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IgG4-related disease (IgG4-RD) presenting with raised serum IgG2 – real timeline of IgG4-RD?

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Abstract

IgG4-related disease (IgG4-RD) has rarely been reported as presenting with Adult Onset Asthma with Periorbital Xanthogranulomatosis (AAPOX). There is emerging evidence that serum IgG2 elevation may predate IgG4 elevation in both serum and tissues in patients with IgG4-RD. We present here the case of a 57 year old patient who developed AAPOX with no histological or serum evidence of IgG4 elevation, but an isolated raised serum IgG2 at onset. We give evidence that over time her clinical picture became more consistent with IgG4-RD, and that immunosuppression with Methotrexate may have attenuated the serological evolution of disease. We believe that further work is required to elucidate the true natural history of serological and histological progression in IgG4-RD as, at least in a sub-set of patients, isolated serum IgG2 elevation at presentation appears to be a precursor to disease.

Key message

Elevation of serum IgG2 may be a precursor to classical IgG4-related disease

Case report

Dear Sir,

A 57 year old female baker presented with a 7 year history of systemic illness comprising cervical lymphadenopathy, sinusitis, smell and taste disturbance, adult-onset asthma and bilateral eyelid swellings. Biopsy of the eyelids confirmed xanthogranulomatous inflammation with Touton giant cells without evidence of elevated IgG4 plasma cells [Fig 1]. The patient was known to be a haemochromatosis carrier, but had no other past medical history. Treatment was with beclometasone and salbutamol inhalers only.

Baseline blood tests showed elevation of serum IgG2, normal IgG4 and a peripheral eosinophilia (see below) Erythrocyte sedimentation rate and C-reactive protein were within normal limits and have remained so.

An initial diagnosis of adult onset asthma with periorbital xanthogranulomatosis (AAPOX)[1,2] was made. Haematological review showed no evidence of underlying haematological malignancy; CT of the chest, abdomen and pelvis showed bilateral isolated 13mm axillary lymph nodes, felt to be reactive . X-rays of the long bones showed no changes consistent with Erdheim Chester disease (known to be associated with AAPOX) [1,2] .

Empirically the patient was treated with a short course of oral prednisolone, 30mg once daily for 14 days, to assess reversibility of symptoms. Wheeziness, smell / taste disturbance and orbital swelling all improved. Based on the available literature[1,2], Methotrexate 15mg once weekly was commenced to suppress the systemic inflammation.

Clinically the Methotrexate was well tolerated but there was no definitive improvement in the orbital swelling or severity of asthma. Serologically, the peripheral eosinophilia and IgG2 levels reduced whilst on Methotrexate, but there was no response in the persistently raised IgE. Serum IgG4 remained normal immediately prior to commencing Methotrexate [see below].

After 15 months on Methotrexate, given the uncertainty about clinical effectiveness, the Methotrexate was reduced with a view to stopping. At 7.5mg weekly, the patient felt that her upper and lower respiratory symptoms had worsened, and she had also developed episodes of increased orbital swelling. Methotrexate was not increased however as she was retiring from work, where her occupational exposure to fine, gluten free flour had been suspected as a possible trigger to her original illness (symptoms began shortly after this occupational exposure 9 years earlier). Retirement did not bring a resolution of her symptoms, but she started to experience general malaise associated with Methotrexate and stopped this herself 29 months after commencing.

Off Methotrexate her systemic symptoms were a little worse – increased nasal symptoms predominantly; wheeziness stable on inhaled therapy [Fluticasone/ Vilanterol combination inhaler]. The orbital swelling continued to be variable as it had been throughout the course of the illness. Serological markers however were all increased, with recurrence of peripheral eosinophilia and elevated serum IgG2 as at presentation. More interestingly, 6 months earlier, whilst still on low dose oral Methotrexate, the serum IgG4 had been measured as high for the first time, and after 3 months off Methotrexate the serum IgG4 level had reached nearly 9 times the upper limit of normal [see below]. The patient remains clinically well off all systemic treatment, but under continued observation.

The serological progression over time is summarised as follows: March 2013 (pre-treatment) IgG2 7.24g/L (1.2-6.6), IgG4 0.38g/L (0-1.3), eosinophils $1.3x10^9$/L (0.04-0.5), February 2014 pre-methotrexate but after steroids 6.27, 0.4 and 1.39 respectively, with IgE 231 KU/L (0-81), June 2016 whilst on Methotrexate 6.43, 5.26, 0.55 respectively, with IgE 303. December 2016, off all treatment for 3 months, all elevated at 11.7, 11.5, 1.07 respectively, IgE 420.

Although rare, IgG4-RD presenting as AAPOX has been reported previously[3] . Serological IgG2 elevation in isolation, as a precursor for IgG4-RD, has also recently be reported in a large case series of patients with orbital disease by ourselves, in collaboration with colleagues in Singapore[4] . What

remains uncertain is the timeline. Is IgG2 elevated in all patients with IgG4-RD as a precursor to disease or just a sub-set? Does the IgG4 rise inexorably over time, in this case months to years, or does immunosuppressive treatment attenuate this? Did the treatment with Methotrexate here suppress and delay the emergence of elevated serum IgG4 or would the curve of serum IgG4 have progressed exponentially regardless?

Either way, at presentation this patient had neither serological nor histological evidence of IgG4-RD. Over time, a more classical serological pattern consistent with IgG4-RD has emerged, in a clinically consistent context. More work is required to ascertain the natural history of this condition, in particular the timeline of relevant serological markers in all patients with IgG4-RD. What this case does illustrate, however, is that in patients with a clinical picture suggestive of IgG4-RD, isolated elevation of serum IgG2 at presentation can be relevant and a precursor to the full clinical syndrome, at least in a sub-set of patients.

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Figure 1 legend

Haematoxylin & Eosin stained tissue section showing numerous foamy histiocytes (black arrow) with some other mixed inflammatory cells comprising lymphocytes and plasma cells and fibrosis. Touton giant cells were scattered around the lesion (inset top right).

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