



## Case report

## Immunoglobulin G4-related pleuritis – A case report



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## ABSTRACT

Immunoglobulin G4-related disease (IgG4-RD) is a chronic disease that presents with inflammation and fibrosis of involved tissue. It encompasses several disorders previously described using different terms, but all disorders are characterised by IgG4-positive plasma cells and lymphocytes infiltration of tissues. We report a rare case of a 58-year-old man with IgG4-related pleural disease without other systemic manifestations. The diagnosis was based on characteristic changes on PET-CT and typical histopathology in a pleural specimen. The patient's condition improved following immunosuppressive therapy.

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## 1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a relatively new entity. The clinical symptoms are vague and nonspecific and early diagnosis is therefore challenging. Tissue infiltration with IgG4-positive plasma cells and lymphocytes is characteristic [1] and elevated serum levels of IgG4 are also common. The formation of chronic fibrosis and inflammation may occur in nearly every organ although the most frequently affected are the submandibular glands, lymph nodes, orbit, pancreas, retroperitoneum, lungs and parotid glands [2]. The epidemiology of the disease remains poorly described and literature is scarce on the global incidence and prevalence of IgG4-related diseases [3]. We report a rare case of IgG4-RD with isolated pleural involvement.

## 2. Case report

A 58 year-old man was referred due to IgG4 related pleural disease. He presented two years earlier with unexplained weight loss. He had no dyspnoea, cough or chest pain. He did not report fever, night sweat or any other symptoms. He denied allergic rhinitis or asthma. His brother suffered from asbestos-triggered pleural plaques but he had no family history of collagen or

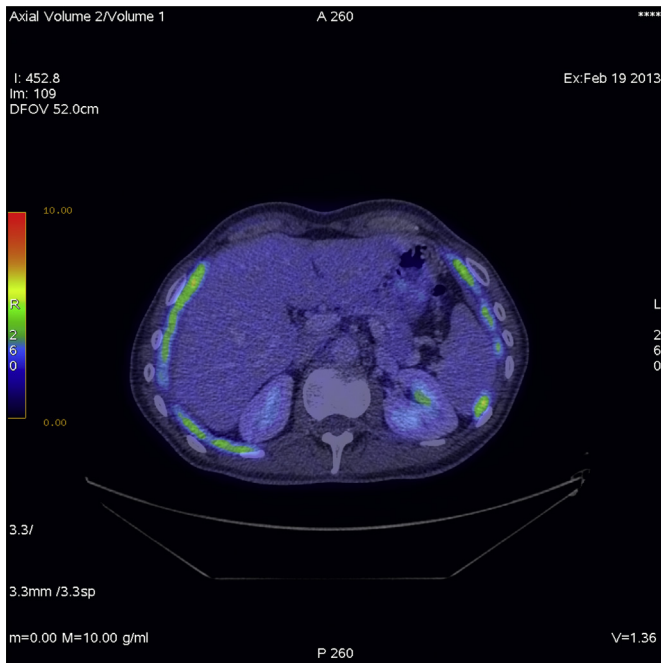
autoimmune disease. In his youth, he used to work as a blacksmith where he was exposed to dust and fumes from welding as well as asbestos. Number of asbestos fiber-years was low according to an evaluation by specialists in occupational medicine. In the last 20 years prior to admission he worked as a salesman and environmental consultant in agriculture. He was an ex-smoker (2 pack years). He reported to have an active lifestyle.

During admission he had grade 2 dyspnoea according to the Medical Research Council dyspnoea scale, but still no cough or sputum. His physical examination was normal. Lung function was reduced: Forced vital capacity (FVC) was 56% of the predicted; forced expiratory volume in 1 second (FEV1) was 57% of the predicted; FEV1/FVC ratio was 0.8; total lung capacity (TLC) was 72% of predicted and diffusing capacity for carbon monoxide (DLCO) was 74% of the predicted. Electrocardiography and echocardiography were normal. Laboratory examinations showed a normal peripheral white blood cell count ( $8.25 \times 10^9/L$ ), C-reactive protein (4.4 mg/L), albumin (37 g/L), lactate dehydrogenase (175 U/L), haemoglobin (8.5 mmol/L). Total serum IgG was normal, 12 g/L but sIgG4 was increased, 1.410 g/L (0.039–0.864 g/L).

