Pleural effusion related to IgG4

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Purpose of review
The causes of exudative pleural effusions are diverse and frequently remain unclear despite exhaustive examinations. Recently recognized IgG4-related disease (IgG4-RD) is a fibroinflammatory disorder that can affect nearly any organ including the lungs. This review will focus on the involvement of IgG4 in exudative pleural effusion of unknown cause.

Recent findings
IgG4 is found to be involved in a proportion of patients with undiagnosed pleural effusions. Pleural involvement in IgG4-RD can be seen in isolation or association with other organ disease. Pleural thickening and/or effusion are common clinical features of IgG4-related pleural lesions, and this condition is histologically characterized by a lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells in the pleura. Although the pathogenesis of IgG4-RD is poorly understood, there is a growing body of evidence that indicates an antigen-driven process requiring T-cell and B-cell interaction in which autoantibodies, plasmablasts, follicular helper T cells and CD4+ cytotoxic T lymphocytes participate.

Summary
The possibility of IgG4-related pleural lesion should be considered in patients with pleural effusion of unexplained cause when lymphoplasmacytic infiltration is seen in a pleural biopsy specimen. This condition is responsive to systemic steroid therapy.

Keywords
corticosteroid, fibrinous pleuritis, IgG4-related disease, nonspecific pleuritis, pleural thickening

INTRODUCTION

Pleural effusion is a common presentation, originating from a wide range of disorders, including congestive cardiac failure, pneumonia and cancer [1–4]. The cause of a pleural effusion frequently remains unclear after thoracentesis. Light's criteria are used to help differentiate exudates from transudates by measuring the protein and lactate dehydrogenase (LDH) concentrations in the pleural fluid and the serum [2,4], and algorithms for the investigation of exudative pleural effusion have been developed [1,5–7]. Nonetheless, the cause of exudative effusion remains uncertain in a substantial percentage of patients with lymphocytic pleural effusion after extensive examinations including thoracoscopic pleural biopsy [8,9]. Approximately 30% of cases of exudative pleural effusion are reported to be diagnosed with nonspecific pleuritis, that is no specific diagnosis, even after a complete investigation including thoracoscopy, and 12–15% of nonspecific pleuritis are ultimately diagnosed with pleural malignancy after a mean interval between thoracoscopy and the final diagnosis of 4.4–9.8 months [10,11]. Therefore, 12–16 months of follow-up is suggested following thoracoscopy for patients with nonspecific pleuritis to exclude malignancy [12–16]; however, unexplained pleural effusions often present a management dilemma for clinicians because of ongoing uncertainty about the possibility of a false-negative result from sampling error. In addition, the clinical course of such pleural effusions varies, for example resolving, persistent and progressive. Hence, new approaches are needed to detect their causes. Recently, increasing attention has been drawn to IgG4-related disease (IgG4-RD), a fibroinflammatory disorder of

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KEY POINTS

- IgG4-RD accounts for a proportion of patients with pleural effusions of idiopathic cause.
- Pleural effusions occur in IgG4-RD with or without associated extrathoracic manifestations.
- The possibility of IgG4-RD should be considered in patients with unexplained pleural effusions showing IgG4-positive plasma cell infiltration in pleural biopsies and/or pleural fluid cell blocks.
- IgG4-related pleural lesions are responsive to systemic steroid therapy.

uncertain cause that affects various organs including the pleura. Several lines of evidence indicate that IgG4-RD accounts for a proportion of patients with pleural effusions of idiopathic cause.

IgG4-RELATED DISEASE

IgG4-RD is a chronic, systemic fibroinflammatory disorder characterized by lymphoplasmacytic infiltration of IgG4-positive plasma cells, storiform fibrosis, obliterative phlebitis and often but not always elevated serum IgG4 levels [17,18]. IgG4-RD was first described in the pancreas, formerly known as autoimmune pancreatitis [19], and subsequently salivary and lacrimal glands which has long been known as Mikulicz's disease [20]. Currently, IgG4-RD is shown to affect essentially any organ system including biliary tree, kidneys, retroperitoneum, prostate, aorta, pericardium, lungs, thyroids, lymph nodes, meninges and skin.

