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## IGG4-RELATED HYPERTROPHIC PACHYMENINGITIS COEXPRESSING ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES

### OPEN

IgG4 disease was first described in 2001 in a seminal paper by Hamano and colleagues: Syndrome of exocrine gland infiltration with associated raised serum IgG4 levels. IgG4 disease is manifested by the hallmark histopathologic features of lymphoplasmacytic infiltration of IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis. Hypertrophic pachymeningitis (HP) has been increasingly recognized as a clinical manifestation of IgG4-related disease (IgG4-RD) and is likely to account for a significant number of cases previously reported to be “idiopathic.” HP has been associated with alternate autoimmune disorders, specifically granulomatosis with polyangiitis (Wegner granulomatosis) with antineutrophil cytoplasmic antibody (ANCA) positivity. A subgroup of patients previously believed to have idiopathic HP have positive perinuclear ANCA (p-ANCA).<sup>1</sup> This has been proposed as a separate disease entity. Co-occurrence of IgG4-RD and ANCA seropositivity has been reported in 4 cases in the literature to date, and this case serves to expand our current understanding of what likely represents a subpopulation of immune-mediated HP.<sup>1–4</sup>

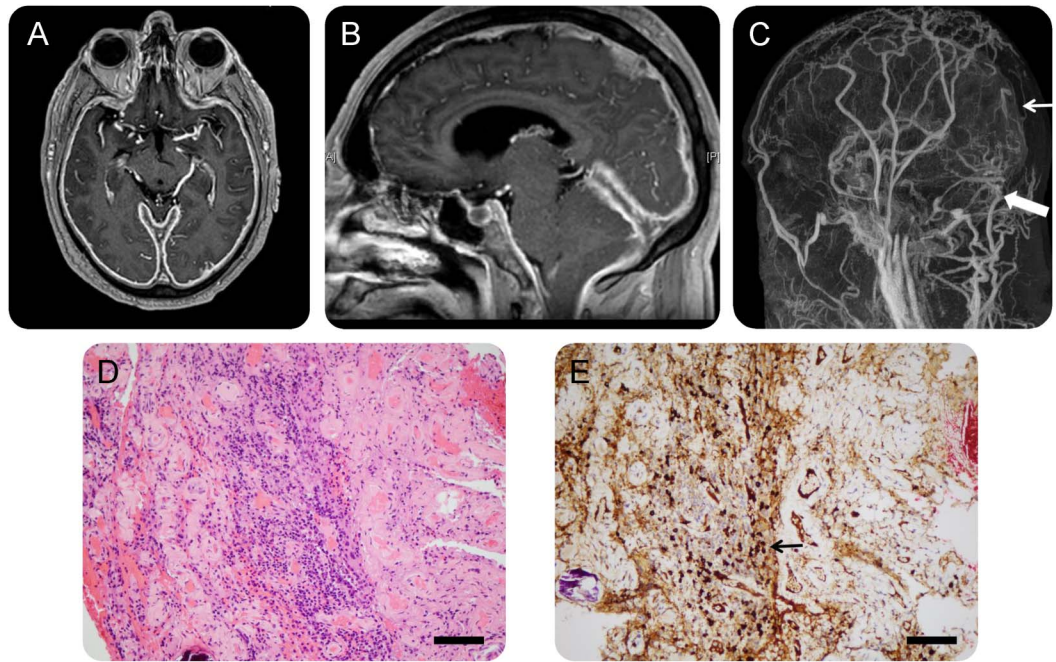
**Case report.** A 70-year-old man presented with a 3-month history of occipital headache, episodic transient visual loss, and syncope associated with Valsalva maneuvers or cough. In addition, he reported a 4-month history of progressive right monocular visual loss to the point of object differentiation. Medical history was notable for ischemic heart disease, type 2 diabetes mellitus, and impaired renal function secondary to ureteric obstruction 8 years prior with suspected enlargement of retroperitoneal lymph nodes on CT imaging. Clinical findings were of a right relative afferent pupillary defect with associated decreased visual acuity to shape recognition, bilateral papilledema, and moderate bilateral hypoacusis. No systemic features of vasculitis including involvement of respiratory, renal, or ear-nose-throat systems were detected.

