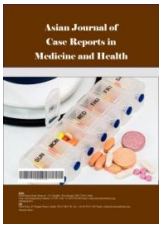

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Pleural Effusion as Manifestation of IgG4 Related Disease

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Authors' contributions

This work was carried out in collaboration among all authors. Authors NK, NM and SC designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors NM, RG, NB managed the analyses of the study. Author IY managed the literature searches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Immunoglobulin G4-related disease is a very rare and little known sclerosing inflammatory disease. This pathology has been reported in various organs. Of these, there are only 9 reports describing pleuritis as IgG4-related disease with no other organ involvement. We report the original observation of an isolated pleural effusion as manifestation of IgG4 related disease in a 60-year-old woman. We suggest the possibility to includ IgG4 related disease in the differential diagnosis of unexplained pleuritis. Our observation is distinguished by the isolated nature of pleural involvement and the spontaneous regression of pleural effusion.

Keywords: IgG4 ; inflammatory disease; plasma cells ; pancreatitis ; lung.

1. INTRODUCTION

IgG4-related disease (IgG4-RD) is a newly recognized rare systemic fibroinflammatory disease [1]. It was described for the first time in Japan, in 2003 by Hamano H et al, as an association of high serum IgG4 level and Lymphoplasmacytic sclerosing pancreatitis/ autoimmune pancreatitis [1,2].

The name IgG4-RD was subsequently proposed by Kamisawa T et al, to define the new

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clinicopathological entity associating: multiple organs fibroinflammatory sclerosis, tissue infiltration of IgG4 + plasma cells, and high levels of circulating IgG4 [2].

Then , it was demonstrated that IgG4-RD can affect any organ in the human body [3]. IgG4 related respiratory disease can include interstitial pneumonia , pseudotumor , inflammatory airway disease, pleural thickening and effusion [4]. Herein, we report the case of a sixty years old woman presenting with a left pleural effusion as the sole manifestation of IgG4-RD.

2. CASE REPORT

A 60-year old woman, in good general health, with a medical past record of osteoporosis and helicobacter pylori gastric infection, complained of left pleuritic chest pain without fever or astenia three months before presentation to our hospital. She had never smoked and not been exposed to asbestos. She had no family history of tuberculosis nor neoplasic disease. The chest radiography showed a large left pleural effusion. Physical examination was normal. Her pulse oxygen saturation at room air was 98%. Laboratory workup showed the following values (Table 1).

Serum autoantibodies and tumor markers were negative. Brain natriuretic peptide was normal and cardiac function was well preserved on echocardiography. CT scan showed a large left pleural effusion, without evidence of pulmonary infiltrates, tumors, or intrathoracic lymphadenopathy. The percutaneous exploration of the pleural effusion showed exsudatif fluid based on Light's criteria (48g/l pleural fluid protein) with mononuclear cell predominance and negative results for cytologic and bacteriological culture.

Polymerase chain reaction (PCR) analysis of the pleural effusion for Mycobacterium tuberculosis was negative.

Biopsy specimens, retrieved by parietal pleural biopsy, revealed a diffuse and dense inflammatory infiltrates of the parietal pleura with fibrinous exsudate (Fig. 1). The inflammatory infiltrates was composed by lymphocytes and numerous plasma cells (Fig. 2). Immunohistochemical examinations were performed showing a moderate infiltration by IgG4-positive plasma cells in the specimens (Fig. 3).

The serum concentrations of the IgG4 subclass was normal.

Diagnosis of pleuritis from IgG4-related disease was established. Corticosteroid treatment was refused by the patient given the history of osteoporosis. During the follow-up a spontaneous regression of the pleural effusion was noted.

