

IgG4-related midline destructive lesion

Midline destructive lesion (MDL), also known as 'lethal midline granuloma', represents a fibroinflammatory condition characterised by relentless erosion of the nose, paranasal sinuses and palate.^{1 2} Disease attribution remains elusive for many cases, which continue to be labelled 'idiopathic'.²

Four patients, two males and two females, were referred because of progressive erosion of midline facial structures that had occurred over 2–3 years. Their median age was 40 years (range 27–54). Presenting symptoms included chronic sore throat, difficulty swallowing (nasal regurgitation) and progressive nasalisation of speech. Tissue destruction developed insidiously in all four patients, initially as small ulcerative lesions of the soft palate and nasal septum that enlarged gradually into perforations of palatal and nasal structures. Spontaneous loss of the uvula occurred in three patients. Three had palatal prostheses assembled in order to prevent the passage of food into the nasopharynx (figure 1A,B). All four developed saddlenose deformities.

Two patients had histories of allergic rhinitis, chronic sinusitis and recurrent ear infections since childhood. One of those also reported bilateral symmetric submandibular enlargement, and the other had a history of cholangitis and multiple biliary duct strictures. All patients were active, heavy tobacco smokers. One reported cocaine inhalation, but had not used cocaine for 6 years before the onset of her symptoms. Physical examination was normal except for palatal and nasal septal defects, absent uvulae and saddlenose deformities. Nasolaryngoscopic evaluation revealed erosions of the nasal septum and soft palate, confirmed by CT (figure 1C).

The differential diagnosis in these patients initially focused on malignancies (extranodal NK/T cell lymphoma, sarcomas and carcinomas) and chronic infections (mycobacterial, fungal,

spirochetal). We also considered granulomatosis with polyangiitis, relapsing polychondritis, sarcoidosis and cocaine-induced MDL.^{2 3} These alternative diagnoses were excluded by negative assays for antineutrophil cytoplasmic antibodies and other auto-antibodies, serological tests for syphilis, toxicology screens and cultures for fungi and acid-fast bacilli. Serum IgG4 concentrations were normal in all cases.

All four patients had histopathological evidence of IgG4-related disease (IgG4-RD). Biopsies from the edges of the palatal perforations revealed lymphoplasmacytic infiltrates and storiform fibrosis (figure 2A). Immunohistochemistry showed abundant IgG4-positive plasma cells (>50/HPF; IgG4/IgG range 30–60%) (figure 2B). No cellular atypia, microabscesses, leucocytoclastic vasculitis, fibrinoid necrosis, granulomatous inflammation or multinucleated giant cells were observed.^{2 3} In situ hybridisation for the Epstein–Barr encoding region, immunohistochemistry for cytoplasmic CD3, κ and λ chains and PCR for T cell receptor, all performed in two of the patients, revealed no clonal lymphoproliferative disorders. All four patients had dramatic oligoclonal expansions of circulating CD19+CD27+CD38+IgG4+ plasmablasts, a cell population recently described as an IgG4-RD biomarker (figure 2C) (personal communication Mattoo *et al*, 2014 and Wallace *et al*, 2014).

One patient was treated with multiple regimens of antibiotic and antifungal therapies together with mycophenolate mofetil (1500 mg daily) for 1 year with no improvement. Rituximab (1 g at day 0 and 15) stabilised the disease for several months. A similar evolution was noted in a second patient who received a 2-month trial of prednisone (60 mg/day), gradually tapered over 2 months. One year later, the patient lost the superior teeth necessary for anchoring the palate prosthesis.

IgG4-RD is a fibroinflammatory disorder characterised by tumefactive lesions. Hallmark pathology features are lymphoplasmacytic infiltrates with abundant IgG4-positive plasma cells,

