Clinical Reasoning:
A 74-year-old woman with bilateral foot pain and a palmar rash

SECTION 1
A 74-year-old woman with a history of asthma, Crohn disease, and osteoporosis presented with acute onset, constant sharp pain in the dorsal and plantar aspects of her bilateral feet. She endorsed associated paresthesias, but denied weakness. Several weeks after the onset of the pain, she developed pruritic palmar erythema. She denied dry eyes, dry mouth, or having had a rash like this before, but did endorse scaling on her hands following her biannual injection of denosumab for osteoporosis.

Examination. On the bilateral palms were reticular erythematous patches (figure, A). There were no other areas of involvement, including the mucous membranes. Sclera and funduscopic examination were normal. Strength was 5/5 with hip and knee flexion, knee extension, and ankle dorsiflexion and plantarflexion bilaterally. She had decreased sensation to pinprick, light touch, and vibratory sensation over the entire foot up to the ankle bilaterally. Her left Achilles deep tendon reflex was trace, but all other reflexes were 2+ with downgoing toes and no ankle clonus. Gait was normal, Romberg sign was absent, and the remainder of the general and neurologic examination was normal.

Questions for consideration:
1. What is the localization?
2. What is the significance of a palmar rash in neurologic disorders?
Figure: Patient rash at different stages of the disease process, with histopathology of the second rash

(A) Reticular erythematous patches on the palms bilaterally. (B) Grouped petechiae and purpura on the lateral left lower extremity, bilateral ankles, and medial and lateral feet. (C) Punch biopsy from the right medial ankle demonstrates a superficial and deep perivascular and interstitial infiltrate consisting of numerous eosinophils and scattered neutrophils. There was focal vasculitis and thrombosis with erythrocyte extravasation (hematoxylin & eosin, ×200). (D) Direct immunofluorescence performed on a punch biopsy from the right lateral foot highlights eosinophils in the dermis. Diffuse staining in the dermis indicates eosinophilic infiltration and degranulation (eosinophil major basic protein 1, ×100). Photograph courtesy of Dr. Kristin Leiferman of the immunodermatology laboratory at the University of Utah.
SECTION 2
The patient’s examination localizes to the distal-most sensory peripheral nerves. The severe pain, loss of pinprick sensation, and loss of vibratory sensation point to both small and large fiber nerve involvement. The trace Achilles tendon reflex demonstrates involvement of the afferent arc, which is seen early on in peripheral neuropathies.

Disorders to consider in the setting of a palmar rash with neuropathy include Crohn disease, psoriasis, toxins such as arsenic (which can cause palmar hyperkeratosis), infections such as syphilis and human T-lymphotropic virus-1 (HTLV-1), vasculitides such as polyarteritis nodosa, and chemotherapeutic agents such as vincristine.1–5 Other systemic issues that could be responsible for palmar erythema, but unrelated to the neuropathy, include rheumatoid arthritis, cirrhosis, and drug eruptions.4

Questions for consideration:
1. What is your differential diagnosis for this case?
2. What further investigations should be considered and why?
SECTION 3

The differential diagnosis for peripheral neuropathy leading to symmetric, distal sensory deficits with or without motor involvement is broad. In this case, the differential can be narrowed via the acute onset and presence of severe pain. Causes of neuropathy with an acute onset and associated pain include diabetes, amyloidosis, vasculitis, medications, toxins (e.g., arsenic and thallium), Sjögren disease, paraneoplastic disorders, and HIV.5

Further investigations included laboratory studies, spinal imaging, and skin biopsy. Normal laboratory studies included hemoglobin A1c, thyroid-stimulating hormone, free T4, antinuclear antigen, antineutrophil cytoplasmic antibodies panel, rapid plasma reagin, HIV, HTLV-1, vitamin B12, heavy metal screen (including arsenic and thallium), complement components 3 and 4, serum protein electrophoresis, Sjögren antibodies (SSa/b), and paraneoplastic antibodies (anti-Hu and anti-Yo). Abnormal laboratory studies included liver function studies such as alkaline phosphatase of 779 U/L (reference range 38–126 U/L), aspartate aminotransferase of 139 U/L (reference range 16–40 U/L), and alanine aminotransferase of 135 U/L (reference range 5–60 U/L). Other abnormal values included an erythrocyte sedimentation rate of 72 mm/h (reference range 0–20 mm/h) and a mild leukocytosis of 10,640 cells/μL with eosinophilia of 38% (reference range 0%–6.0%).

An MRI of the spine revealed a subacute compression fracture of the L1 vertebrae on top of old wedge compression deformities in L2 and T11. A punch biopsy obtained from the right hypothenar eminence revealed superficial perivascular dermatitis with subtle, focal interface change. This was reported as a non-specific finding with a pathologic differential diagnosis that included a drug eruption, viral exanthema, or a late lesion of pernio.

Questions for consideration:
1. How would the above information change your differential diagnosis?
2. What additional tests might you order and why?
SECTION 4

The liver involvement and eosinophilia are concerning for a number of possibilities, including a drug reaction, parasitic infection, or a hematologic malignancy that may or may not be related to the neuropathy. To this end, a peripheral blood smear, cytology, and flow cytometry should be obtained. Vasculitic disorders could still be considered despite the results of the skin biopsy. Given the severe eosinophilia and history of asthma, eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg-Strauss syndrome) should be high on the differential. Lung parenchyma and cardiac involvement are commonly seen in EGPA, so chest imaging and echocardiography should be performed.² Nerve conduction studies (NCS) and EMG could help to better characterize the neuropathy, specifically to determine whether nerve root involvement is responsible for the patient’s current symptoms.