3. DISCUSSION

Although the initial description of IgG4-RD was about IgG4-related pancreatitis, it now appears that any organ can be involved and some patients present with multi-organ manifestations. [5,6]

Umehara clinical, laboratory, and histologic criteria were proposed to facilitate and harmonize the diagnosis of this disease. These criteria include: Diffuse or localized swelling or masses in single or multiple organs, elevated serum IgG4 concentration (≥135 mg/dL) and histopathological examination showing marked lymphocyte and plasma cell infiltration, fibrosis, and infiltration of IgG4 + plasma cells (ratio of IgG4+ to IgG+ cells greater than 40% and greater than 10 IgG4+ plasma cells/high-power field). Definite cases of IgG4-RD must meet all 3 criteria [7].

The epidemiology of the IgG4-RD remains poorly described, but certain striking demographic features are evident. It affects mainly adults and more commonly men (sex ratio 0,8) [8]. The median age is 60 - 65 years [6]. We herein described a sixty years old woman with left lymphoplasmacytic pleuritis finally identified as having IgG4-related disease after pleural biopsy. Autoimmunity , genetic susceptibility and some microorganisms such as Helicobacter pylori have been suggested to be involved as predisposal factors [9,10]. Our patient has been treated for helicobacter pylori gastric infection several years before her pleural effusion.

Pleural manifestations of IgG4-RD can occur alone, with parenchymal lung lesions or with extrapulmonary manifestations [9]. To the best of our Knowlege, only 9 cases of pleural IgG4 RD with no other organ involevement are available on data [11]. We have summarized these 9 cases and the present case in Table 2.

Table 1. Results of laboratory workup

Laboratory workup	Value	Normal range
peripheral white blood cell (µL)	6400	4000-1000
Hemoglobine(g/dl)	13,3	12-16
Plaquettes (µL)	230000	150000-450000
C-reactive protein (mg/dL)	1,2	<5
erythrocyte sedimentation rate (mm/h)	90	<30
Creatinine (µmol/l)	64	44-106

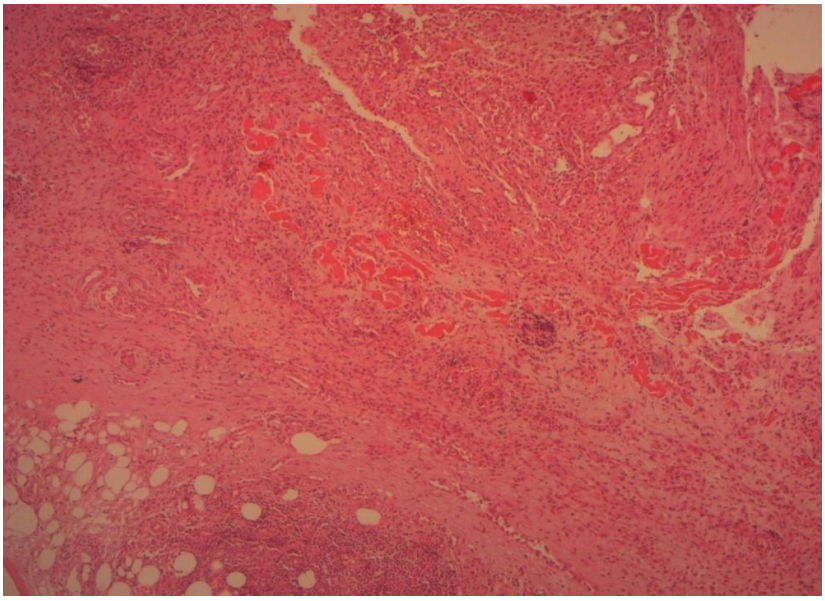

Fig. 1. A diffuse and dense inflammatory infiltrates of the parietal pleura with fibinous exsudate (HE x 50)

