SHORT COMMUNICATION

Extensive Nasal Plaque: An Unusual Presentation of IgG4-related Disease

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IgG4-related disease (IgG4-RD) is a fibro-inflammatory condition characterized mainly by tissue infiltration by IgG4$^+$ plasma cells with a tendency to mass forming. IgG4-RD can involve any part of the body, including the skin. We report here a rare case of cutaneous IgG4-RD presenting with a nasal infiltrative lesion. To our knowledge, this is the first report of this rare clinical presentation.

CASE REPORT

A 67-year-old man with no relevant clinical history presented with an erythematous asymptomatic plaque in the nasal ala, which had appeared 6 months earlier. The lesion spread progressively to the entire nasal pyramid and left infraorbital region (**Fig. 1**a). He had no systemic symptoms. Blood count, biochemical profile and haemostasis were normal, and bacterial, fungal and mycobacterial cultures were unremarkable. Computed tomography (CT) scan and magnetic resonance imaging (MRI) showed a large infiltrative lesion affecting cutaneous and subcutaneous tissue in both nasal alae (Fig. S1a[1]). Positron emission tomography (PET) scanning confirmed the findings (Fig. S1b[1]). Thoraco-abdominal CT scan was performed and no relevant anomalies were detected. Serum protein analysis showed increased levels of gamma-globulins with total IgG levels of 19.2 g/l (normal 7.5–16 g/l) and IgG4 3.8 g/l (0.08–1.4 g/l). Serological tests for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and anti-neutrophil cytoplasmic antibodies (ANCA) were negative. Biopsy of the lesion revealed a dense dermic lymphoplasmacytic infiltrate with a background of neutrophils, eosinophils and histiocytes with prominent storiform fibrotic stroma (**Fig. 2**a). Focal images of lymphocytic venulitis without necrosis were also observed (Fig. 2b). Immunohistochemical analysis highlighted a large number of IgG4$^+$ plasma cells (Fig. 2c). IgG4$^+$ plasma cells were present at approximately 60–140 per high-power field (Fig. 2d). The ratio of IgG4$^+$/IgG plasma cells ranged from 30% to 70%. Epstein-Barr virus hybridization was negative and clonal rearrangements in the T-cell receptor were not detected. Based on these findings a diagnosis of IgG4-RD was finally established. Methyl-prednisolone, 0.5 mg/kg/8 h iv, was initiated for 1 week. Subsequently, prednisone was changed to 0.5 mg/kg day for 2 weeks with progressive decrease until a maintenance dose of 5 mg/day. After one month, the lesion had disappeared (Fig. 1b) and serum IgG4 levels decreased until normalization. After 8 months, the corticosteroids were stopped, and there is no evidence of disease recurrence after 3 years of follow-up.

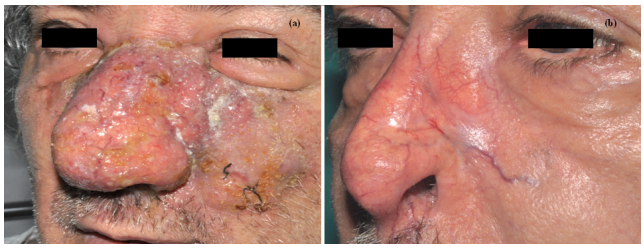

Fig. 1. Clinical findings. (a) Large inflammatory tumour involving the nose, left cheek and infraorbital region. (b) Four weeks after the start of steroid therapy. Marked signs of scarring and atrophy are visible.

DISCUSSION

IgG4-RD is a recently described clinical entity characterized by tissue infiltration of IgG4$^+$ plasma cells, variable degree of fibrosis and often, but not always, elevated serum concentrations of IgG4, which was recognized as a systemic condition in 2003 (1). Since then, many medical conditions, such as Mikulicz's syndrome, Kuttner's tumour, and Riedel's thyroiditis, which were previously known as organ-specific disorders, have been classed as part of the spectrum of IgG4-RD (2).

