The Many-Faced God: IgG4-Related Disease- a Clinical Review.

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Abstract:

IgG4-related disease (IgG4-RD) is a complex fibroinflammatory disease first identified in 2003. It has been described in every organ. Type-2 helper T cell immune-mediated responses are thought to be pathogenic. Serum IgG4 levels are not always elevated and immunohistochemical analysis is the gold standard for diagnosis. When available, histopathology typically reveals lymphoplasmacytic infiltration, fibrosis, and abundant IgG4-positive plasma cells.

Here, we review clinically salient features of IgG4-related disease including its epidemiology, pathophysiology, diagnosis, and emerging treatment strategies.

Keywords: IgG4-RD, Pericarditis, Autoimmunity, Aortitis

1. Introduction

IgG4-related disease (IgG4-RD) is a complex, fibroinflammatory condition that remains relatively unknown. Unrecognized for over a century, it was formally identified in 2003 when the first reported case appeared in the literature. Mikulicz's disease, Riedel's thyroiditis, Morbus Ormond, or Küttner's tumor are single-organ manifestations of IgG4-RD that were first discovered in the 19th century at the advent of histopathological analysis.[1] IgG4-RD links many conditions like these, once regarded as isolated, single-organ diseases.[2] Now, thanks to ongoing diagnostic advancement, it is apparent that IgG4 is a condition comprised of a collection of disorders that share particular pathologic, serologic, and clinical features[2,3].

In 2014, Atallah, et al reported a case of IgG4-RD presenting with effusive-constrictive pericarditis, cardiac tamponade, and hepatopathy[4]. Cardiovascular manifestations of IgG4-RD are extremely rare, and this particular triad had not been previously published. Case reports like this one, detailing novel presentations of this unique disease process, continue to appear in the literature and underscore our evolving understanding of this emerging clinicopathological entity. It is important for clinicians to consider and appropriately diagnose IgG4-related disease because it is treatable and, more importantly, because early diagnosis improves patient outcomes.

2. Epidemiology

IgG4-RD epidemiological data is scarce. 62 to 83% patients are men and older than 50 years of age. 40% of patients with IgG4-RD have a history of allergic diseases such as bronchial asthma, chronic sinusitis, or seasonal allergies[4]. It is believed to be underdiagnosed in Europe and North America, where awareness is low when compared to Asian countries, where the disease was originally discovered[5]. In a cohort of 235 Japanese patients with IgG4-RD, 60% presented with pancreatitis, further 34% with sialadenitis, 23% with tubulointerstitial nephritis, 23% with dacryoadenitis, and 20% with periaortitis. In total, 58% had multiple organs involved, whereas the

most frequent solitary manifestation was pancreatitis[6]. It is possible however, that European/American, and Asian patients differ in the overall prevalence of IgG4-RD, but also in the frequency of certain organ manifestations[7].

3. Pathophysiology

IgG4-RD has now been described in essentially every organ. The most commonly involved organs are the major salivary glands, the orbital and periorbital tissues, the pancreas, the retroperitoneum, and lymph nodes[8]. It is thought to be an immune-mediated condition; however, the exact pathophysiologic mechanism of IgG4-RD remains unknown. Autoimmunity, infectious agents, and molecular mimicry are thought to be potential triggers for disease development. Type-2 helper T cell immune-mediated responses are thought to be pathogenic[9]. Okazaki, et al suggest that depletion of naive Treg cells in the periphery may allow autoreactive CD4+ T cell infiltration in various organs. These CD4+ T cells activate macrophages and induce further proinflammatory activation[10]. Interestingly, Sakamoto, et al reported that IgG4 and soluble interleukin-2 receptors (sIL2R) were high in patients with coronary artery stenosis over 50%, suggesting that IgG4-related immuno-inflammation may be associated with the pathogenesis of coronary atherosclerosis [11]. Conversely, conflicting data suggests that IgG4-positive plasma cells might increase as a protective response of chronic inflammatory change such as atherosclerosis, rather than play a critical role in its generation[12].

4. Diagnostic Approach

IgG4-related disease often causes major tissue damage and can lead to organ failure, but it generally does so subacutely[3]. Its clinical presentation can be insidious and physical findings vary depending on the organ system involved.

Elevated serum IgG4 levels were initially thought to be the key to diagnosing IG4-RD. It turns out, they are not. In fact, elevated IgG4 is not present in a significant amount of cases of histologically proven IgG4-RD. Only a small minority of patients with elevated IgG4 levels actually have definite IgG4-

RD[13]. The diagnostic value of IgG4 levels strongly depends on the underlying population. Studies using databases of patients with any IgG4 elevation usually report a sensitivity for IgG4-RD at ~90% and a specificity of 80% or less[13]. Alternatively, among biopsy-proven patients, the retrospective diagnostic value of IgG4 levels appears to be poor (approximately 51%)[14].

