can confirm examination findings, assist with localization, and better characterize the process as axonal, demyelinating, or both. This can narrow the list of potential etiologies and determine the severity of the damage.

Electrodiagnostic testing revealed decreased amplitude of right radial sensory response, with normal distal latency and conduction velocity while the left sural sensory NCS showed no response (Table 1). Right ulnar motor nerve conduction studies (NCS) showed severely reduced amplitude and mildly prolonged distal latency, while left ulnar motor responses were normal. Motor NCS of the right fibular showed no response, whereas the left fibular showed

markedly reduced amplitude with normal distal latency. Concentric electromyography revealed a pattern consistent with ongoing denervation more severe in ulnar and median innervated muscles than femoral and fibular-innervated muscles. No volitional motor unit activity could be seen in any tested muscle except for the right abductor pollicis brevis, which showed severely reduced amplitude of polyphasic motor units.

This pattern of changes is consistent with a severe and ongoing, asymmetric, and multifocal sensorimotor axonal process, without clear evidence of demyelination. These findings confirm the initial hypothesis of a mononeuritis multiplex. The differential diagnosis includes inflammatory (nonvasculitic, vasculitic, and sarcoidosis), metabolic (diabetes), infectious (Lyme, hepatitis, HIV, West Nile, and Syphilis), paraproteine-mic, and paraneoplastic etiologies. Focused laboratory evaluation is based on the differential diagnosis developed from careful history taking and examination.

Complete blood count with differential showed marked leukocytosis with eosinophilic predominance (Table 2). Electrolytes, renal and hepatic function, and cardiac enzymes were normal. She had an elevated C-reactive protein level but normal erythrocyte sedimentation rate and immunoglobulin E (IgE) level. Further studies revealed a positive antineutrophil cytoplasmic antibody (ANCA) IgG titer and elevated myeloperoxidase (MPO) level (Table 2). She had normal cerebrospinal fluid, thyroid function studies, glucose tolerance test, vitamin B12, serum protein electrophoresis, and paraneoplastic and antinuclear antibody panels.

Table 2. Laboratory Results.

	Patient Value	Normal Value
Hematology		
White blood cells, cells/ μ L	22.0×10^3	$3.6-11.1 \times 10^3$
Eosinophil, %	60	1-8
Absolute eosinophil count, cells/ μ L	10417.1	100-300
C-reactive protein, mg/L	75.15	0.3-8
Erythrocyte sedimentation rate, mm/h	20	0-30
Autoimmune studies		
Antineutrophil cytoplasmic antibody titer, IgG	1:20	Negative
Antiperinuclear cytoplasmic antibody titer, IgG	Negative	Negative
Myeloperoxidase antibody reflex, AU/mL	438	0-19
dsDNA antibody titer	Negative	Negative
ENA screen with reflex	Negative	Negative
Rheumatoid factor	<20	<20
Paraneoplastic panel	Negative	Negative
Serum protein electrophoresis	Negative	Negative
IgE level total, IU/mL	130	0-180

Abbreviations: dsDNA, double-stranded DNA; ENA, Extractable Nuclear Antigen Antibodies; Ig, immunoglobulin.

Laboratory evaluation in this patient suggests an inflammatory as opposed to an infectious, metabolic, or neoplastic process, with a vasculitis being overwhelmingly the most likely cause given the step-wise pattern of events. Vasculitides can be classified by the underlying pathogenesis, divided broadly into ANCA-associated and non-ANCA associated disorders. The ANCA is suspected to play a primary role in driving the inflammatory response by activating neutrophils that express proteinase 3 and MPO, antigens that allow for enhanced binding to endothelial cells. This is followed by further release of inflammatory mediators including cytokines, reactive oxygen species, and proteolytic enzymes causing direct damage to endothelial cells. The ANCA is also thought to hinder the resolution of inflammation by impairing neutrophil apoptosis, ultimately leading to vessel wall necrosis.¹ Based on elevated ANCA and MPO titers, the differential diagnosis in this case can be narrowed to 2 disease processes: eosinophilic granulomatosis with polyangiitis (GPA; Churg-Strauss syndrome [CSS]) and microscopic polyangiitis (MPA).² Finally, within the context of recurrent sinusitis and adult onset asthma, prominent eosinophilia suggests a diagnosis of a vasculitic neuropathy secondary to CSS. Pathological confirmation of this diagnosis by muscle biopsy is critical not only to avoid diagnostic error but also to assist in guiding treatment plans moving forward. Aggressive long-term immunomodulatory therapy is often required in these cases and proceeding in the absence of a pathologic diagnosis can be fraught with problems down the line.