Thoracic involvement can be seen in approximately 40% of IgG4-RD patients. In a Chinese IgG4-RD patient cohort the frequency of the thoracic involvement was reported to be 87 of 248 (35.1%) patients and pleural effusion and thickening were noted in 4.6 and 16.1%, respectively [21]. Consistent with these results, 22 of 53 (41.5%) IgG4-RD patients had pulmonary manifestations, and three of 22 (13.6%) presented with pleural thickening/effusion in a UK-based cohort of IgG4-RD patients [22▪]. The pleural manifestations of IgG4-RD include pleural mass, pleuritis with fibrosis (nodular or diffuse pleural thickening), and pleural effusion [23]. Although thoracic involvement in IgG4-RD is frequently observed in association with other organ disease such as pancreatitis and sialadenitis [21,22▪,24], it should be emphasized that pleural effusions in IgG4-RD without other organ involvement are also increasingly recognized [25▪,26–28,29▪,30▪▪]. Pleural effusions in IgG4-RD are exudative with cellular constituents rich in lymphocytes and plasma cells. Histopathological examination of biopsied pleura reveals fibrinous pleuritis with lymphoplasmacytic inflammation including numerous IgG4-positive plasma cells and active fibrosis. Plasma cell infiltration with more than 10 IgG4-positive plasma cells/high power field and an IgG4/IgG-positive plasma cell ratio of more than 40% are suggestive of IgG4-RD for biopsied specimens [31].

Two independent studies have recently reported the association of IgG4 with pleural effusions of idiopathic cause [29▪,30▪▪]. Murata *et al.* [29▪] reported that 12 of 35 (34%) patients with pleural effusions undiagnosed during follow-up (median, 5 years; range, 1–10 years) were found to have marked IgG4-positive plasma cell infiltration in the pleura by IgG4 immunostaining along with elevated effusion IgG4 concentrations (Figs. 1 and 2). This study was the first to estimate the frequency of the IgG4-associated cause in idiopathic pleural effusions. Consistently, Kasashima *et al.* [30▪▪] reported that 8/22 (36%) of patients with fibroinflammatory pleural lesions of idiopathic cause met defined diagnostic criteria for IgG4-RD. In this study, 6/8 (75%) patients with IgG4-related pleural lesion had pleural

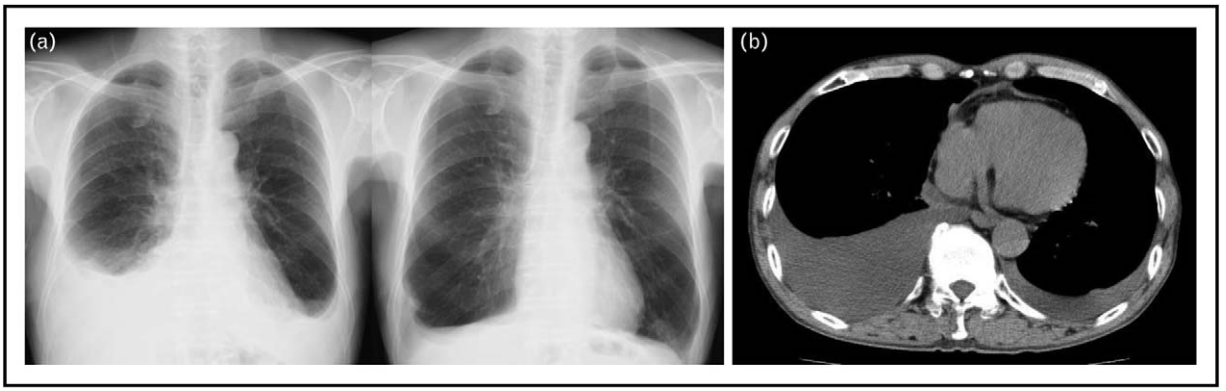

FIGURE 1. (a) Chest radiographs of IgG4-related disease with bilateral pleural effusions in a 75-year-old man. Before (left) and 2 months after the steroid therapy at prednisolone 25 mg/day (right). (b) Chest computed tomography scan of the same patient before the steroid therapy. No specific finding is seen except pleural effusion.

