RHEUMATOLOGY

Letter to the Editor (Case report)

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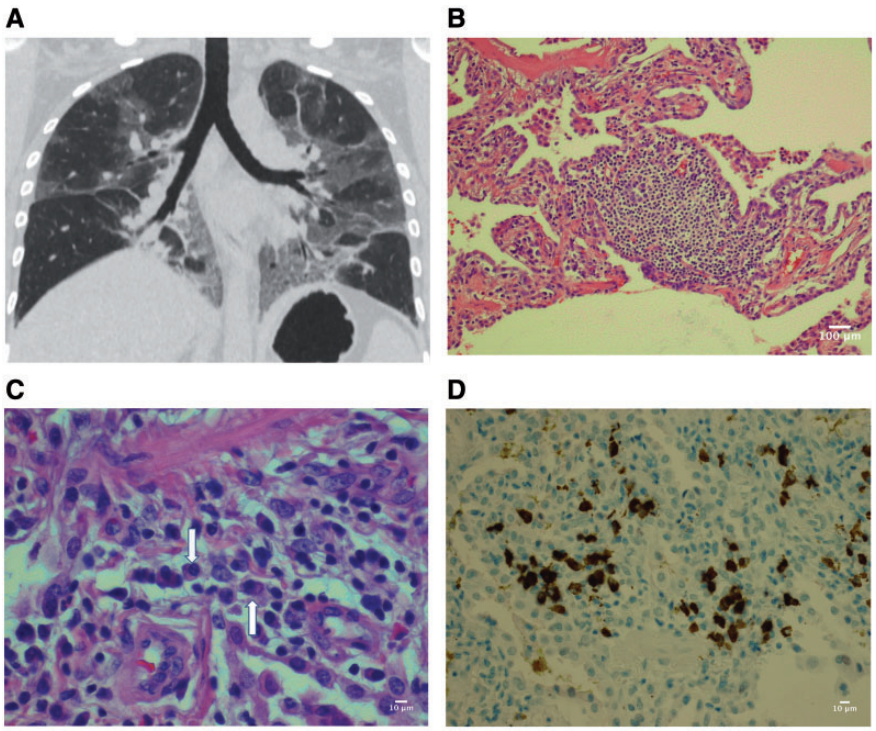
More than meets the eye: IgG4-related disease presenting as isolated interstitial lung disease

Rheumatology key message

- IgG4-related disease can present as isolated interstitial lung disease with a pattern consistent with non-specific interstitial pneumonia.

Sir, Immunoglobulin G4 related disease (IgG4-RD) is an emerging immune-mediated condition characterized by infiltration of IgG4-bearing plasma cells into the involved organs and has typical histopathological findings. It has a heterogeneous clinical presentation, typically involving the pancreas, biliary system, salivary glands, orbits, kidneys and retroperitoneum. On the other hand, lung involvement is relatively uncommon [1, 2]. We describe the case of a 33-year-old caucasian female who presented with isolated non-specific interstitial pneumonia (NSIP) from IgG4-RD. Our patient presented with a 2-year history of dyspnoea. She had progressive functional and physiological decline and soon required oxygen therapy despite treatment with corticosteroids. A surgical lung biopsy was performed and a diagnosis of NSIP was suggested. She was then referred to our institution for lung transplantation evaluation. She was a lifelong non-smoker and had no other medical problems, exposures or significant family history. There were no stigmata of an autoimmune disease. Her physical examination was normal except for bibasilar inspiratory crackles on lung auscultation. Pulmonary function testing revealed forced vital capacity (FVC) 1.50 L (38%), forced expiratory volume in 1 s (FEV1) 1.36 L (44%), FEV1/FVC ratio 91%, forced expiratory flow at 25–75% of FVC 1.88 L (53%), total lung capacity 75% and diffusing capacity of the lung for carbon monoxide 7.2 ml/min/mmHg (26%). A high-resolution CT of the chest showed diffuse ground-glass opacities with areas of reticulation and bilateral septal thickening (Fig. 1A). Laboratory evaluation revealed normal complete

Fig. 1 Interstitial lung disease from IgG4-related disease



(**A**) High-resolution computed tomography coronal view. Patchy areas of ground-glass opacities with central distribution along bronchovascular bundle. (**B**) Haematoxylin and eosin stain, ×100. Interstitial lymphoid aggregate associated with NSIP. (**C**) Haematoxylin and eosin stain ×400. Infiltrate including numerous plasma cells (arrows indicate some examples). (**D**) Immunohistochemical stain for IgG4, ×200. Dark brown indicates IgG4-positive plasma cells.