Figure 1. Muscle and nerve biopsy. A, Photomicrograph (10 $\times$ magnification) of gastrocnemius muscle stained with myosin adenosine triphosphatase (ATPase) and hematoxylin–eosin (H&E), demonstrating chronic neurogenic atrophy with fiber-type grouping and grouped atrophy. There is no muscle inflammation. B, Photomicrograph (10 $\times$) of sural nerve stained with H&E, demonstrating nerve fiber degeneration without demyelination and thickening of the perineurium (arrowheads). Inset, Higher magnification (60 $\times$) view demonstrating vasculitis with prominent eosinophilic infiltration. (*) denotes arterial lumen.

Biopsy of the gastrocnemius muscle showed chronic neurogenic atrophy without inflammation. Sural nerve biopsy showed nerve fiber degeneration, thickening of the perineurium, and prominent eosinophilic infiltration without evidence of demyelination (Figure 1).

Vasculitides affecting the nervous system can be classified pathologically in various ways including vessel size, pathophysiology, and target organs (including central vs peripheral nervous system). Peripheral nerve involvement in diseases such as CSS results from inflammation and necrosis of the vasa nervorum, the small- and medium-sized blood vessels that supply peripheral nerves. Large myelinated fibers are more susceptible than small unmyelinated fibers.² Final pathological diagnosis in

this case was concordant with the clinical diagnosis of vasculitic neuropathy secondary to CSS.

Discussion

Churg-Strauss syndrome is a rare systemic vasculitic syndrome with an annual incidence estimated at 0.5 to 4.2 cases per million individuals per year and prevalence estimated at 11 to 14 cases per million adults.³ Average age of onset is typically 40 to 60 years of age, with no clear predominance based on gender or ethnicity.³ Some studies have suggested that the presence of HLA DRB 1*07 and HLA DRB 1*04 alleles or certain IL-10 gene polymorphisms confers a genetic predisposition to CSS.³ Medications such as leukotriene receptor antagonists (LTRAs), largely used in the management of more severe forms of asthma, have been implicated in the development of CSS. The main concern is that LTRAs may generate a direct idiosyncratic immune-mediated response leading to the development of CSS. However, review of case reports suggests that use of LTRAs may simply unmask underlying CSS as they allow for weaning of systemic corticosteroids or may represent the natural course of the disease among patients with severe asthma.⁴ Further studies are needed to establish whether this association does represent causality.

Churg-Strauss syndrome typically involves 3 phases. A prodromic allergy phase is marked by asthma exacerbations, allergic rhinitis, and recurrent sinusitis. The eosinophilic phase is characterized by infiltration of peripheral tissues including lungs, heart, and gastrointestinal (GI) tract. The final phase is vasculitic.² The most common organs involved in the vasculitic phase are the peripheral nervous system (65%-76%), lungs (51%-65%), and skin (52%-57%).⁵ Peripheral neuropathy often heralds the onset of the vasculitic phase, presenting as axonal degeneration, most commonly affecting the fibular, tibial, median, ulnar, radial, and sciatic nerves.⁶ This patient had experienced the prodromic allergic phase for several years before presenting to the ED in the vasculitic phase, given the presence of constitutional symptoms and a vasculitic polyneuropathy.

