Involvement of the Peripheral Nervous System in Polyarteritis Nodosa and Antineutrophil Cytoplasmic Antibodies–Associated Vasculitis

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KEYWORDS

- Antineutrophil cytoplasmic antibodies (ANCA) • Granulomatosis with polyangiitis
- Microscopic polyangiitis
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
- Polyarteritis nodosa • Mononeuritis multiplex • Ischemic neuropathy

KEY POINTS

- Peripheral nerve involvement is common in polyarteritis nodosa and the antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides, particularly eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).
- The underlying mechanism is arteritis of the vasa nervorum, leading to ischemic neuropathy.
- The classic presentation is stepwise involvement of 1 or more named peripheral nerves in the setting of weeks or more of antecedent constitutional symptoms.

OVERVIEW

Polyarteritis nodosa (PAN) and the antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides commonly affect the peripheral nervous system, especially early in the course of disease. Neuropathies develop in most (65%–85%) patients with PAN.[1] Among the ANCA-associated vasculitides, peripheral nerve involvement is more prevalent in eosinophilic granulomatosis with polyangiitis (EGPA), occurring in upwards of 80% of cases, than in microscopic polyangiitis (MPA) and occurs least often in granulomatosis with polyangiitis (GPA) (~25%).[2–6] The shared mechanism is vasculitis of the vasa nervorum, the small nutrient arteries that supply peripheral nerves, leading to nerve ischemia.[1–8] The classic clinical presentation is acute or

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subacute mononeuritis multiplex-stepwise involvement of 2 or more named nerves, leading to motor and sensory deficits in the distribution of the affected nerves.[1–8] Pain is common and usually severe.[1,9,10] Additive ischemic insults to multiple nerves can produce diffuse, but often asymmetric, sensory and motor deficits.[1,9,10] Uncommon manifestations include distal sensory neuropathy, radiculopathies, and lumbar or brachial plexopathies.[1–11]

PATHOLOGIC FINDINGS

After entering the nerve, the vasa nervorum branch into complex, anastomosing microvascular networks that run primarily within the epineurium, the connective tissue that surrounds peripheral nerves and also occupies the interfascicular space.[1] PAN and the ANCA-associated vasculitides cause a necrotizing arteritis of vessels within the epineurium and rarely affect the perineurial and endoneurial vessels.[1,2,5,6,9,10] Histologic features of affected vessels include focal fibrinoid necrosis, transmural inflammation, luminal occlusion, and recanalization.[1,2,5,6,9,10] The inflammatory infiltrates usually are mixed, composed of both mononuclear cells and neutrophils.[1,2,5,6,9,10] Eosinophils are prominent in vasculitis due to EGPA.[2,5] Necrotizing arteritis is often segmental, and the involved segments can be a short as 50 microns in length.[1,10] Evidence of ischemic neuropathy is always present, but the severity of the ischemic changes varies.[1,10] Ischemia induces axonal degeneration. Features suggestive of ischemic neuropathy include asymmetry of involvement between and within fascicles and axonal degeneration that is predominantly within the central region of fascicles.[1,10] True nerve infarction is uncommon on biopsy samples of affected sural and superficial peroneal nerves, likely due in part to the segmental nature of the arteritis and to the plexus-like nature of the epineurial circulation, which protects against ischemic injury (ie, the nerves are protected against infarction because epineurial vessels are not necessarily end arteries).[1,10]

CLINICAL SYNDROMES

The peripheral nervous system can be the first organ system affected in PAN and the ANCA-associated vasculitides, particularly EGPA and MPA.[1–6] However, antecedent constitutional symptoms such as weight loss, fatigue, malaise, and low-grade fever usually have been present for weeks to several months.[1–6] The onset of the neuropathy is often abrupt with pain, sensory loss, and weakness in the distribution of 1 (mononeuritis) or more (mononeuritis multiplex) named peripheral nerves (**Table 1**).[1,9,10] The pain is severe and more often described as throbbing or aching than burning. The peroneal nerve is most often affected, followed by the tibial, ulnar, median, and radial nerves.[1,9,10] Involvement can progress in a stepwise to affect additional nerves over weeks to months. Multiple nerves, however, can be affected simultaneously, or the progression of the neuropathy can be rapid, leading to a generalized multifocal neuropathy that may require careful examination to demonstrate that the process is asymmetric.[1,9,10] Uncommon manifestations of systemic arteritis include distal symmetric sensory neuropathies, polyradiculopathies, plexopathies, and purely motor neuropathies.[9–11]

DIAGNOSIS

Systemic vasculitis should always be the primary diagnostic consideration when mononeuritis or mononeuritis multiplex develops in the setting of a systemic illness. The history and physical examination often provide important clues about the correct