Vasculitic neuropathy associated with IgG4-related kidney disease: A case report and literature review

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Abstract. IgG4-related disease is an immune-mediated systemic inflammatory condition characterized by tissue infiltration of IgG4-positive plasma cells and elevated serum IgG4 concentrations. Peripheral neuropathy is an atypical manifestation of this disease. We describe an unusual case of vasculitic neuropathy in a patient with IgG4-related kidney disease. A 55-year-old woman presented with right leg weakness progressing to bilateral leg weakness, pain and numbness of the legs, and impaired gait. She was previously evaluated for weight loss and anemia with a CT scan of the abdomen due to concern for malignancy. Abnormal enhancement of the kidneys was seen, and laboratory work-up and kidney biopsy were consistent with IgG4-related disease. Myeloperoxidase-antineutrophil cytoplasmic antibodies were also positive. In combination with the patient’s asymmetric leg weakness and painful neuropathy, this raised concern for vasculitis. Sural nerve biopsy confirmed vasculitic neuropathy. Recent studies have demonstrated an overlap in the clinical characteristics of IgG4-related disease and the anti-neutrophil cytoplasmic antibody-associated vasculitides, which are known to cause vasculitic neuropathy. Clinicians should recognize this association, and IgG4-related disease should be considered in the differential diagnosis in patients with peripheral neuropathy in the right clinical context.

Case description

A 55-year-old woman with a history of allergic rhinitis and asthma presented with right leg weakness, which then progressed to bilateral leg weakness. She reported 14 kg of unintentional weight loss over the past year, and laboratory evaluation revealed iron deficiency anemia. This was concerning for malignancy and prompted CT scan of the abdomen that demonstrated bilateral enlargement of the kidneys with heterogeneous contrast enhancement and loss of normal corticomedullary differentiation. Kidney biopsy showed storiform fibrosis and plasma cell-rich interstitial inflammation with IgG4 immunostaining showing clusters of IgG4-positive plasma cells (Figure 1), suggestive of IgG4-RKD. Serum creatinine was 1.1 mg/dL. There was no protein or active sediment in the urine. Additional laboratory evaluation (summarized in Table 1) was notable for serum IgG level of 177 mg/dL (2.4 – 121 mg/dL), IgE level of 1,309.7 IU/mL (1.5 – 165.3 IU/mL),
erythrocyte sedimentation rate (ESR) of 77 (< 30 mm/h), positive myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA) by ELISA, and antinuclear antibody ≥ 1 : 1,280. Anti-double stranded DNA (anti-dsDNA) antibody was negative, and complement levels were normal.

The patient was subsequently seen in neurology clinic prior to initiation of immunosuppressive therapy. By this time, her leg weakness had been present for 8 months, and she also reported 6 months of burning pain and numbness of her lower extremities. Examination was notable for bilateral weakness of ankle dorsiflexion and plantarflexion, loss of pinprick and vibration sense distal to the ankles, and a tentative gait. Electrodiagnostic testing showed a length-dependent sensorimotor axonal polyneuropathy. Given the initially asymmetric pattern of leg weakness, the severity of her pain, and positive MPO-ANCA, there was concern for vasculitic neuropathy.

Biopsy of the left sural nerve was performed, which showed severe myelinated and unmyelinated fiber loss in all fascicles, a recanalized epineurial blood vessel, and dense perineurial mononuclear cell infiltrates, consistent with vasculitic neuropathy. IgG4 immunohistochemical staining demonstrated a few scattered IgG4-positive plasma cells (Figure 2). Baseline positron emission tomography (PET) scan for evaluation of further organ involvement was not approved by the patient’s insurance company.

The patient was treated with prednisone 40 mg daily and had resolution of neuropathic pain and improvement in gait within 4 weeks. Prednisone was tapered off over a 6-month period. She also received IV immunoglobulin 0.5 g/kg/day for 4 doses then 0.4 g/kg weekly for 8 weeks, followed by rituximab 1 g every 6 months. Subsequent examination demonstrated improvement in lower extremity strength and normal gait. At 6 months of therapy, serum IgG4 level normalized to 57.1 mg/dL, IgE level decreased to 283 IU/mL, and ESR normalized to 25 mm/h. Her kidney function remained normal.
Discussion

The patient’s combination of histopathologic findings, radiographic findings, and elevated serum IgG4 level meet criteria for definite IgG4-RD based on proposed comprehensive diagnostic criteria as well as organ-specific diagnostic criteria for IgG4-related kidney disease [3, 4]. Vasculitic neuropathy is an atypical feature of IgG4-RD. Aortitis can be seen, but inflammation of smaller arteries was previously thought to be
rare [1]. However, there is a growing body of literature demonstrating the co-occurrence of IgG4-RD and vasculitis, with or without neuropathy.

ANCA-associated vasculitides (AAV), which include microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and granulomatosis with polyangiitis (GPA), are systemic vasculitides commonly associated with neuropathy that can have clinical characteristics similar to IgG4-RD, and should be considered in the differential diagnosis of IgG4-RD [5]. Recent studies suggest that the similarities extend beyond shared clinical characteristics and have demonstrated ANCA positivity in patients with IgG4-RD, histopathologic and serologic features of IgG4-RD in patients with AAV, and patients diagnosed with both IgG4-RD and AAV concomitantly [5 6, 7, 8].

In one study, researchers examined sural nerve biopsy specimens of 149 patients with neuropathy who had clusters of inflammatory cells on histopathology. 29 patients had IgG4-positive cell infiltration on histopathology, of which 20 also had elevated serum IgG4 levels. 23 of the 29 patients were previously diagnosed with a primary vasculitic neuropathy such as MPA or EGPA [5].

Another case report described a patient who was diagnosed with EGPA in the setting of multiple mononeuropathies and purpura, with skin biopsy showing leukocytoclasic vasculitis. The patient also had enlarged lacrimal and submandibular glands and was concomitantly diagnosed with Mikulicz’s disease, a manifestation of IgG4-RD [6]. Other studies have described patients meeting criteria for both IgG4-RD and AAV in the absence of peripheral nerve involvement [7, 8].

**Conclusion**

The relationship between IgG4-RD and vasculitic neuropathy has not yet been fully delineated. The patient in this case met criteria for definite IgG4-RD, and also had a vasculitic neuropathy with positive MPO-ANCA. Clinicians should recognize the possibility of this co-occurrence and understand that positive ANCA does not exclude a diagnosis of IgG4-RD, and likewise, an elevated serum IgG4 level does not exclude a diagnosis of AAV. In addition, IgG4-RD should be considered in the differential diagnosis in patients with peripheral neuropathy and evidence of systemic inflammatory disease.

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**Conflict of interest**

All authors have nothing to declare.

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