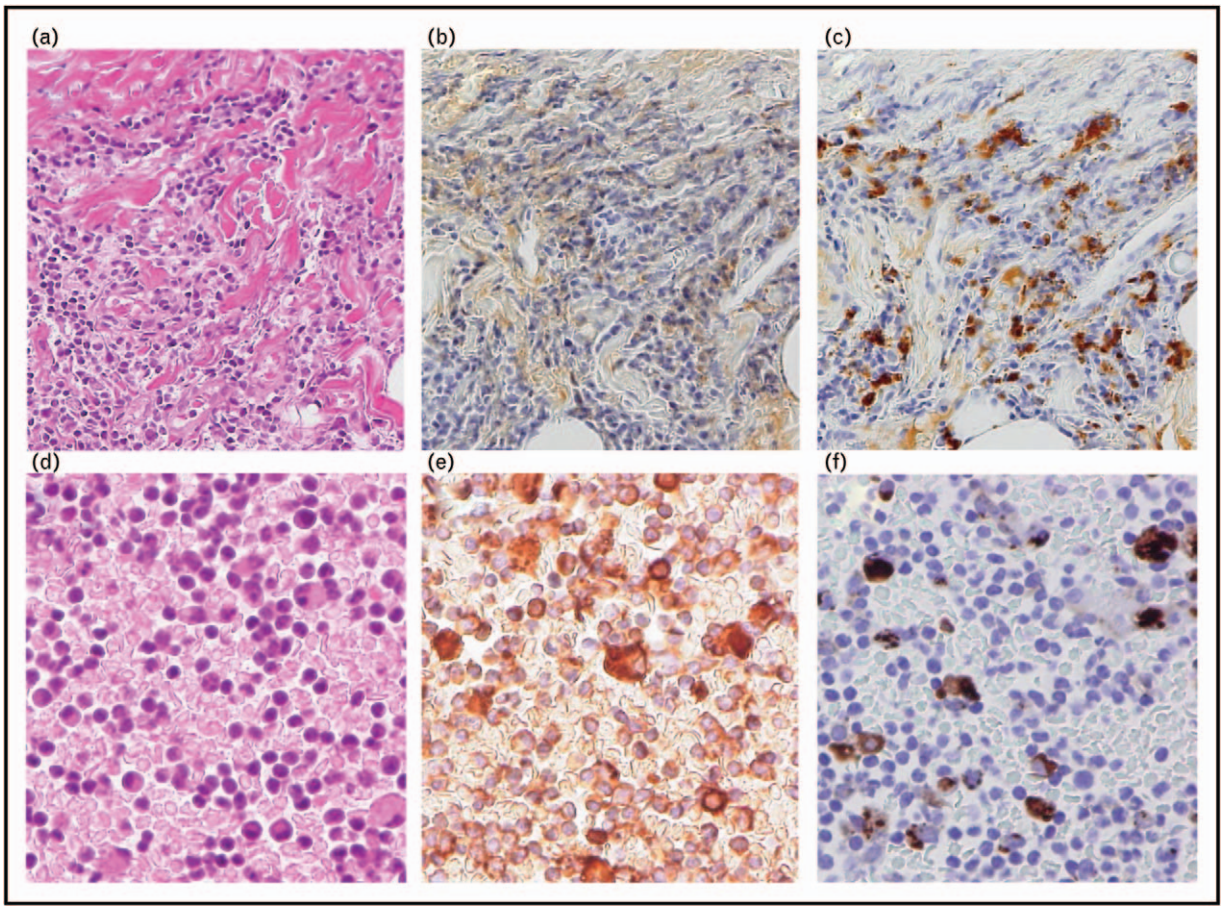

FIGURE 2. Histopathological features of the parietal pleura (a–c) and pleural fluid cell block preparation (d–f) of the patient in Fig. 1. Hematoxylin and eosin staining (a and d), Immunostaining for IgG (b and e) or IgG4 (c and f), (a–c) magnification × 200. (d–f) magnification × 400. Diffuse sclerosing inflammation with lymphoplasmacytic infiltration, but no malignant cells, was identified. Fibrosis was pronounced on the side of the pleural cavity (a–c, top). The cell block was prepared at the time of relapse of pleural effusion. The parietal pleura and the pleural fluid cell block reveal the abundance of IgG4-positive plasma cells and a high IgG4/IgG-positive plasma cell ratio.

