IgG4 Related Disease of the Head and Neck

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Abstract IgG4 related disease of the head and neck region represents one of the more common manifestations of IgG4 related disease. Involvement of the submandibular and parotid glands, the orbit and thyroid represent some of the more common sites involved by IgG4 related disease. Eosinophilic angiocentric fibrosis, Mikulicz disease and Riedel thyroiditis are also members of the family of IgG4 related disease. Clinically, the disease is characterized by tumefactive lesions, often multicentric, that show a swift response to immunosuppressive therapy. An elevated serum IgG4 represents the only validated blood based biomarker. However, elevated serum IgG4 is detected in only half the patients with this disease. Histology continues to represent the gold standard for the diagnosis of IgG4 related disease: storiform-type fibrosis and obliterative phlebitis constitute characteristic features of this disease. A definitive diagnosis of IgG4 related disease also requires the presence of elevated numbers of IgG4 positive plasma cells as well as an IgG4 to IgG ratio of greater than 40 %. In isolation, elevated numbers of IgG4 positive plasma cells represents a non-specific feature, detected in a variety of other inflammatory as well as neoplastic diseases. Attention to the clinical context, histological features, as well as an elevated IgG4 to IgG ratio is critical to avoiding overdiagnosis of IgG4 related disease.

Keywords IgG4 related disease · IgG4 · Eosinophilic angiocentric fibrosis · Thyroiditis

IgG4 related disease involving the head and neck represents one of the more common manifestations of this disease [1, 2]. IgG4 related disease involves the major and minor salivary glands as well as the orbital region. In addition, involvement of the upper aerodigestive tract and paranasal sinuses is well recognized. With regards to the thyroid, Riedel thyroiditis (RT) is characterized as a member of the IgG4 related disease spectrum, however, the relationship between Hashimoto's thyroiditis (as well as its fibrosing variant) is still a matter of debate [3, 4].

Histology continues to represent the gold standard for the diagnosis of IgG4 related disease, and although the diagnosis is often suspected on clinical and serologic parameters, a definitive diagnosis is seldom achieved without a biopsy [1, 2, 5]. This paradigm is unlikely to change, primarily because the disease mimics neoplastic disorders, and in many circumstances, without a biopsy, it is virtually impossible to exclude a malignant process—prompting the often-quoted axiom, 'tissue is the issue'.

This review will attempt to provide the reader a guide to the histologic diagnosis of IgG4 related disease. However, since this diagnosis is seldom made in a clinical vacuum, the review will also illustrate the serologic, radiologic, and other allied studies that could support the diagnosis of IgG4 related disease. Although neither the therapy of IgG4 related disease nor the mechanistic aspects are the focus of this review, a few comments on these facets of the disease are touched upon, but only as relevant to the practicing pathologist.

A Brief Guide to the Diagnosis of IgG4 Related Disease

The disease generally presents with enlargement of one or more organs. The involvement of multiple organs, and a

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disease that evolves over many years (occasionally decades), is a particularly characteristic feature of IgG4 related disease. Imaging may occasionally offer diagnostic clues, particularly at sites such as the pancreas and liver [1, 2, 5]. However, in the head and neck region, cross sectional imaging features are relatively non-specific. Instead, these mass-forming lesions may occasionally result in destruction of the underlying bone, an appearance that mimics malignancy [6].

The disease is characterized by a set of clinical features; when viewed individually are nonspecific, but collectively provide strong evidence in support of the diagnosis of IgG4 related disease [5, 7, 8].

1. Presence of tumefactive lesions involving organs commonly affected by IgG4 related disease such as the pancreas, liver, salivary glands, pachymeninges, retroperitoneum, lung, and lymph nodes, among others.
2. Involvement of multiple organs (listed above), either synchronously or metachronously.
3. Subacute onset without rapid onset of constitutional features.
4. Presence of elevated serum IgG4.
5. Elevated plasmablast levels [9, 10].
6. Swift response to immunosuppressive therapy. However, it should be recognized that a variety of other inflammatory diseases (and some neoplastic diseases, albeit temporarily) could also respond to steroids.

