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Letter to the Editor (Case report)

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Granulomatous uveitis secondary to IgG4-related disease

Dear Editor, A 69-year-old male with IgG4-related disease (IgG4-RD) presented to the emergency department with left eye pain, redness and tearing. Six years before this presentation, the patient developed anorexia, a 12.5 kg unintentional weight loss and dry mouth. He was diagnosed at that time as having new-onset type 2 diabetes mellitus. A CT scan of the chest demonstrated multifocal reticulonodular opacities in the lungs. PET-CT of the chest, abdomen and pelvis demonstrated cervical, axillary, mediastinal, hilar, pelvic and inguinal adenopathy that was fluorodeoxyglucose avid. Fluorodeoxyglucose avidity was also present in the infrarenal abdominal aorta and in the head of the pancreas.

During that evaluation, the patient developed progressive renal insufficiency and mild proteinuria. His serum creatinine peaked at 3.3 mg/dl. A CT scan of the abdomen demonstrated a striated, hypodense appearance of the renal cortices. The serum IgG4 concentration was 767 mg/dl (reference: 4–86 mg/dl), and the levels of complement components C3 and C4 were profoundly depressed: C3 50 mg/dl (81–157 mg/dl) and C4 $<$6 mg/dl (12–39 mg/dl). A kidney biopsy demonstrated severe chronic active interstitial nephritis with $>$10 IgG4$^+$ plasma cells per high power field. He met the 2019 ACR/EULAR classification criteria for IgG4-RD [1] and was diagnosed as having that condition. He began a prednisone taper and experienced the nearly complete resolution of his lymphadenopathy and pulmonary opacities within 2 months. His renal function and serum complement levels also normalized.

Over the next 3 years, the patient had mild flares manifested by worsening renal function, hypocomplementaemia, lymphadenopathy and elevated serum IgG4 concentrations. These disease flares were treated with intermittent courses of prednisone and rituximab. Two years before his current presentation, he developed palpable purpura on his lower extremities in the setting of a systemic disease flare. His serum IgG4 concentration was 259.3 mg/dl at that time. A skin biopsy demonstrated a leucocytoclastic vasculitis. The patient's cutaneous vasculitis and other IgG4-RD flare manifestations responded well to treatment with prednisone and rituximab. He was then lost to follow-up until presenting 11 months later with left eye pain, redness and tearing.

The ophthalmological evaluation revealed bilateral conjunctival injection. Slit-lamp examination of the eyes demonstrated inflammatory cells in the anterior chamber, suggestive of anterior uveitis, and synechiae from posterior uveitis. B-scan US revealed vitreous opacities consistent with intermediate uveitis. Large, diffuse keratic precipitates (cellular deposits on the corneal epithelium) were present (Fig. 1). These findings were consistent with granulomatous panuveitis in both eyes.

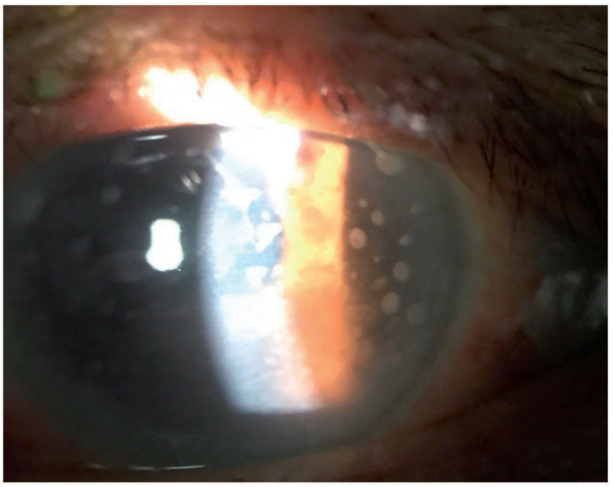
Laboratory evaluation at the time of presentation with granulomatous uveitis revealed negative tests for ANCAs, HLA-B27, Lyme antibody, IFN-γ release assay and syphilis antibody. The serum IgG4 concentration was elevated at 151.1 mg/dl (4–86 mg/dl), and the complement concentrations were both again profoundly low: C3 43 mg/dl (82–185 mg/dl) and C4 $<$6 mg/dl (15–53 mg/dl). The serum creatinine had risen to 1.7 mg/dl, above the patient's previous baseline of 1.2 mg/dl. The patient was treated with prednisolone ophthalmic solution and oral prednisone, and his uveitis and other features of IgG4-RD flare responded to glucocorticoid treatment.

IgG4-related disease is a systemic fibroinflammatory disease that frequently involves the lacrimal glands, extraocular muscles and orbital soft tissue in addition to various other organs, including the salivary glands, thyroid, lungs, lymph nodes, pancreas, bile ducts, aorta, retroperitoneum and kidneys [1–3]. Although scleritis and uveitis, including panuveitis, have previously been described in IgG4-RD, this is the first case, to our knowledge, to be associated with granulomatous uveitis [2]. The case therefore broadens the understanding of disease entities that can be associated with granulomatous uveitis.

Granulomatous uveitis is a form of inflammatory eye disease characterized by large 'mutton-fat' keratic precipitates detected on slit-lamp examination [4–6]. Although this type of uveitis is observed most frequently in granulomatous diseases, such as sarcoidosis and tuberculosis, the term granulomatous refers not to the histopathology of the inflammation but rather to the appearance and size of the keratic precipitates [4–7]. Indeed, granulomatous uveitis has been demonstrated in conditions that are not associated with true granulomatous inflammation, such as birdshot retinochoroiditis [6, 7]. This distinction is of particular importance with regard to IgG4-RD because the presence of granulomatous inflammation is highly atypical of that condition and should prompt clinicians to question the diagnosis of IgG4-RD [1].

Our case demonstrates that granulomatous uveitis can be a feature of IgG4-RD and reminds us that the disease manifestations of IgG4-RD frequently unfold in a metachronous manner, adding new types of organ involvement as the disease evolves. In this case, the patient's tubulointerstitial nephritis, cutaneous vasculitis and granulomatous uveitis all developed sequentially following his initial presentation with pulmonary and pancreatic disease. The case also serves as an important reminder that despite its name, the term granulomatous

Fig. 1 Slit-lamp examination demonstrating diffuse large keratic precipitates consistent with granulomatous uveitis



uveitis does not necessarily imply the presence of granulomatous inflammation on histopathology, and that this finding can be present in non-granulomatous diseases.

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Data availability statement

All relevant data are included in the manuscript.

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