Brain MRI revealed extensive pachymeningeal thickening involving the intracranial dura. There was evidence of tonsillar descent to the level of C1-2 with associated compression, and the sella was noted to have an empty appearance consistent with changes of intracranial hypertension (figure, A and B). MR venogram showed occlusion of the sagittal, straight, and right transverse sinuses secondary to dural thickening (figure, C). The presence of tonsillar herniation in the context of exertional headache and papilledema was consistent with a diagnosis of CSF obstruction and raised intracranial pressure secondary to HP; lumbar puncture was, therefore, contraindicated.

Laboratory workup revealed p-ANCA directed against myeloperoxidase of 30 U/mL (<5 U/mL) and a p-ANCA titer of 1:80. Antibodies against proteinase 3 were 5 U/mL (<5 U/mL). IgG subsets were requested, and an elevated IgG4 level of 2.33 g/L (0.08–0.89 g/L) was detected. CT of abdomen confirmed areas of soft tissue density consistent with retroperitoneal fibrosis. Meningeal biopsy revealed hypertrophic fibrotic tissue in a storiform pattern with dense plasma cell infiltrate and increased numbers of IgG4 staining in the plasma cells (>50 per high-powered field) without evidence of granulomatosis (figure, D and E). These features in addition to the presence of obliterative phlebitis are in keeping with the core histopathologic criteria of IgG4-RD.<sup>5</sup> Flow cytometry on meningeal tissue was unremarkable.

High-dose methylprednisolone as pulse therapy followed by tapering therapy was initiated with clinical improvement. At 3 months, IgG4 level had normalized to 0.45 g/L (0.08–0.89 g/L), and p-ANCA was no longer detectable. Repeat brain MRI demonstrated mild improvement in the degree of pachymeningeal enhancement.

**Discussion.** IgG4-RD is an emerging cause of HP and is likely to account for a substantial proportion of cases previously labeled idiopathic. In addition, a population of HP cases exists with overlapping ANCA-associated disease.<sup>1–4</sup> The clinical features of obstructive hydrocephalus, meningeal biopsy meeting the histopathologic criteria for the



Pachymeningeal thickening with enhancement on postcontrast axial imaging (A). Evidence of associated tonsillar herniation on sagittal postcontrast T1-weighted MRI (B). Sagittal MRV demonstrating sites of venous sinus occlusion; absence of the transverse sinus (thick arrow) and sagittal sinus (thin arrow) (C). Paraffin-embedded dural biopsy; H&E  $\times 200$ , fibrotic dura with diffuse plasma cell infiltrate, scale bar 200  $\mu\text{m}$  (D). Diffusely positive IgG4 staining on immunohistochemistry  $\times 200$  ( $>50$  IgG4-positive cells, black arrow), scale bar 200  $\mu\text{m}$  (E). H&E = hematoxylin and eosin; MRV = MR venogram.

diagnosis of IgG4-RD, the presence of a positive p-ANCA, in addition to the exclusion of differential diagnoses including lymphoma and granulomatous polyangiitis (GPA), confirm the diagnosis of IgG4-RD with additional ANCA-associated HP.<sup>6</sup> There are limited cases, to date 4 patients, who appear to express dual immunopathologic drivers for disease, representing a distinct clinical phenotype with p-ANCA positivity and elevated serum IgG4 level. p-ANCA does not appear to be the key driver for disease, given the pathologic absence of vasculitis. The case series of patients to date meet the Watts algorithm for GPA vasculitis on the basis of serology and surrogate markers,<sup>7</sup> although would be excluded from a diagnosis of GPA given the atypical histopathology. Treatment regimens for both conditions involve immunosuppression; however, corticosteroids frequently fail to control disease as monotherapy in cases of ANCA-related HP and adverse effects can be challenging. Escalation to rituximab therapy has been beneficial in a subgroup of patients.<sup>4</sup> This case serves to increase the literature on cases of dual-antibody disease with the aim of aiding the descriptive phenotype of

these cases and guide neurologists on future management.

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