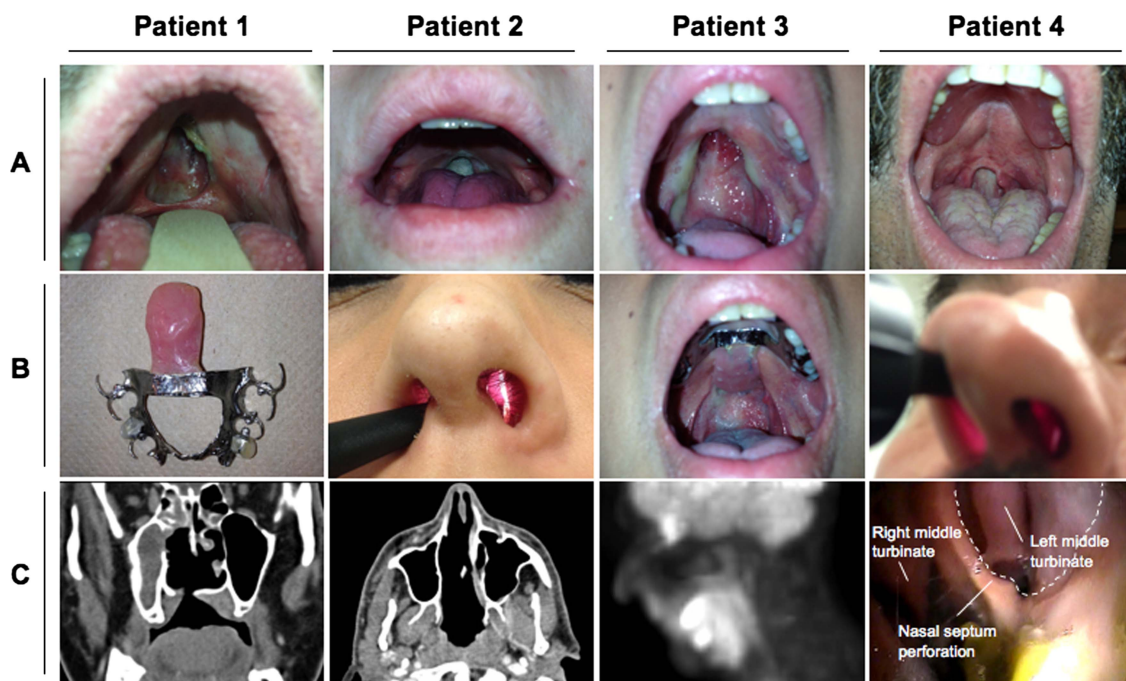


Figure 1 Clinical and radiological features of IgG4-related midline destructive lesion in four patients. (A) Soft palate erosion with uvula reabsorption. (B) Nasal septum perforations (patients 2 and 4) and the palatal prostheses used by patients 1 and 3. (C) Computed tomography scan of the head and neck showing destruction of the hard palate with communication between the oral and nasal cavities (patient 1), and erosion of the nasal septal cartilage, ethmoid bone and vomer (patient 2). A positron emission tomography study revealed ¹⁸fluorodeoxyglucose uptake in the soft palate (patient 3). Nasolaryngoscopy showing nasal septal perforation (patient 4).

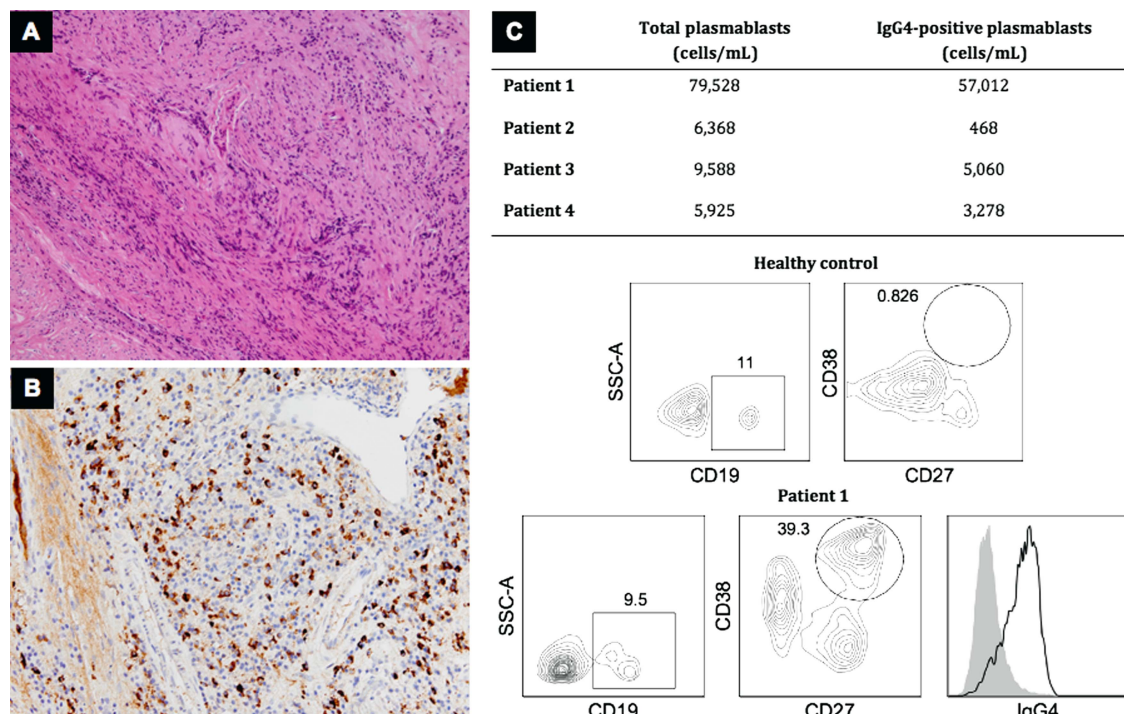


Figure 2 Histological and immunopathological features of IgG4-related midline destructive lesion (MDL). Biopsy from the edges of the palatal perforation of patient 1. (A) A lymphoplasmacytic infiltrate surrounded by storiform fibrosis (magnification $\times 200$). (B) The number of IgG4-positive plasma cells/high power field was 100; the ratio of IgG4 to total IgG in the tissue was >0.4 (magnification $\times 400$). (C) Plasmablasts were identified by flow cytometry as cells positive for CD19, CD27 and CD38. A majority of these plasmablasts also expressed surface IgG4. Data from a healthy control and patient 1 are representative of the 14 healthy donors and the 4 patients with IgG4-related MDL, respectively. Data are expressed in percentages.

storiform fibrosis, obliterative phlebitis and tissue eosinophilia.⁴ Over the past decade, IgG4-RD has been recognised as a cause of lesions in nearly every organ system and identified as a unifying diagnosis for multiple conditions previously regarded as separate entities.^{5–7} These cases of IgG4-related MDL presented with tissue destructive lesions, which have been described in other patients with IgG4-RD involving the aorta, middle ear, sinuses and other organs. The management for such patients remains unclear but likely involves a combination of immunosuppression to control inflammation and surgery to close mucosal lesions and improve oronasopharyngeal function. The optimal time for surgery ideally corresponds to the absence of active inflammation, and, thus, peripheral plasmablast measurements may be useful in following disease activity.

In summary, we demonstrate that a proportion of cases of idiopathic MDL are manifestations of IgG4-RD. Distinguishing this entity from the other conditions known to cause MDL is essential because of the important differences in the management approaches.

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Contributors ED-T and JHS conceived of and conducted the clinical studies. HM and VSM conducted laboratory studies with guidance from SP. DK and PS helped with clinical diagnosis and management of patients. VD helped with pathological diagnosis of patients. ED-T and JHS drafted the manuscript. All authors read and approved the final version.

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