Peripheral blood smear, cytology, and flow cytometry were not concerning for hematologic malignancy or parasitic infection. A hepatitis viral panel was also negative. A chest CT revealed several small ground-glass opacities in the lungs bilaterally. A transthoracic echocardiogram showed normal heart function with an ejection fraction of 60%. NCS on the right demonstrated absent tibial and peroneal motor responses. Sural nerve amplitude, latency, and conduction velocity were all within normal limits. Needle EMG on the right revealed high motor amplitudes in muscles supplied by the peroneal and tibial nerves.

Two months after her initial evaluation, the patient developed acute onset right foot drop. She also noted a new rash on both feet and endorsed worsening malaise with a weight loss of 16 pounds. Examination revealed grouped petechiae and purpura, some of which were palpable, on the lateral left lower extremity, bilateral ankles, and medial and lateral feet (figure, B). She had new weakness in the right lower extremity with 0/5 ankle dorsiflexion and foot eversion but 5/5 plantarflexion and foot inversion.

Questions for consideration:
1. How would you interpret the results of the electrophysiologic studies?
2. Localize the right ankle drop.
3. How has your differential changed given the new rash and foot drop?

GO TO SECTION 5
On NCS, absence of motor responses to both the tibial and peroneal nerves indicates a lesion to a nerve or root that supplies both nerves, like the sciatic nerve or L5 nerve root. The intact sural nerve indicates the L5 nerve root more than the sciatic nerve. On needle EMG, the high motor amplitudes in muscles innervated by these nerves further supports that interpretation, and indicates a chronic injury. These findings are likely incidental, and unrelated to the underlying disease, which had not fully manifested itself at the time of this study.

When localizing foot drop, or ankle dorsiflexion weakness, one should consider an L5 nerve root lesion vs a peroneal neuropathy. An L5 nerve root lesion would present with weakness during ankle dorsiflexion, eversion, and inversion, whereas a peroneal nerve lesion would present with weakness during ankle dorsiflexion and foot inversion. Our patient’s second examination is more consistent with a peroneal nerve lesion. The common peroneal nerve can be damaged at the fibular head as the result of a compression injury; however, since it is a long nerve it is often one of the first affected as the result of a compression injury; however, since it is a long nerve it is often one of the first affected.

A punch biopsy obtained from the right medial ankle revealed epidermal necrosis, vasculitis of small to medium vessels, and an eosinophil-rich infiltrate (figure, C). Direct immunofluorescence performed on a punch biopsy obtained from the right lateral foot revealed immunoglobulin G (IgG), IgG4, IgM, IgA, and C3 in several blood vessels throughout the dermis with extensive perivascular deposition of fibrinogen throughout the dermis. There was a prominent eosinophil infiltration as evidenced by positive eosinophil granule major basic protein 1 (figure, D). These findings were consistent with EGPA.

**DISCUSSION**

EGPA is a small vessel vasculitis associated with asthma and eosinophilia that can affect a variety of systems including the lungs, heart, kidneys, and peripheral nerves. The CNS is rarely affected, but there are reports of both ischemic and hemorrhagic stroke secondary to EGPA. The American College of Rheumatology proposed 6 diagnostic criteria for EGPA including asthma, eosinophilia >10%, neuropathy, nonfixed lung infiltrates, paranasal sinus abnormalities, and biopsy demonstrating extravascular eosinophil infiltration. If 4 or more of the above criteria are met, a diagnosis of EGPA can be made.

The disease process is often broken down into 3 different phases, although the distinction among these phases is not always clear. They include an allergic phase with asthma and recurrent sinusitis, eosinophilic phase (>10% eosinophilia) with lung or heart involvement, and a vasculitic phase. The vasculitic phase is characterized by peripheral neuropathy in roughly 70% of cases and can manifest as a symmetric or asymmetric polyneuropathy or, more commonly, a mononeuritis multiplex. This neuropathy appears to be secondary to occlusive transmural inflammation of vessels supplying the nerve, resulting in acute ischemia. Despite reports demonstrating eosinophilic infiltration and granuloma formation in nerve biopsies, subsequent pathologic studies have shown infiltrating cytotoxic CD8+ T cells are much more numerous and play a larger role in the pathogenesis of neuropathy.

We report a case of EGPA manifesting as a distal, symmetric polyneuropathy that later evolved into a mononeuritis multiplex affecting the peroneal nerve. The patient’s eosinophilia was initially thought to be secondary to an allergic reaction, supported by the biopsy of palmar erythema that was consistent with a drug eruption. Had NCS/EMG studies been done after the patient’s second presentation, we would have likely seen evidence of acute mononeuropathies. This case highlights the importance of revisiting previously considered diagnoses as a patient’s clinical course evolves.

Although there is no standardized treatment strategy for EGPA, a combination of glucocorticoids in the acute stage with long-term immuno-suppressants is described in most case reports. Our patient was started on a 3-day course of IV methylprednisolone (1 g/d) followed by an oral prednisone taper and long-term cyclophosphamide therapy. Her neuropathic pain was successfully treated with pregabalin and amitriptyline. Her eosinophilia improved dramatically following the initiation of steroids. At 4-month follow-up, she had not had a relapse in symptoms; however, her ankle dorsiflexion weakness was only minimally improved.

**AUTHOR CONTRIBUTIONS**

Don Raphael P. Wynn: study concept and design, acquisition of data. Jessica M. Donigan: analysis and interpretation of data, critical revision of manuscript for intellectual content. Aleksander Tkach: analysis and interpretation of data, critical revision of manuscript for intellectual content.
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Don Raphael P. Wynn, Jessica M. Donigan and Aleksander Tkach
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