effusions, which was the most common manifestation of IgG4-related pleural lesion. No extrapulmonary involvement in IgG4-RD was observed in the majority of patients with pleural effusion in these two studies. Kasashima *et al.* also reported a comparable histological feature of IgG4-positive plasma cell infiltration in the pleural biopsy specimens and the pleural fluid cell blocks, showing the utility of pleural fluid cell blocks for supporting the diagnosis of IgG4-RD. Thus, it is worth examining cases of undiagnosed pleural effusions by IgG4 immunostaining if other causes of effusion including malignancy are excluded with detailed exploration.

DIAGNOSIS OF IgG4-RELATED PLEURAL LESION

Establishing a diagnosis of IgG4-RD is based on international consensus histopathology criteria [31] in the context of clinical, biochemical, radiological and histological correlation. The critical histopathological features are a dense lymphoplasmacytic infiltrate, obliterative phlebitis and storiform fibrosis, and the presence of more than 10 IgG4-positive plasma cells per high-power field and an IgG4/IgG-positive plasma cell ratio of more than 40% are secondary in importance. On the other hand, epithelioid cell granuloma, a prominent neutrophilic infiltrate, abscess and necrosis are relatively inconsistent with the diagnosis of IgG4-RD. It should be noted that the pulmonary histopathology in IgG4-RD is different from that of more solid organs such as pancreas or kidney, and storiform fibrosis may not be a prominent feature in thoracic IgG4-RD [22▪,23,32]. In addition, either storiform fibrosis or obliterative phlebitis cannot always be observed in biopsy specimens [33]. Overall, IgG4-RD should not be diagnosed based on biopsy alone, and careful and deliberate clinicopathological correlation is needed when pleural effusion is the only manifestation of the disease.

IgG4-RD is a disease of middle-aged to elderly patients, with an average age of 50.3 ± 14.9 years at disease onset ($n = 125$, mean $\pm$ SD, range 12–82 years) and predominates in men (60.8%) [34]. Elevated serum IgG4 ($\geq$135 mg/dl) was once presumed to be a hallmark of the disease but was not found to be observed in nearly 50% of biopsy-proven, clinically active IgG4-RD patients [34]. Consistent with this finding, pleural fluid IgG4 level may not be elevated in all patients with IgG4-related pleural lesion [29▪]. In contrast, approximately 5% of healthy individuals have elevated serum IgG4 levels. Therefore, relying on IgG4 levels alone may result in under-diagnosis or over-diagnosis, and the lack of elevated IgG4 level does not exclude this diagnosis. Inflammatory markers such as C-reactive protein and LDH levels are often within normal limits in IgG4-RD [30▪▪,35] although LDH levels were elevated in some cases [25▪,36]. In general, IgG4-RD tends to show relatively weak inflammation signs [37]. Adenosine deaminase (ADA) level in pleural fluid is associated with the activation of lymphocytes and is widely used in the auxiliary diagnosis of tuberculous pleuritis [38]. Although ADA is often normal in pleural effusions of IgG4-RD [28,30▪▪], elevated ADA levels (>40 IU/l) were also reported in pleural fluids of some IgG4-RD patients [26,39] and careful workup is needed to differentiate IgG4-related pleural lesion from tuberculous pleuritis by combination with Ziehl-Neelsen stain, PCR, cultures on solid and liquid media, IFN-γ release assay, pleural biopsy and so on.

Common radiologic features of thoracic involvement in IgG4-RD include pleural thickening, mediastinal lymphadenopathy, bronchial wall thickening and pericarditis [40,41], but these radiographic findings are not always detected in isolated pleural involvement in IgG4-RD. A fluorodeoxyglucose-PET (FDG-PET) is not recommended to detect pleural lesions because accumulation of FDG is not always noted in the pleura of patients with isolated IgG4-related pleural lesion [26,28]. When thoracic IgG4-RD is suspected, cervical and abdominal computed tomography should also be performed to examine the presence of extrathoracic lesions of IgG4-RD.