An elevated serum IgG4 represents the only validated blood based biomarker of IgG4 related disease. However, only about 50 % of patients with IgG4 related disease show an elevated serum IgG4. Patients with disease confined to a single organ often show normal serum IgG4. However, it is the relatively low specificity that is of greater concern: elevated levels of serum IgG4 are identified in a variety of inflammatory and neoplastic diseases [9, 10]. Of note, markedly elevated levels of serum IgG4 is often identified in patients with allergic diseases involving the upper aerodigestive tract.

Elevated levels of plasmablasts may provide another blood based assay for the diagnosis of IgG4 related disease, particularly in patients that lack elevated serum IgG4 levels [10]. Plasmablasts are antibody-secreting activated B cells that have down regulated CD20, and represent an intermediate developmental stage between an activated B cell and fully differentiated plasma cell—operationally defined as CD19 intermediate, CD38 positive, CD27 positive.

Although IgG4 is the best available biomarker for IgG4 related disease, little is known about its biologic role in this disease, and this constitutes one of the more intriguing aspects of this disease. While a detailed review of the antibody is beyond the scope of this review, it is worth

considering the biology of this unusual IgG isotype [1, 5, 11]: (1) The antibody is functionally monovalent: there are two distinct antigen recognition sites, a consequence of inefficient disulfide bridges between the heavy chains of the molecule resulting in Fab arm exchange, (2) failure to bind efficiently to FcRs and C1q makes it inefficient at phagocyte activation, antibody-dependent cellular cytotoxicity, and complement mediated damage. All of these factors make for an extremely inefficient antibody, and it is generally believed that IgG4 is an inhibitory antibody, blocking the progression of the immune response. The biology of IgG4 related disease (destructive tissue infiltrates) runs counter to the anti-inflammatory nature of this antibody. One potential hypothesis to explain these apparently contradictory findings is that the excess IgG4 may represent an attempt to localize the inflammatory response, although there is currently no direct proof to support this hypothesis. Alternatively, the excess antibody may simply represent an epiphenomenon. Nevertheless, this antibody does have the potential to behave as a pro-inflammatory molecule—IgG4 immune complexes are identified in cases of membranous glomerulonephritis, and these deposits may activate complement (albeit to a lower degree) through the alternate or lectin pathway.

Histologic Features of IgG4 Related Disease

Storiform-type fibrosis and obliterative phlebitis represent the most characteristic histologic features of IgG4 related disease [2, 8, 12, 13]. An unequivocal diagnosis of IgG4 related disease requires the presence of elevated numbers of IgG4 positive plasma cells. In addition, an elevated IgG4 to IgG ratio (>40 %) is also strongly recommended for diagnosis. This is an intuitive addition to the diagnostic algorithm—the number of IgG4 positive plasma cells may increase proportionally to the total number of plasma cells, and the IgG4 to IgG ratio helps correct for this bias. Thus, IgG4 related disease with fewer plasma cells would tend to show lower numbers of IgG4 positive plasma cells, but would nevertheless reveal elevated IgG4 to IgG ratio.

Differential Diagnosis of IgG4 Related Disease

The disease mimics a variety of inflammatory and neoplastic diseases, and in an individual case the diagnostic possibilities depend significantly on the site of disease as well as the clinical presentation. Mistaking malignancy for IgG4 related disease represents the most significant pitfall in this field. This error is often prompted by elevated serum IgG4 levels in some patients with malignancy, and/or a peritumoral lymphoid infiltrate that is rich in IgG4 positive

plasma cells. The key to circumvent this pitfall is to avoid relying solely on serum and tissue IgG4 levels.

IgG4 Related Submandibular Disease

IgG4 related disease was initially recognized in the pancreas and it is interesting to note that the salivary gland disease and autoimmune pancreatitis type 1 (the pancreatic manifestation of IgG4 related disease) show remarkably similar histologic features: both diseases display the complete histologic spectrum of IgG4 related disease [14–17]. In contrast, sites such as the orbit lack one or more of the histologic features of IgG4 related disease, and thus the diagnosis at these sites is often far more challenging.

