Coexistence of IgG4-related disease and PR3-ANCA-positive granulomatosis with polyangiitis

Sirs,

IgG4-related disease (IgG4-RD) is a systemic fibroinflammatory disorder characterised by tumefactive organ lesions, dense lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells and variable storiform fibrosis or obliterative phlebitis, typically affecting salivary and lacrimal glands, pancreas, biliary tree and retroperitoneum (1). ANCA-associated vasculitides (AAV), especially granulomatosis with polyangiitis (GPA), are necrotising small-vessel vasculitides that commonly involve the upper airways and lungs, may present with leukocytoclastic vasculitis and vasculitic neuropathy, and are serologically associated with anti-proteinase 3 (PR3) or anti-myeloperoxidase (MPO) antibodies (2). Although IgG4-RD and AAV are generally considered alternative diagnoses, several reports have described patients fulfilling clinical and/or pathological criteria for both diseases, often in older men and with synchronous onset (3). Most of these overlaps are MPO-ANCA-positive and kidney-centred (4).

We present an atypical case of PR3-ANCA-positive granulomatosis with polyangiitis (GPA), salivary index organ and synchronous multiorgan vasculitic involvement, and we discuss it in light of current concepts on the immunological crosstalk between IgG4-RD and AAV (5).

A 70-year-old man with type 2 diabetes mellitus and chronic liver disease/steatosis was referred to the Rheumatology Division because of a rapidly growing right parotid mass detected during outpatient evaluation in mid-2024. The mass was initially suspected to be neoplastic. Core biopsy of the parotid gland demonstrated a lymphoplasmacytic inflammatory infiltrate with IgG4-positive plasma cells and granulomatous/inflammatory foci, supporting the diagnosis of IgG4-related disease (Fig. 1A).

Fig. 1A. Parotid biopsy (H&E, 5×): marked lymphoplasmacytic infiltration with an IgG4/IgG plasma-cell ratio greater than 40%, confirmed by immunohistochemistry.

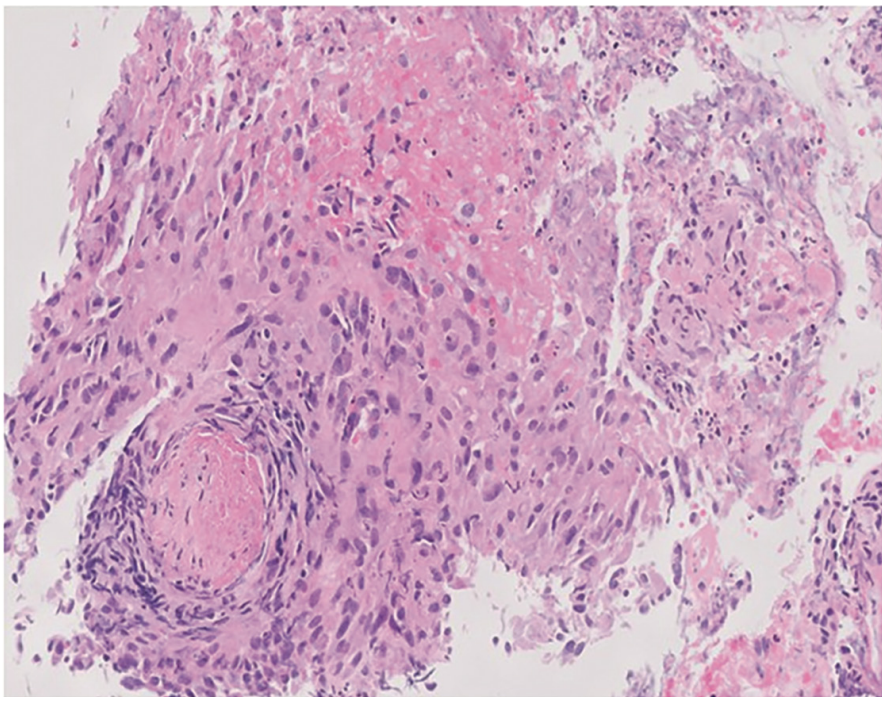

Fig. 1B. Bronchoscopy lung biopsy (H&E, 20×) demonstrates multinucleated giant cells, fibrino-leukocytic membranes, areas of erosion and ulceration, and vessels exhibiting features of thrombosis and vasculitis.