DIFFERENTIAL DIAGNOSIS

In differential diagnosis of IgG4-RD, several multiorgan diseases including sarcoidosis, connective tissue disease, lymphoma and multicentric Castleman's disease (MCD) need to be ruled out because of the association with pleural effusion and IgG4.

Sarcoidosis can often exhibit hilar/mediastinal lymphadenopathy. Serum angiotensin converting enzyme level would be useful for differential diagnosis whereas soluble IL-2 receptor level in serum may not because it can rise in both IgG4-RD and sarcoidosis. Histologically, epithelioid granuloma is common in sarcoidosis while IgG4-RD is characterized by lymphoplasmacytic infiltration rich in IgG4-positive plasma cells.

Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), two of the most common connective tissue diseases, are important in differential diagnosis. Although SLE is considered a disease of a young woman, lung involvement is more common in men. The presence of pleural disease is often accompanied by multisystem involvement [42] and clinical features of SLE including specific cutaneous manifestations can be helpful in distinguishing SLE from IgG4-RD. Serum antinuclear antibodies have been used as a serological test for diagnosis of SLE, and the pleural effusion antinuclear antibodies at a titer of at least 1 : 160 is a sensitive and specific diagnostic biomarker in SLE [43]. Patients with RA and pleural effusion are usually middle-aged men (>50 years), with high titers of rheumatoid factor, rheumatoid nodules and a higher prevalence of HLA-B8. Pleural effusion tends to occur in patients with long-standing arthritis, usually appearing years after the diagnosis of RA.

Lymphoma accounts for 6–15% of malignant pleural effusions and resembles IgG4-RD histologically. Pleural effusion cytology is important in the initial diagnosis of lymphoma [44]. Further studies including flow cytometry, morphology and immunohistochemistry are performed to determine monoclonality and karyorrhexis of lymphocytes for differential diagnosis. Although pleural involvement in lymphoma is commonly associated with widespread systemic disease, primary effusion lymphoma can occur as a distinct clinicopathological entity caused by human herpesvirus-8 and HIV infection [45,46]. In addition, there are series of cases describing lymphomas detected concurrently or asynchronously with IgG4-RD. The majority of these cases are reported to be MALT lymphomas occurring in the ocular adnexa, but lymphomas in IgG4-RD may be more varied in location and type [47]. Although it remains unknown whether IgG4-RD confers an increased risk of lymphoma, pathologists need to be aware of the potential for lymphoma to develop in patients with IgG4-RD.

MCD is a polyclonal lymphoproliferative condition characterized by lymphoplasmacytic infiltration with IgG4-positive plasma cells similarly to IgG4-RD but differs in responsiveness to corticosteroids. MCD presents multiple lymphadenopathy and involvement of lung parenchyma [35], and hence the differentiation of MCD from IgG4-RD can be sometimes difficult. MCD patients are

significantly younger than those with IgG4-RD, and serum C-reactive protein levels are elevated in contrast to those in IgG4-RD patients [48]. Elevated serum IL-6 level is also useful to distinguish MCD from IgG4-RD [48].

