IgG4-related interstitial lung disease: a new and evolving concept

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Purpose of review

This review examines recent advances in our knowledge of the clinical, pathological, diagnostic, and therapeutic aspects of IgG4-related interstitial lung disease (ILD).

Recent findings

A recent case series of ILD with IgG4-positive plasma cells suggested grade 1 lymphomatoid granulomatosis. The presence of the IgG4-positive plasma cells with the lack of atypical cells favored IgG4-related ILD as a diagnosis. In another case study, four out of 30 patients with autoimmune pancreatitis developed pulmonary involvement during follow-up. Elevations of IgG4 and Krebs von den Lungen-6 levels were associated and thought to be predictive of the development of IgG4-related lung disease. A retrospective analysis investigating radiological/pathologic correlation in IgG4 lung disease identified computed tomographic features pathologically corresponding to IgG4-related sclerosing inflammation in the pulmonary interstitium.

Summary

IgG4-related ILD is a new and evolving entity. It can occur with or without systemic involvement. Larger studies are necessary to elucidate the exact mechanism and clinical characteristics of this disorder.

Keywords

autoimmune pancreatitis, IgG4, interstitial lung disease

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Introduction

IgG4-related disease is a relatively newly discovered systemic sclerosing disease typically associated with autoimmune pancreatitis (AIP) [1–3]. Other organ involvements take the form of sclerosing cholangitis, sclerosing cholecystitis, sclerosing sialadenitis, retroperitoneal fibrosis, and interstitial nephritis [4–7]. Recently, lung diseases related to IgG4 have been described to occur with or without other organ involvement. These diseases include interstitial lung disease (ILD), pulmonary inflammatory pseudotumor, and lymphomatoid granulomatosis (LYG). This review will focus on IgG4-related ILD and examine recent advances in the epidemiology, pathology, diagnosis, and treatment of the disease.

Epidemiology and pathology

From the collective reports available describing IgG4-related ILD, it appears that male patients are affected more than female patients [8–13,14•,15,16•,17]. Most of these cases occur in combination with AIP, which also appears to have a general preponderance for men. Taniguchi *et al.* [12] provided the first description of ILD associated with AIP in a 63-year-old man who presented with honeycombing of bilateral lower lung fields detected on an abdominal computed tomography (CT) scan during follow-up of AIP. A transbronchial lung biopsy from the affected area showed marked thickening of the alveolar septa with infiltration by lymphocytes and IgG4-positive plasma cells, suggesting IgG4-associated lung disease. Although most cases occur in combination with AIP, isolated IgG4-related ILD can occur. Takato *et al.* [13] reported on a 59-year-old man who was found to have reticular changes in both lower lungs on chest radiograph with subsequent chest CT scan showing ground-glass opacities and traction bronchiectasis in the lower lobes. Surgical lung biopsy obtained by video-assisted thoracoscopic surgery (VATS) under histological examination showed a pattern similar to fibrotic nonspecific interstitial pneumonitis (NSIP). Subsequent immunostaining for IgG4 showed infiltration of the interstitium with IgG4-positive plasma cells. The authors noted that AIP was not present at this time and suggested that IgG4-related ILD can occur in the absence of AIP. However, it is unclear from the report how the authors concluded there was no AIP, as the results of a CT of the abdomen or endoscopic retrograde cholangiopancreatography (ERCP) were not presented in the study.

The true incidence of IgG4-related ILD and moreover the incidence of AIP are unknown. A study that followed

30 patients with the diagnosis of AIP showed that four of them eventually developed ILD [15]. The onset of lung involvement varied from onset of AIP in one patient to up to 1 year later in another patient. In a separate study that examined the long-term prognosis of AIP, Hirano *et al.* [17] reported that three of the 19 patients initially treated for AIP with corticosteroids developed ILD. The period of onset of ILD was 15, 26, and 45 months after the initial diagnosis of AIP for the three cases.