One possible explanation for these findings is the "Prozone effect." This is due to excess antigen in the test system, which can inhibit agglutination, and leads to artificially low serum levels of IgG4. This can be prevented by proper sample dilution[14,15].

Patients with elevated IgG4 tend to have more extended organ involvement, higher inflammatory marker alterations, and lower complement levels than patients who do not[5]. IgG4 molecules may contribute directly to tissue injury in some fashion (immune complexes), but it now seems unlikely that IgG4 itself is the primary element driving the pathophysiology[8]. Recent research suggest that B cells and other cells of their lineage, particularly plasmablasts, play an important role in IgG4-RD. Both B cells and plasmablasts are elevated in active disease regardless of serum IgG4 concentrations[8,16]. Plasmablasts, in particular, may become important in both diagnosing IgG4-RD and monitoring disease activity[8].

Histopathology is ultimately key and biopsy remains the gold standard for diagnosis. The three central diagnostic features include lymphoplasmacytic infiltrates that stain positive for IgG4 bearing plasma cells in affected organs, storiform fibrosis, and obliteritive phlebitis[2].

Diagnostic imaging may be helpful, but plays a minor role in the diagnosis of IgG4-RD. The majority of imaging appearances are non-specific and the distinction between IgG4-RD and potentially more serious conditions such as malignancy is usually not possible based on imaging findings alone[17].

One area of research that is proving to be an exception is, PDG-PET/CT imaging which can be of diagnostic and prognostic value[12]. PET scans can detect IgG4-related lesions as long as there is active inflammation. Although the

relationship between the initial high intensity FDG uptake in the IgG4-related lesion and its subsequent response to corticosteroid treatment has not been proven, current research suggests that lesions without FDG uptake do not respond to corticosteroid therapy. Persistent uptake of FDG during corticosteroid therapy is considered to be a continuation of active inflammation, which indicates an increase of future relapse[12]. This data suggests that 18F-fluorodeoxyglucose positron emission tomography (FDG PET)/CT may be an effective diagnostic utility in IgG4-RD. It can highlight active inflammatory lesions and estimate the extent of disease. In this way it can be used for staging and monitoring disease activity, for assessing response to treatment, and for guiding biopsies[5].

5. Treatment

Corticosteroids are the mainstay of treatment. Patients typically have a robust response. Treatment is indicated in all patients with symptomatic and active IgG4-RD, and is particularly important for patients with IgG4-related kidney disease, autoimmune pancreatitis, fibrotic lung disease, and aortitis. Patients at risk for irreversible damage in any organ should be treated urgently regardless of symptoms. Indications for urgent treatment include tubulointerstitial nephritis, autoimmune pancreatitis, biliary tract disease, retroperitoneal fibrosis, and aortitis[8].

The extent of fibrosis is an important determinant in the responsiveness to immunosuppressive therapies[18]. As the disease progresses and fibrosis increases, responsiveness to corticosteroid therapy decreases. For this reason, early treatment is critical to improving patient outcomes. The typical treatment regimen is Prednisone 40 mg/day for 2 to 4 weeks and then slowly tapered over 2 to 6 months. The effects of corticosteroid therapy can be confirmed by concomitant decreases in serum IgG4, IgG, and IgE levels and inflammatory markers, like ESR, CRP and sIL2R. As mentioned, improvement in the size and amount of FDG uptake in inflammatory lesions may also be seen on CT or PET imaging[12].

Steroid-sparing agents are typically used in the event of relapse or in conjunction with glucocorticoids for severe disease or if relapse could lead to significant morbidity or mortality[19]. Despite this approach, there is no high-quality evidence to suggest that agents such as methotrexate, azathioprine, mycophenolate mofetil, and other medications employed for this purpose are as effective as treatment with corticosteroids[8].

The CD4+ SLAMF7+ cytotoxic T cell, believed to be central to the pathogenesis of IgG4-RD, is also a potential therapeutic target in the future[8].

6. Conclusion

Greater familiarity with the many faces of IgG4-RD will benefit patients by early recognition, and prompt treatment, thereby limiting morbidity, reducing unnecessary testing, and maximizing patient outcomes. Increased cognizance of the multi-organ potential of the IgG4-RD disease entity, as well as additional research is needed. Other essential research targets are the elucidation of possible antigenic triggers initiating IgG4-RD and B- and T-cell interactions, including the mechanisms ultimately leading to fibrosis[20].

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