The differential diagnosis of Churg-Strauss includes other disorders associated with asthma, eosinophilia, or vasculitis. Allergic bronchopulmonary aspergillosis and chronic eosinophilic pneumonia can be considered on the differential diagnosis of asthma with eosinophilia but these entities lack extrapulmonary manifestations. Idiopathic hypereosinophilic syndrome typically presents with eosinophilia and occasional bronchial reactivity but again lacks signs of vasculitis. Other ANCA-associated vasculitides, such as MPA and GPA, typically have findings consistent with small to medium vessel vasculitis but are not associated with asthma or eosinophilia.⁵

Diagnosis of CSS is largely clinical and relies on the presence of a constellation of clinical and diagnostic findings that vary by phase of illness. Multiple classification criteria have been developed to diagnose CSS. In 1984, Lanham et al

suggested diagnosis could be made in the presence of asthma, eosinophilia >1500 cells/mm³, and clinical or histological evidence of vasculitis involving at least 2 extrapulmonary organs.⁷ The most commonly accepted classification criteria come from the American College of Rheumatology (ACR), developed in 1990, which identified the following 6 criteria for diagnosis of CSS: asthma, eosinophilia $>10\%$, neuropathy (mononeuropathy or polyneuropathy), nonfixed pulmonary infiltrates, paranasal sinus abnormalities, and extravascular eosinophilic infiltration on biopsy.⁸ More recently, an algorithm was developed that states that a diagnosis of CSS can be made if either the Lanham or ACR criteria were met in the presence of histological evidence or positive markers for vasculitis.⁹ According to this algorithm, this patient would meet diagnostic criteria for CSS based on the presence of 4 ACR criteria (asthma, eosinophilia $>10\%$, neuropathy, and extravascular eosinophilia) as well as positive ANCA serology.⁵

Classification of patients based on ANCA serology has been found to be clinically useful. An estimated 38% to 73% of patients with CSS are ANCA positive, with 74% to 90% having a perinuclear immunofluorescence pattern, corresponding to the presence of MPO.³ Studies have shown that ANCA-positive individuals more commonly present with complications associated with small or medium vessel vasculitis, including renal and peripheral nervous system involvement, as opposed to ANCA-negative patients who more commonly have cardiac complications. Recent evidence has suggested that ANCA plays a direct role in the pathophysiology of CSS as they activate neutrophils causing release of reactive oxygen species and proteolytic enzymes that causes direct endothelial damage. Histological evidence of this process includes necrotizing vasculitis, fibrinoid necrosis, eosinophilic tissue infiltration, and extravascular granulomas, though these lesions are only rarely seen in unison.¹⁰ Indeed, while the nerve and muscle biopsy of our patient had no evidence of necrosis, it nevertheless showed evidence of eosinophilic infiltration, which is the characteristic of CSS.

The mainstay of treatment for CSS is immunosuppression, though the specific treatment largely depends on clinical criteria that act as prognostic indicators. These include serum creatinine >1.58 mg/dL, proteinuria >1 g/d, GI involvement, cardiomyopathy, or CNS involvement, together called the 5-factor score (FFS).⁵ A FFS greater than 1 corresponds to a 5-year mortality rate between 26% and 46%, whereas an FFS of 0 corresponds to a 5-year mortality rate of 12%. Among those with a FFS of 0, including our patient, clinical remission is achieved in greater than 90% of patients with corticosteroids alone, though nearly 35% relapse requiring additional immunosuppression, such as pulsed cyclophosphamide or azathioprine.⁵ Individuals with an FFS of 1 or greater are typically treated more aggressively, with steroids and pulsed cyclophosphamide concurrently. Individuals with CSS often require long-term immunosuppression, with tapering of steroids once clinical remission is achieved and initiation of steroid-sparing agents such as azathioprine

or methotrexate.⁵ Our patient was treated with prednisone 1 mg/kg/d for 5 days. Her steroid dosage was tapered to 10 mg daily over the course of several months as azathioprine was initiated. She has had minimal improvement in strength but no further worsening.

Authors' Note

This article has not been submitted for publication elsewhere. All authors have contributed substantively to the conception, design, and analysis of the data; the drafting of the article and critical revision for important intellectual content; and final approval of the version to be published. Informed consent was obtained from the patient.

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