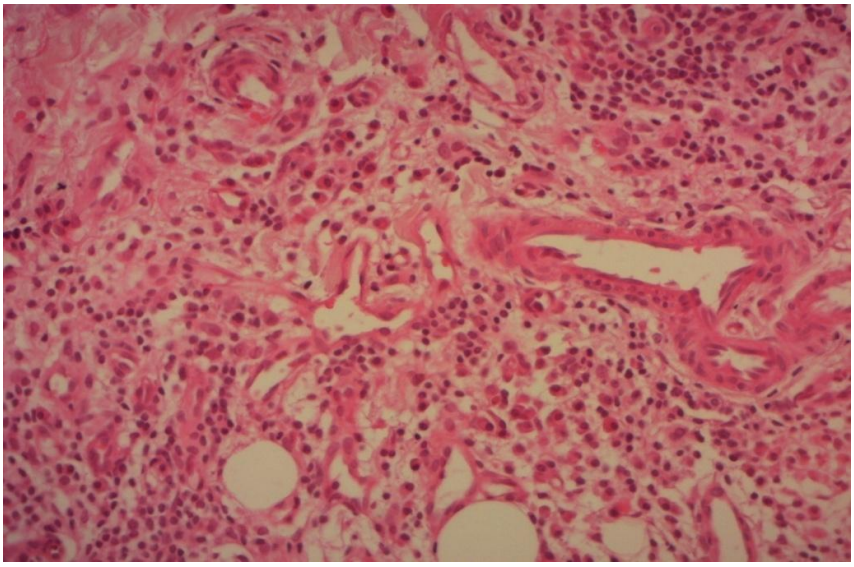

Fig. 2. The inflammatory infiltrates was composed by lymphocytes and numerous plasma cells (HE x 200)

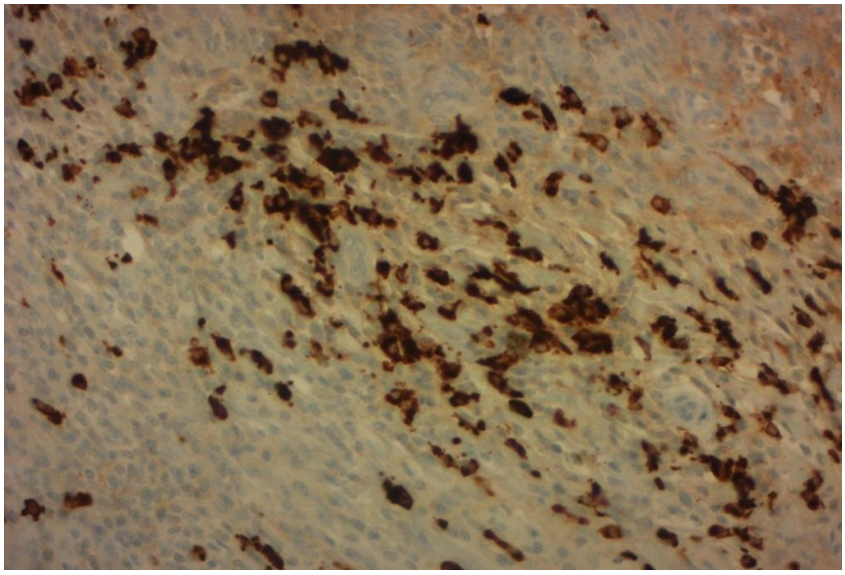

Fig. 3. Numerous plasma cells stained with IgG4 (IgG4 x 200)

Table 2. Reported cases describing IgG4 related pleural disease

Author	Sex	Age	Side	IgG4 (mg/ml)		Pathological features
				Serum	PL	
Yamashita and et al. [24]	M	74	Right	NA	NA	Lymphoplasmacytic infiltration + fibrous thicking ofvisceral pleura
Yamamoto and et al. [16]	M	78	Bilateral	483	590	Lymphoplasmacytic infiltration + mild fibrosis
Sekigushi and et al. [15]	F	29	Bilateral	136	NA	Lymphoplasmacytic infiltration + mild fibrosis
Ishida and et al. [25]	F	71	Right	684	NA	Lymphoplasmacytic infiltration + fibrosis
Ishida and et al. [26]	F	74	Bilateral	740	NA	Lymphoplasmacytic infiltration + fibrosis
Kato and et al. [11]	M	69	Bilateral	277	571	Lymphoplasmacytic infiltration + fibrosis
Corcoran and et al. [27]	M	63	Right	284	NA	Lymphoplasmacytic infiltration without fibrosis
Gajewska et al. [28]	M	58	Right	141	NA	Lymphoplasmacytic infiltration + fibrosis
Kita et al. [21]	M	65	Bilateral	164	NA	Lymphoplasmacytic infiltration + fibrosis
Present case	F	60	Left	573	NA	Lymphoplasmacytic infiltration + fibrosis