In the weeks preceding admission, he developed cough. Shortly afterwards, he presented migratory, inflammatory polyarthritis affecting large and small joints, with partial and transient response to oral prednisone (20 mg/day). Symptoms recurred when prednisone was tapered below 10 mg/day. Laboratory tests showed elevation of erythrocyte sedimentation rate (49 mm/h) and C-reactive protein (6.26 mg/dL) as well as mildly positive rheumatoid factor. Antinuclear antibodies and viral serologies were negative. However, serological testing revealed markedly positive PR3-ANCA (200 UI/ml; normal values less than 5 UI/ml)). He was admitted in July 2024 because of persistent inflammation and the coexistence of the parotid lesion. On admission he was afebrile but in poor functional condition, with blood pressure 150/94 mmHg and heart rate 109 bpm. Physical examination revealed non-blanching palpable purpura on the anterior aspects of both legs and feet and polyarthritis involving joints of hands and ankles. A punch biopsy from the skin lesions on the lower limb showed leukocytoclastic vasculitis. Soon after admission he developed haemoptysis. Chest CT showed bilateral nodular lesions and ground-glass opacities compatible with inflammatory or haemorrhagic involvement. Flexible bronchoscopy with bronchial biopsies from the right upper lobe demonstrated dense mixed inflammatory infiltrate with active small-vessel vasculitis and vascular thrombosis, accompanied by multinucleated giant cells (Fig. 1B). Bronchoscopy yielded negative microbiological studies. Special stains (PAS, Grocott, Ziehl-Neelsen) were negative for pathogens. An ^{18}F-FDG PET-CT demonstrated increased uptake in the right parotid gland, nasal septum and cavum, as well as inflammatory uptake in the prostate, favouring a systemic inflammatory process. CT of the facial sinuses did not show destructive lesions. During the same flare he developed right optic neuritis with partial visual loss and, later on, right peripheral facial palsy. Nerve conduction studies disclosed mononeuritis multiplex evolving to a severe, asymmetric sensorimotor axonal polyneuropathy, consistent with vasculitic neuropathy. Kidney function remained preserved, and urinalysis showed only mild microalbuminuria. Due to the presence of organ-threatening disease, treatment was initiated with high-dose intravenous methylprednisolone pulses (500 mg/day for three consecutive days), followed by therapeutic plasma exchange (three sessions). Intravenous cyclophosphamide (500 mg every other week) was administered twice in August 2024 as induction therapy. Rituximab 1,000 mg was added later in August (two infusions 2 weeks apart). The patient received trimethoprim–sulfamethoxazole prophylaxis and bone-protective measures. In the following weeks, pulmonary infil-

trates regressed radiologically, cutaneous vasculitis did not recur and inflammatory markers declined. However, gait unsteadiness, distal paraesthesias and partial visual deficit persisted, compatible with fixed vasculitic damage. A plan was made to complete cyclophosphamide 500 mg intravenously every other week for a total of 6 doses for induction (September and October 2024: 500 mg every other week) and to maintain B-cell depletion with rituximab every 6 months, together with gradual tapering of oral glucocorticoids.

This patient presented two converging disease processes. First, the parotid lesion, an organ typically affected in IgG4-RD, which was histologically consistent with IgG4-related sialadenitis (1). Second, he showed a fully expressed, systemic GPA characterized by high-titre PR3-ANCA, pulmonary inflammatory/haemorrhagic opacities, leukocytoclastic vasculitis, nose, and throat inflammatory involvement and vasculitic neuropathy (2). In this case, the temporal simultaneity of both processes and the involvement of distinct target organs strongly suggest a true overlap rather than an IgG4-RD with incidental ANCA positivity, which has been described but rarely evolves to frank vasculitis (3, 4).

Most published overlaps between IgG4-RD and AAV occur in older men, present simultaneously and are MPO-ANCA-positive with kidney-centred disease (3, 4). Our case differs in three aspects: (i) ANCA specificity was PR3, pointing to a GPA phenotype; (ii) the index organ was salivary, pathologically proven to be IgG4-RD; and (iii) multiorgan vasculitic involvement was present in the same episode. Such a combination broadens the clinical spectrum of this overlap.

An immunological review on IgG4-RD/AAV overlap highlights a shared B-cell-centric pathway in both diseases, driven by aberrant B-cell activation, T-follicular helper skewing, Th2 responses and increased BAFF/APRIL, which can promote both IgG4 class switching and ANCA production (5). Neutrophil activation and antigen exposure then sustain autoreactive B cells, creating a milieu in which a tumefactive IgG4-RD lesion and a small-vessel ANCA vasculitis can arise simultaneously in the same host (5). This model explains why patients may have synchronous expression of both entities and also why B-cell depletion is an attractive therapeutic strategy.

Therapeutically, the organ-threatening manifestations in this patient clearly belonged to the vasculitic component of the overlap, so management followed AAV treatment protocols: high-dose glucocorticoids, cyclophosphamide and plasma exchange in the acute phase (6), which was in line with previously reported overlap cases when vital organs were involved (3, 4). Rituximab was subsequently introduced, not only as maintenance for AAV, where it is established, but also as targeted therapy for IgG4-RD, for which B-cell depletion has shown consistent efficacy (7, 8). The partial neurological recovery observed here is consistent with the notion that established vasculitic nerve damage may be only incompletely reversible despite adequate immunosuppression.

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