Sir,
IgG4 orbitopathy: unravelling a multisystem diagnostic challenge

Immunoglobulin-G4-related disease (IgG4RD) is a newly emerging clinical entity presenting clinicians with a diagnostic challenge, due to simultaneous or sequential involvement of multiple organs. We present a case of a patient who initially underwent extensive and invasive investigations to determine the cause of bilateral cervical lymphadenopathy, before an orbital biopsy finally provided a definitive diagnosis. She was successfully treated with corticosteroids, with a dramatic and rapid response.

Case report

A 60-year-old woman presented with intermittent eyelid swelling and marked bilateral cervical and pre-auricular lymphadenopathy. CT scanning revealed a perirenal mass, enlarged salivary glands, and widespread lymphadenopathy suggesting sarcoidosis. A biopsy of the perirenal mass was reported as retroperitoneal fibrosis. There was marked eosinophilia, hyperimmunoglobulinaemia, particularly IgG, and a normal serum-ACE. She underwent additional biopsies, providing no definitive diagnosis. She subsequently developed bilateral, preseptal orbital infiltration, with MRI demonstrating enlarged lacrimal glands (Figures 1a–c).

Orbital biopsy showed a reactive T- and B-cell infiltrate associated with IgG4+ plasma cells in a fibrotic background (Figures 2a–d). Expert review of previous pathological specimens, including the perirenal mass, hysterectomy specimen, submandibular gland (Figure 2e), and facial lymph node (Figure 2f), revealed similar features.

Daily corticosteroid therapy (40 mg prednisolone) resulted in rapid resolution of her orbital masses and lymphadenopathy.

Comment

Immunoglobulin G4-related disease (IgG4RD) is an emerging idiopathic inflammatory fibrosing condition presenting clinicians with a diagnostic challenge because of the involvement of multiple organs, including the lacrimal and salivary glands, pancreas, kidneys,

hepatobiliary tract, lymph nodes, thyroid, lungs, and retroperitoneum. It is characterised by elevated serum IgG4 (>1.35 g/l), IgG4-producing plasma cell infiltrates associated with fibrotic/sclerotic changes, and a rapid response to corticosteroids.^{1–3} Clinical symptoms are relatively mild and include organ swelling/dysfunction. Occasionally, the disease can be complicated by the development of B-cell lymphoma.⁴

Corticosteroid treatment is effective. However, there is frequent recurrence and relapse following withdrawal.¹ Spontaneous regression without treatment has also been reported.⁵ IgG4RD is often misdiagnosed as sarcoidosis, neoplasia, lymphoma, or Sjögren's syndrome, because serum IgG-subclass analysis and IgG4 immunostaining of specimens are not performed routinely and the affected organs vary. Biopsy is usually required to distinguish IgG4RD from the above diagnoses and serum IgG4 analysis assists both diagnosis and monitoring. PET scanning can help determine disease distribution.⁵

Our case highlights the importance of considering IgG4RD in the differential diagnosis of multisystem diseases. Early diagnosis requires a high index of suspicion, reduces unnecessary investigations, and offers the possibility of timely effective treatment. Ophthalmologists have an important role in diagnosis, as the eyelids, lacrimal glands, and orbit offer frequently involved, easily accessible sites for histological diagnosis.

Conflict of interest

The authors declare no conflict of interest.

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Figure 1 (a) Clinical photograph showing bilateral orbital masses; (b) MRI scan of large preseptal masses involving lacrimal glands; (c) Intra-operative photograph showing firm pink vascular mass anterior to fat pad. The colour reproduction of this figure is available at the *Eye* journal online.

Figure 2 (a) Orbital biopsy showing a reactive T- and B-cell infiltrate with germinal centre (GC) formation in a fibrotic background (Fi). (b) There are >40 IgG4+ plasma cells per high-power field. These appear brown (peroxidase immunostaining technique). (c, d) The IgG4+ plasma cells are polytypic, ie, some express each light chain in an approximately normal physiological ratio of kappa (shown in c) to lambda (shown in d). Positive cells are brown (peroxidase immunostaining technique). The polyclonal nature of the infiltrate was confirmed by a B-cell receptor rearrangement polymerase chain reaction study. (e) Submandibular gland biopsy in which only a few glands (GI) remain, because of destruction by the inflammatory infiltrate, which contains abundant IgG4+ plasma cells (brown—peroxidase immunostaining technique). (f) Facial lymph node showing reactive features, but containing abundant IgG4+ plasma cells (brown—peroxidase immunostaining technique) (scale bars: a 500 microns; b (pertaining to panels b–f) 100 microns).

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