PATHOGENESIS OF IgG4-RELATED DISEASE

The pathophysiology of IgG4-RD remains largely unknown, but remarkable insights to the disease pathogenesis have been recently reported. IgG4 antibodies are generally known as anti-inflammatory, due to the inability to bind to complement component C1q, low affinity to Fcγ receptors and the ability to exchange Fab-arms. Consistent with these anti-inflammatory properties of IgG4 antibodies, injection of IgG1 antibodies of patients with IgG4-RD into neonatal BALB/c mice resulted in pancreatic and salivary gland injuries, but the pathogenic effects of IgG1 antibodies were attenuated when IgG4 antibodies were simultaneously injected [49▪▪]. Notably, IgG4 from IgG4-RD patients had also pathogenic activity although the extent of the injuries was significantly lower in mice injected with IgG4 than with IgG1. The same groups identified laminin 511-E8, one of the extracellular matrix proteins, as the target antigen [50]. Other target antigens identified to date include annexin A11, a 56-kDa cytosolic protein, from human H69 cholangiocyte lysates [51] and galectin-3, a β-galactoside-binding lectin [52]. Furthermore, T follicular helper (Tfh) cells that are involved in the differentiation of naïve B cells into IgG4-producing plasmablasts are found to be expanded in IgG4-RD [53]. Tfh2 cells, a subset of Tfh cells, induce Ig class switching in B cells via secretion of IL-4. The Tfh2 cell count in blood is shown to be correlated with disease activity and may serve as a potential biomarker [53,54▪]. In addition, a novel population of CD4+ effector T cells with cytotoxic function (CD4+ cytotoxic T lymphocytes) has been found to expand in the circulation and affected tissues in IgG4-RD patients [55]. This novel subset of CD4+ T cells arises from chronic antigenic stimulation, due to downregulation of the transcription factor ThPOK, and expresses SLAMF7, granzyme A, proinflammatory IL-1β and profibrotic TGF-β1, presumably associated with the fibroinflammatory condition of the disease.

TREATMENT

Treatment of pleural effusion depends on the severity of symptoms. Isolated pleural involvement of IgG4-RD without multisystem disorder usually follows a benign course, and a watchful waiting with radiographic follow-up is appropriate in patients with small and asymptomatic effusions. On the other hand, patients with pleural effusion accompanying involvement of vital organs, including aortitis, pericarditis, pancreatic enlargement and tubulointerstitial nephritis should be treated urgently because delay in treatment may result in irreversible organ dysfunction [56]. For active IgG4-RD, glucocorticoids are recognized as the first-line treatment [56] and are shown to improve pleural fluids and respiratory symptoms in patients with IgG4-related pleural lesion [25▪,26–28,29▪,30▪▪,39,57]. Japanese consensus criteria recommends prednisolone of 0.5–0.6 mg/kg/day as the initial dose, and this dose can be gradually weaned over subsequent months, depending on the improvement of clinical, laboratory and radiographic features [58]. There is no significant difference in remission induction between high (0.8–1.0 mg/kg/day) and medium doses of glucocorticoids (0.5–0.6 mg/kg/day) [59]. However, the high relapse rate both during and after glucocorticoid tapers in IgG4-RD is a hindrance to this therapy, and a maintenance dose of 5–10 mg/day of prednisolone is recommended for more than 1 year [58]. As an alternative to glucocorticoids, B-cell depletion with rituximab (1 g at days 0 and 15) has been assessed in a prospective open-label trial with 30 IgG4-RD patients, showing disease responses in 97% of patients [60]. A French retrospective study with 33 IgG4-RD patients showed the effectiveness of rituximab for both remission induction and retreatment for relapse and increased relapse-free survival [61]. The rituximab treatment resulted in a concomitant decrease in the numbers of circulating plasmablasts and CD4+ SLAMF7+ cytotoxic T lymphocytes but not CD4+ GATA3+ T_H2 cells or CD4+ CD25+ FOXP3+ regulatory T cells in peripheral blood of IgG4-RD patients [55]. These findings contribute to a better understanding of this novel immune-mediated disorder as well as other autoimmune diseases.

CONCLUSION

Pleural effusion of IgG4-RD is an under-recognized pleural condition. Pleural involvement in IgG4-RD can occur in isolation, or association with extrapulmonary manifestations. In patients with pleural effusion of unexplained cause, IgG4-RD should be considered when lymphoplasmacytic infiltration with IgG4-positive plasma cells is observed in pleural biopsy specimens because this condition responds well to systemic steroid therapy. IgG4 immunostaining of pleural fluid cell blocks can be supportive for the diagnosis of IgG4-related pleural lesion. Importantly, the possibility of IgG4-RD

should be evaluated through multidisciplinary processes in the context of clinical, radiological and histological correlation. It is presumed that pleural effusions in IgG4-RD occur at higher than expected prevalence. Further studies with large numbers of patients are needed to determine the true prevalence of pleural effusion related to IgG4.

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Conflicts of interest

There are no conflicts of interest.

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