IgG4-associated multifocal systemic fibrosis presenting with fever of unknown origin

Sir,

Autoimmune pancreatitis is characterized by significant lymphoplasmacytic infiltration and fibrosis of the pancreas,\(^1\) with high serum IgG4 concentrations and/or IgG4-positive plasma cell infiltration.\(^2,3\) The disease may be complicated by a variety of extra-pancreatic lesions,\(^2,3\) suggesting the possibility of systemic disease, recently described as IgG4-associated multifocal systemic fibrosis.\(^4\)

Of 31 patients admitted to our hospital with a fever of unknown origin (FUO) from 1 October 1997 to 31 July 2005, 10 did not receive a definite diagnosis during their admission.\(^5\) Three of these 10 had evidence of IgG4-associated multifocal systemic fibrosis.

Patient 1 was a 71-year-old man, admitted with a high fever, anorexia, lower back pain and polydipsia. Physical examination showed remittent fever and bilateral swelling of the submandibular gland. Investigation revealed panhypopituitarism and diabetes insipidus. Serum IgG4 and soluble IL-2 receptor (sIL2r) levels were elevated. Imaging studies showed hypophysitis, sialadenitis and retroperitoneal fibrosis, but no pancreatic lesions. Histology of biopsies of the submandibular gland and retroperitoneal fibrosis showed IgG4-positive

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**Figure 1.** a Transcutaneous biopsy of the submandibular gland, showing dense fibrosis and chronic inflammation with marked lymphoplasmacytic infiltration (H-E stain, \(\times 400\)). b Transcutaneous biopsy of the submandibular gland, showing IgG4-positive plasma cell infiltration (IgG4 immunostain, \(\times 400\)). c Transbronchial lung biopsy showing infiltration of lymphocytes and macrophages in the alveolar septa and thickening of the interstitium. d Infiltration of IgG4-positive plasma cells in the alveolar septa (\(\times 400\)). e Specimens obtained by video-assisted thoracic surgery, showing organizing inflammatory cell infiltration with fibrotic changes (H-E stain, \(\times 400\)). f Specimens obtained by video-assisted thoracic surgery, showing IgG4-positive plasma cell infiltration (\(\times 400\)).
plasma cell infiltration (Figure 1, a and b). All symptoms improved after corticosteroid treatment.

Patient 2 was a 67-year-old man, admitted with a high fever. Physical examinations showed remittent fever, fine crackles on chest auscultation and hepatomegaly. Serum IgG4 and sIL2r levels were elevated. Imaging studies showed interstitial pneumonia, but no pancreatic lesions. Transbronchial lung biopsy showed thickening of the interstitial septa in the alveoli with infiltration of the IgG4-positive plasma cells (Figure 1, c and d). Liver biopsy specimens showed diffuse granulomatous lesions, unlike those typical of sarcoidosis or autoimmune hepatitis. He responded favourably to corticosteroids.

Patient 3 was a 37-year-old man, admitted with a high fever and general fatigue. Physical examinations showed remittent fever and tenderness of the neck without lymphadenopathy. Later, he complained of muscle pain and paraesthesia of the lower extremities and of vertigo. Serum IgG4 and collagen disease-related data were within normal ranges. Chest computed tomography and Ga-67 scintigram showed a soft mass in the right lung, and a biopsy specimen showed IgG4-positive plasma cell infiltration (Figure 1, e and f), indicating a pseudotumour composed of plasma cell granulomas. Imaging studies showed no pancreatic lesions. All clinical symptoms improved after the administration of corticosteroids.

The symptoms of these three patients (high serum IgG4 concentration, prominent IgG4-bearing plasma cell infiltration into various organs regardless of the pancreatic involvement, and a favourable response to corticosteroid therapy) correspond favourably to corticosteroids.

The serological characteristics are high serum levels of IgG4 and sIL2r. Levels of sIL2r are also increased in Wegener’s granulomatosis and Churg-Strauss syndrome, which are sometimes causes of FUO. However, interleukin-1β, interleukin-6 and tumour necrosis factor-α were all within the normal range. There was no obvious mechanism for the rising fever in these three patients.

Our experience suggests that it may be useful to measure serum IgG4 in cases of fever where the diagnosis is unclear.

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References
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Calculating eGFR using the MDRD equation

Sir,

In a recent paper, MacGregor et al. suggested that the recently developed IDMS-traceable Modification of Diet in Renal Disease (MDRD) equation should be used to calculate GFR from serum creatinine measurements. This equation was developed for use with creatinine results from measurement procedures with calibrations that are traceable to the isotope dilution gas chromatography mass spectroscopy (IDMS) creatinine reference method. Since most routine measurement procedures for serum creatinine have not been calibrated to be traceable to the IDMS reference method, the authors suggest that measurement-procedure-specific correction factors derived from EQAS data can be used by individual laboratories to adjust the reported values measured in their laboratory to match the IDMS reference method. While this approach has theoretical appeal, it has a significant limitation unless the EQAS materials used to derive the correction factors have been validated to demonstrate commutability with native clinical