The histological hallmark of IgG4-related ILD appears to be the presence of an interstitial mononuclear infiltration of lymphocytes and IgG4-positive plasma cells. The IgG4-positive lymphoplasmacytic infiltration typically occurs along the bronchovascular bundles, interlobular/alveolar septa and may extend into the pleura [12,14•, 16•]. Furthermore, the mononuclear cells infiltrate small arterial and venous structures in the lung; as a result, the vessels are stenosed and show obliterative arteritis and phlebitis. The differences between the vascular involvement described here and a true vasculitis include a lack of significant fibrinoid necrosis and granulomas. Furthermore, the demonstration of abundant IgG4-positive plasma cells is paramount to confirming the diagnosis. In our opinion, predominance of IgG4-positive plasma cells should be uniform throughout the area of plasma cell infiltration, and careful examination should be exercised to exclude focal accumulation of IgG4-positive plasma cells that can be seen in certain infectious or vasculitic processes. As for the percentage of IgG4-positive plasma cells that is required to make a confident diagnosis of IgG4-related ILD, to date there is no clear consensus established from the current available literature. One immunohistochemical study that examined three cases of IgG4-related ILD showed the percentage of IgG4-positive plasma cells among IgG-positive plasma cells to be 46, 47, and 85%, respectively [14•]. In another study, Zen and coauthors studied nine cases of inflammatory pseudotumor with presence of IgG4-positive plasma cells and found the ratio of IgG4 to IgG-positive plasma cells to be $56.5 \pm 12.5\%$. This was significantly higher than the frequency of IgG4 plasma cells of $3.4 \pm 0.4\%$ found in the seven cases of idiopathic interstitial pneumonia that they used as disease control for comparison. Unfortunately, other studies have used less accurate terms such as 'abundant' or 'numerous' to describe the degree of IgG4-positive cell tissue infiltration or they have simply used the presence of IgG4-positive plasma cells as criteria for diagnosing IgG4-related ILD [12,13,16•]. The intensity of IgG4-positive cell infiltration in AIP has been reported by Kamisawa *et al.* [7], but due to the relatively rare occurrence and evolving concept of this disease in the lungs, it may prove more difficult to determine the percentage of IgG4-positive plasma cells that is necessary to make a confident tissue diagnosis. However, we propose that future studies should include the ratio of IgG4 to IgG positive cells in proposed cases as well as the extent of their distribution in the tissue to aid in creating diagnostic criteria for the disease.

Despite the marked presence of IgG4-positive plasma cells, monoclonal expansion of lymphocytes and cellular atypia suggestive of a neoplastic process are not seen in IgG4-related ILD. In addition, Epstein–Barr virus expression should be absent or extremely minimal. This appears to be important as low-grade LYG may histologically resemble IgG4-related ILD with the presence of interstitial mononuclear infiltrate and lymphocytic angiitis. Features that suggest IgG-related ILD as opposed to LYG include a high percentage of IgG4-positive plasma cells and absent or rare Epstein–Barr virus [14•].

It is important to note that there are case studies that claim lung involvement as one of the systemic manifestations of IgG4-related disease when there is no actual lung biopsy showing IgG4-positive plasma cells [11,15,17]. As the presence of IgG4-positive plasma cells appears to be essential to the diagnosis of IgG4-related ILD, careful diagnostic criteria that include an adequate tissue biopsy need to be used to support the diagnosis of IgG4-related ILD in future studies.

Diagnosis of IgG4-related interstitial lung disease

Many studies that examined IgG4-related ILD have shown several serological assays that may aid in the diagnosis. Although IgG4 is the least abundant of all the subclasses of IgG, responsible for only 3–6% of total serum IgG, high levels of serum IgG4 have been seen in almost all of the patients reported to have IgG4-related ILD. However, an increased serum level of IgG4 can be also be seen in autoimmune and allergic disorders, chronic asthma, and pemphigus vulgaris [18–20]. In addition, serum levels of Krebs von den Lungen-6 (KL-6) also appear to be increased in many of the reported cases of IgG4-related ILD [12,15]. Serological markers suggestive of another systemic autoimmune disease or vasculitis such as antinuclear antibody, anti-ds antibody, rheumatoid factor, anti-SS-A, anti-SS-B, anti-PR3 anti-neutrophil cytoplasmic antibodies (ANCA), anti-myeloperoxide (MPO) ANCA are typically negative or mildly elevated [11,13, 15,16•].