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blood count, ESR, CRP, kidney and liver function tests. Serological testing for the ANA, RF, CCP antibody, anti-Ro/SSA, anti-La/SSB, ANCA and Scl -70 antibody were negative. A 'myositis panel' comprising of antibodies of anti-histidyl-tRNA synthetase (JO 1), anti-threonyl-tRNA synthetase (PL-7), anti alanyl-tRNA synthetase (PL-12), anti-glycyl-tRNA synthetase (EJ), anti-isoleucyl-tRNA synthetase (OJ), anti-signal recognition particle (SRP), anti Nuclear helicase (Mi 2), anti transcription intermediary factor 1-gamma (p155/140), anti- melanoma differentiation-associated gene 5 (MDA 5), anti nuclear matrix protein 2 (NXP2), anti polymyositis/scleroderma (PM/Scl) complex, anti U1, U2 and U3 ribonucleoprotein particle and anti Ku complex was negative as well. Her serum immunoglobulin G levels were normal, however; IgG4 levels were noted to be elevated at 114 mg/dl (normal 4–86 mg/dl).

Having no obvious aetiology for NSIP in this otherwise healthy patient, we suspected IgG4-RD because of elevated serum IgG4 levels. The lung tissue slides were re-examined and revealed diffuse interstitial chronic inflammation with lymphoplasmacytic infiltrate and mildly fibrotic interstitium, consistent with the NSIP pattern. However, when immunohistochemical staining for IgG4 was performed, numerous IgG4-laden plasma cells were seen in the interstitial infiltrates (Fig. 1B–D). These features were felt to be consistent with IgG4-associated pulmonary disease. We initiated treatment with two doses of 1000 mg i.v. rituximab 15 days apart as corticosteroids were tapered. Her symptoms and functional status markedly improved. At follow-up after 8 weeks, the patient no longer required supplemental oxygen and became independent in her regular life activities.

To summarize, this case represents an unconventional manifestation of a rare disease. The true prevalence of this condition remains unknown due to the sporadic nature of published cases, but a national survey in Japan estimated the total number of patients with IgG4-RD to be 8000 in the year 2009 (adult population in the year 2007 was estimated to be 104 197 000) [3]. Male predominance was noted with an average age at diagnosis of 58 years [3]. Our patient's young age, white race and female gender is atypical for IgG4-RD. Pulmonary involvement in IgG4-RD can manifest in various forms as hilar lymphadenopathy, lung nodules, ground-glass opacity, honeycombing, bronchiectasis, thickening of bronchovascular bundles and interlobular septa [4]. Although, lung involvement in the form of an interstitial pneumonitis has been described in the past, most cases were associated with other organ involvement such as autoimmune pancreatitis [5]. Making a diagnosis in isolated pulmonary cases could be challenging and may require a surgical lung biopsy. Elevated serum IgG4 can provide a diagnostic clue; however, its non-specificity precludes it from being a diagnostic marker. Increased levels may be seen in normal individuals and other non IgG4-RD conditions [6]. Conversely, a study of 125 patients with biopsy proven IgG4-RD showed that only 51% of patients had elevated IgG4 levels in blood [7]. A high index of suspicion is therefore warranted to establish diagnosis, which ultimately relies on histopathological examination. The typical microscopic features are lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis and eosinophilic infiltration. Although, storiform fibrosis is a common histological feature, this is not usually present in lung tissue [8]. Lastly, this case also illustrates a favourable treatment response with rituximab in a case refractory to corticosteroid therapy.

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