Zen and et al. [4] reported 21 patients with IgG4-related lung and pleural disease among whom four had isolated pleural disease and one of them had combined pleural and lung manifestations . All five patients had nodular pleural thickening. Chylothorax was described in one patient with IgG4-related pleuritis confirmed on thoracoscopic biopsy [11].

Most common parenchymal lung presentations are mass-like focal opacity , interstitial lung infiltrates [12,13], airways stenosis and tumor [14]. Pulmonary hypertension has been described as well [15].

Approximately half of patients with both parenchymal and pleural IgG4-RD manifested respiratory symptoms such as cough, sputum production, and dyspnea. Fever and weight loss were less common [8,16].

In our case, chest pain was the main symptom in thoracic manifestations.

In the majority of cases , the pleural fluid was exudative with cellular constituents comprising mainly of lymphocytes and plasma cells [17].

Pleuroscopy using a flexirigid videothoracoscope is used for the diagnosis of 90% of pleural effusion with unknown etiology [18]. In our case, the diagnosis was made by transparietal pleural biopsy.

For the histopathologic diagnosis of IgG4-RD, the presence of 2 of the following 3 major features is required: dense lymphoplasmacytic infiltrate, fibrosis arranged at least focally in a storiform pattern and obliterative phlebitis [19] but rigorous diagnostic criteria for IgG4-related lung and pleural diseases have not been established, marked IgG4-positive plasma cell infiltration in the biopsy specimens is accepted [4] .

The majority of patients with IgG4-related disease have elevated serum IgG4 concentrations, but the range varies widely. Approximately 30% of patients have normal serum IgG4 concentrations [18].

Sah et al. [20] had shown in their data that Serum IgG4 level is elevated (>140 mg/dL) in only 70% of patients with systemic IgG4-RD. That was the case of our patient. She also had a normal range of serum IgG4 concentration.

Although no randomized treatment trials have been conducted, several points about treatment are clear.

Aggressive treatment is needed when vital organs are involved, because IgG4-related disease can lead to serious organ dysfunction and failure. However, not all manifestations of the disease require immediate treatment. Some patients with IgG4-related disease may not require systemic therapy [18] like some asymptomatic patients with pleural thickening or mass [4]. In our case, spontaneous regression of pleural effusion was noted during follow up.
Glucocorticoids are typically the first line of therapy. Typical treatment consists of oral prednisone ranging from 30 mg/d to 1 mg/kg/d. Favorable response is usually observed after 2 to 4 weeks of corticosteroid. The prednisone dose is gradually tapered over the following several months [16]. When contraindication , appearence of adverse effects or recurrence during corticosteroid therapy the use of immunomodulating agents such as azathioprine or methotrexate is required [21].

Both intrathoracic and extrathoracic IgG4 –RD responded generally well to treatment.

Long-term follow-up data on IgG4-related diseases is still poor and it seems difficult at this point to conclude that IgG4- related disease increases the risk of pulmonary adenocarcinoma. There have been 2 reports describing a relationship between IgG4-related disease and malignant lymphoma. [22,23].

It is necessary to follow the history of patients with IgG4- related lung disease for longer to accurately reveal the risk of lung cancer, malignant lymphoma or systemic involvement. IgG4-related pleural disease might thus have a relatively favorable prognosis [23].

CONCLUSION

IgG4-related disease is a recently recognized condition with pathological features that are consistent across a wide range of organ systems.

There have been few reports of IgG4-related pleural disease, however, the present case is original due to the fact that our patient was diagnosed to have IgG4-related localized pleural disease based on the findings of a percutaneous pleural biopsy. The IgG4-related disease should be considered in the differential diagnosis of recurrent pleuritis.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline patients consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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