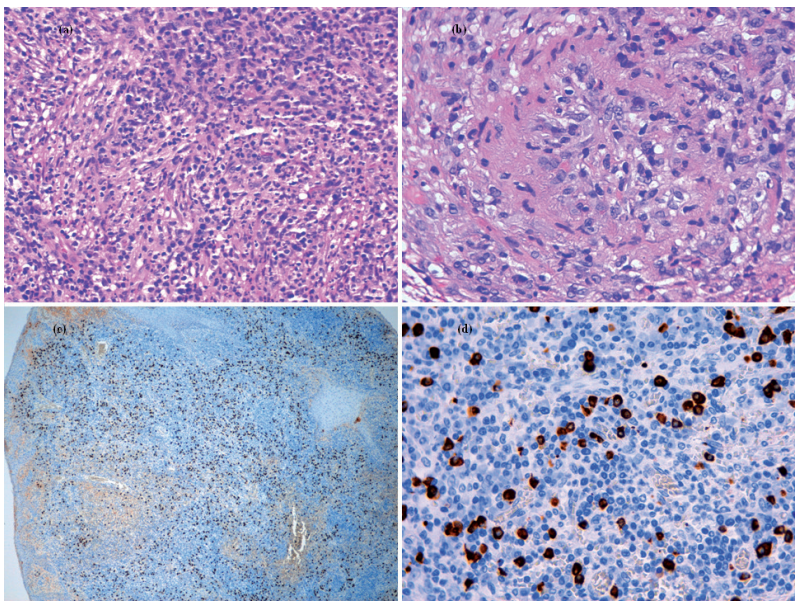

Fig. 2. Histological and immunohistological findings. (a) A skin biopsy specimen showed lymphoplasmacytic infiltrate with storiform fibrosis (H&E 40×). (b) Lymphocytes, plasma cell, eosinophils and focus of lymphocytic venulitis (H&E, 40×). (c) Immunohistochemical staining of IgG4 showed dense infiltration of IgG4$^+$ plasma cells. (d) High-power field showing approximately 80 IgG4$^+$ plasma cells (×400).

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The pathogenesis of IgG4-RD is poorly understood; findings consistent with both an autoimmune disorder and an allergic disorder may be present (3, 4). Affected patients are primarily middle-aged and older men (5), although rare paediatric cases have been described (6).

The disease can manifest in almost any organ or anatomical site; the most common are the pancreas, biliary tract, and salivary and lacrimal glands. However, cutaneous involvement is rare (7). IgG4-RD typically manifests in the skin as papules or plaques, which can be solitary or grouped, and are sometimes described as mass or subcutaneous nodules. A rare case of alopecia has been reported (8). The most commonly affected regions are the head, face and neck; however, lesions have also been seen on the trunk and limbs. In addition, IgG4-related skin disease usually accompanies extracutaneous symptoms (79%). Cases affecting only the skin, as described here, are extremely rare. A review of case reports has postulated 7 different cutaneous presentations of IgG4-RD: (*i*) cutaneous plasmacytosis, (*ii*) pseudolymphoma and angiolymphoid hyperplasia with eosinophilia, (*iii*) Mikulicz's disease, (*iv*) psoriasis-like eruption, (*v*) unspecified maculopapular or erythematous eruptions, (*vi*) hypergammaglobulinaemic purpura and urticarial vasculitis, and (*vii*) ischaemic digit. It is considered that subtypes 1–3 are primary IgG4-related skin diseases, induced by direct infiltration of $IgG4^+$ plasma cells. Meanwhile, secondary IgG4-related skin disease shows inflammatory skin manifestations of systemic IgG4-RD (9). Although the diagnosis of IgG4-RD is based on the combination of clinical features, serology, imaging, histopathology and immunohistochemistry findings, histopathology is the key component for diagnosing IgG4-RD. An international consensus statement on the pathology of IgG4-RD was published in 2012, according to which the diagnosis should be based primarily on general morphological criteria in routine staining. The main microscopic findings in tissue include a lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis (10). Tissue IgG4 counts and $IgG4^+$/IgG ratios are of secondary importance. An $IgG4^+$/IgG ratio greater than 40% is considered supportive of IgG4-RD. The exact cut-off for IgG4 count differs in different organs and, for skin, it set at 200 per high-power field. However, this value is based on a limited number of cases and is not widely accepted. Since many reports do not meet this diagnostic criteria it has been suggested that the cut-off value should be reconsidered (11). Elevated concentration of serum IgG4 (>135 mg/dl) is another characteristic of the disease, although serum IgG4 concentration may be normal in 30–40% of patients with histopathologically confirmed IgG4-RD (12). Imaging studies reveal an increase in the size of the affected organ or a regional fibrosing compromise. PET scan allows detection of increased metabolism in the affected organs, but does not differentiate between the other aetiologies with this pattern.

Differential diagnosis of IgG4-RD is broad and depends on the specific site of involvement and clinical presentation. In our case, the differential diagnosis was based mainly on the extranodal natural killer (NK)/T-cell lymphoma, nasal type and granulomatosis with polyangiitis.

There are no treatment guidelines for exclusive skin IgG4, and most of the data come from patients with systemic involvement. Systemics glucocorticoids are currently the first-line treatment for IgG4-RD (13), regardless of the organ involved. Response to glucocorticoid therapy is usually seen within days or weeks, often accompanied by a decrease in serum IgG4 levels. Skin lesions of IgG4-RD respond well to oral glucocorticoids, but the response to topical corticosteroids is poor. In refractory cases, surgery, immunosuppressive agents, thalidomide, infliximab and rituximab, according to involvement (single-organ or systemic) and the severity of the disease can be considered (14, 15).

In conclusion, the cutaneous manifestations of IgG-RD are poorly understood. This new case with an unusual presentation will enable better characterization of the disease.

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