In two studies that have pulmonary function values available, it appears that lung volumes such as vital capacity or total lung capacity are preserved whereas diffusion capacity is moderately to severely reduced [13,15]. Therefore, it is understandable that many of these patients complain of cough or shortness of breath with a moderate to severe degree of hypoxemia. One can

speculate that these findings may be due to the involvement of the vascular structures in the lung.

Inoue *et al.* [16•] performed a retrospective analysis of the radiological characteristics in 13 patients with a diagnosis of IgG4-related lung disease and correlated these with pathologic findings. The authors identified four predominant radiographic patterns associated with IgG4-related lung disease. The majority showed interstitial patterns including alveolar interstitial type with honeycombing, bronchiectasis, and diffuse ground-glass opacity ($n = 2$), and thickened bronchovascular bundles and interlobular septa ($n = 5$). Other patterns such as solid nodules or mass-like lesions ($n = 4$) and round-shaped ground-glass opacities ($n = 2$) were also observed. For the patients who showed radiographic patterns consistent with an interstitial process, the initial radiographic diagnosis included NSIP, sarcoidosis, and lymphoproliferative disorders. Patients with ground-glass opacities in radiological studies showed inflammation with mononuclear cells in the interstitium and occasional lymphoid follicles in biopsy specimens. There was no temporal heterogeneity, and the pattern was considered most consistent with NSIP. Honeycomb and bronchiectatic findings on radiographs correlated histologically with thickened alveolar structures with interstitial scarring and cystic dilation. Finally, areas of thickened bronchovascular bundles or interlobular septa correlated with stromal fibrosis and lymphoplasmacytic inflammation along the peribronchiolar interstitium in tissue specimens. Obliterative phlebitis or arteritis was only seen in cases that had nodular or mass-like lesions on radiographs. This study had some limitations in that only seven of the 13 cases had lung biopsy to confirm the presence of IgG4-related lung disease.

Treatment and prognosis

For the most part, IgG4-related ILD appears to be one of the systemic manifestations of IgG4 autoimmune sclerosing disease. However, the true extent of its relation to systemic IgG4 disease remains obscure. As for treatment strategies, corticosteroids appear to be effective in the majority of the reported cases [11–13,14•,15,17]. The most commonly used dose was prednisolone at 1 mg/kg/day. This is typically followed by improvement or resolution of radiographic changes in weeks to a few months. Corticosteroids were then tapered and maintained for weeks to even up to 29 months. In some cases, doses of prednisolone that were higher to maintain remission of AIP were necessary to treat IgG4-related ILD [17]. One case of IgG4-related ILD that did not improve with prednisolone was treated effectively with cyclosporine [14•]. Spontaneous resolution of IgG4-related ILD has been seen, though the patient relapsed after 18 months with development of involvement in the pancreas and kidney [16•].

Decrease in serum IgG4 levels usually correlates with the radiographic and clinical improvement of patients in many of the reported cases [13,14•,15]. In addition to its diagnostic indication for IgG4-related ILD, perhaps serum IgG4 levels may also be used to assess the effectiveness of the treatment and to follow these patients for recurrences.

The prognosis of the disease still remains to be elucidated. However, due to the relative effectiveness of corticosteroids, though the data are limited, IgG4-related ILD appears to have a favorable clinical course. Recurrences have been reported especially when the dose of prednisolone is tapered and therefore close monitoring would be imperative.

Conclusion

IgG4-related ILD is a new and evolving concept. It typically occurs in combination with systemic IgG4 autoimmune sclerosing disease. The diagnosis requires the clinician to suspect this condition with the combination of key clinico-radiologic-pathological features. Differential diagnosis may include idiopathic interstitial pneumonitis, sarcoidosis, and lymphoproliferative disorders. Response to corticosteroids is good, and follow-up is needed to observe for recurrence. Future studies with pathologic diagnosis are needed to further elucidate the true nature of this disease.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 526).

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