A PET-CT scan showed FDG uptake in pleura, mostly on the right side with bilateral pleural thickening and calcification (Fig. 1). Due to the suspicion of a mesothelioma, a pleural biopsy was performed and the suspicion of a malignant lesion was ruled out. Histology revealed chronic fibrotic inflammation and infiltration with plasma cells, characteristic for IgG4-related disease. A storiform pattern and an obliterative phlebitis were also present. The number of

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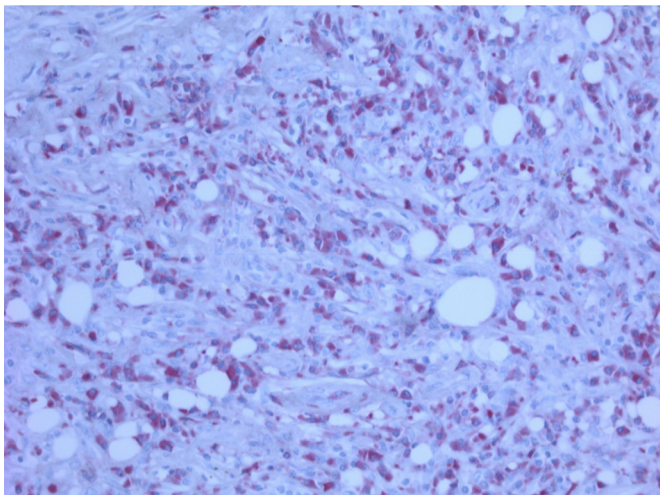
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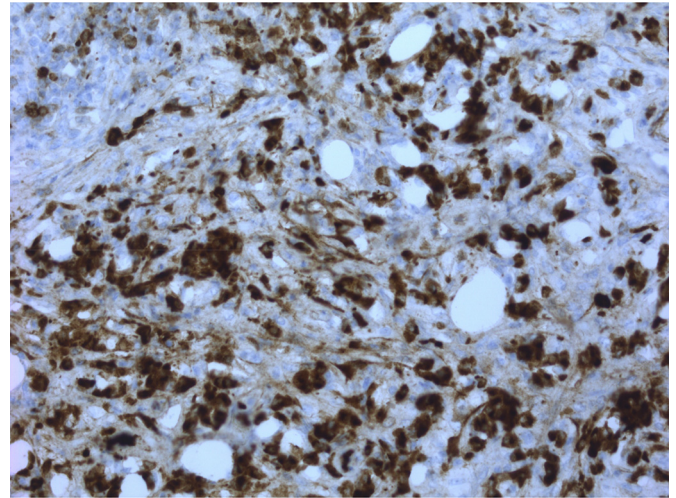
**Fig. 1.** PET-CT showing pathological changes of the pleura before the immunosuppressive treatment.

IgG4-positive plasma cells was on average 52 per high power field (HPF) with IgG4+/IgG plasma cell rate of 50% (Figs. 2 and 3). An elevated IgG4-positive to IgG-positive plasma cell rate greater than 30% is helpful in distinguishing IgG4-related from non-IgG4-related inflammatory conditions [4]. The number of IgG4+ plasma cells over 50 per HPF is found to be highly specific. In conclusion IgG4-related pleura disease was considered the most likely diagnosis.

The patient started treatment with prednisolone 37.5 mg per day, gradually tapered over time. Follow-up PET-CT showed first good response to the treatment (Fig. 4), and then progression of fibroinflammatory changes during prednisolone tapering. Glucocorticosteroid therapy was continued with prednisolone, 7.5 mg per day, and added azathioprine 50 mg bid. Azathioprine was discontinued due to gastro-intestinal side effects. Instead, methotrexate 15 mg weekly was found to be a good alternative as



**Fig. 2.** Immunoglobulin G immunostaining showing IgG positive plasma cells.

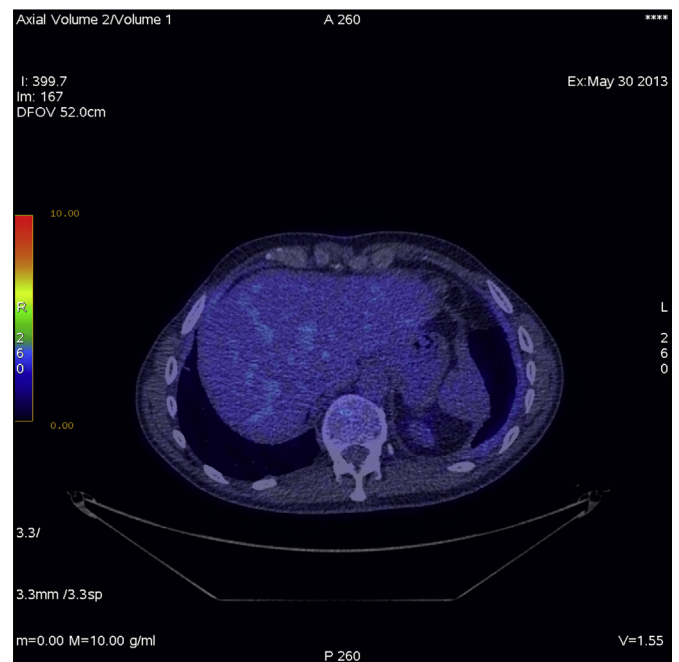


**Fig. 3.** Immunoglobulin G4 immunostaining showing IgG4 positive plasma cells.

maintenance therapy. The patient has now been stable for one year with a combination of prednisolone with temporary increase of dose and immunomodulating treatment.

### 3. Discussion

IgG4-related disease is a fibroinflammatory condition characterised by a tendency to form tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, frequent but not invariable elevations of serum IgG4 levels, and a swift initial response to glucocorticoids provided that tissue fibrosis has not supervened [5]. This diverse entity can affect nearly every organ and systemic manifestations usually occur [6]. Few cases of extensive multiorgan involvements have been published [7,8]. Isolated IgG4-pleuritis has been described in only



**Fig. 4.** PET-CT showing complete remission of pleural activity after high dose prednisolone.

two cases [9,10], both with pleural effusion. We report a rare case of an isolated IgG4-RD pleural involvement presenting with bilateral pleural thickening and calcification without pleural effusion. Nonspecific clinical signs such as weight loss and slowly worsening of dyspnoea suggested malignancy. Bilateral pleural biopsy and right-side pleurectomy was necessary to achieve relevant specimen and exclude malignancy. Histopathological diagnosis demands differentiation from desmoplastic mesothelioma and inflammatory myofibroblastic tumour. According to consensus statement, a histopathological diagnosis of IgG4-RD requires two of the following major features: Dense lymphoplasmacytic infiltrate, fibrosis arranged at least focally in a storiform pattern, and obliterative phlebitis [11]. These features were all present in the biopsy thus confirming the diagnosis of IgG4-RD-pleuritis.

The imaging diagnostics also presented with a classical picture of the disease. PET-CT is an accurate tool for detecting IgG4-RD-related lesions as the levels of FDG uptake reveals the activity of those lesions [12]. It is also found to be the best tool for follow-up on disease progression. In our case it helped to notice immediate response to systemic steroid therapy as well as relapse of inflammatory changes after discontinuation of treatment.

Increased serum IgG or IgG4 level can help confirm the diagnosis but is not specific enough for disease and therapy monitoring. Classic IgG4-RD can be active in the absence of elevated serum IgG4 concentrations and not all patients with IgG4-RD have an elevated serum IgG4 level at baseline. Many patients have a substantial decline in serum IgG4 concentrations following treatment, but some never normalise [13].

IgG4-RD Responder Index (IgG4-RD RI) has been developed and may be a helpful tool in follow up of the disease. It permits objective quantification of the treatment response by providing standardised outcome measures and may be used by physicians during clinical visits [14].

Systemic corticosteroids are thought to be the first line treatment; in some cases the use of immunomodulating agents such as azathioprine or methotrexate are required [15]. Alone or in combination with B-cell depletion with rituximab, prompt clinical improvement can be obtained. Nevertheless, treatment discontinuation usually leads to quick relapse of IgG4-pleuritis [6,16]. Our case reflects the typical response to the applied treatment. However, further research in this field is needed, especially in relation to cases with mono-organ affection, where systemic therapy is often associated with side effects.

### Conflicts of interest

The authors state that they have no Conflicts of Interest (COI).

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