Clinical Features

As with the other head and neck manifestations of the disease, the skewed age distribution (older patients) and male predominance seen in other forms of IgG4 related disease is less pronounced [12, 13, 18]. In fact, the disease may affect younger individuals, and not infrequently female patients. Symmetrically enlarged and firm submandibular glands are characteristic of this disease.

The submandibular gland enlargement may be accompanied by swelling of the parotid and lacrimal glands (and occasionally the sublingual glands): symmetrical enlargement of these glands is also referred to as Mikulicz's disease (see section on "Mikulicz's Disease"). In cases with multiorgan involvement, a biopsy from the submandibular salivary gland may provide the simplest means of establishing a diagnosis of IgG4 related disease: biopsies from the pancreas and liver are technically far more challenging.

Fig. 1 IgG4 related sialadenitis. This low power view illustrates the classic features of this disease—jigsaw puzzle-like appearance. Note the reactive germinal centers

Histologic Features

The low-power appearance is highly characteristic: a jigsaw puzzle like appearance created by the 'blue' inflamed lobules surrounded by an expanded stroma—the latter appearing 'pink' (Fig. 1) [14–16]. Another striking feature is the presence of large often irregularly shaped and floridly reactive germinal centers. On high power, the diagnostic features are found in the interlobular septa. The expanded interlobular septa are infiltrated by lymphocytes, plasma cells, and a generous sprinkling of eosinophils. Also present within the septa are a large number of myofibroblasts. These latter cells (that are positive for smooth muscle actin) are organized to create a storiform pattern. The obliterated veins are identified within these expanded interlobular septa. Totally obliterated veins are often easily overlooked (Fig. 2). The arteries and veins run in parallel, and thus a circumscribed focus of inflammation adjacent to an arterial channel would help identify totally obliterated venous channels. However, in some circumstances an elastic stain may represent the only means of uncovering totally obliterated veins. It is important to emphasize that the fibroinflammatory infiltrate within the obliterated venous channel is similar to that seen in the interlobular septa—a finding that distinguishes obliterative phlebitis, a virtually diagnostic parameter for IgG4 related disease, from other causes of obliterated veins such as an organized thrombus.

An unequivocal diagnosis of IgG4 related salivary gland disease requires documenting >100 IgG4 positive cells per HPF as well as an IgG4/IgG ratio of >40 % [2]. This requires the counting of 3 HPFs on the IgG4 preparation as well as the 3 corresponding fields on the IgG preparation. Unfortunately, the latter preparation invariably shows non-specific stain in the background. An in situ hybridization stain helps surmount this problem (Fig. 3).

Differential Diagnosis

The principal differential diagnoses include other forms of chronic sialadenitis as well as a low-grade lymphoma: [15, 16] the latter is easily excluded, given the polyclonal nature of IgG4 related disease, and the lack of a monotonous population of lymphocytes. However, in our experience, the former is often confused with IgG4 related sialadenitis. The presence of sclerosis as well as elevated numbers of IgG4 positive plasma cells in both forms of sialadenitis enhances the overlap. Careful attention to the presence of storiform pattern of fibrosis within the interlobular septa as well as obliterative phlebitis can readily distinguish IgG4 related disease from other forms of chronic sialadenitis (Fig. 4). It should be noted that IgG4 related sialadenitis is

Fig. 2 IgG4 related sialadenitis. Partially obliterated vein, (a) and totally obliterated vein (b). Arrow marks the totally obliterated vein

Fig. 3 Comparison of an in situ hybridization assay for IgG4/IgG with the immunohistochemistry platform. *In situ* hybridization for IgG4, (a) and IgG, (b) (ViewRNA, Affymetrix, CA). Immunohistochemistry for IgG4, (c) and IgG, (d). The IgG

immunohistochemistry is generally associated with strong background signal, precluding the quantification of the IgG4 to IgG ratio, a critical element of the diagnostic algorithm

not associated with sialolithiasis. It is important not to rely solely on the presence of elevated numbers of IgG4 positive cells: elevated numbers of IgG4 positive plasma cells are identified in a variety of other inflammatory as well as neoplastic diseases.

Mikulicz's Disease

Mikulicz's disease (MD) is defined by the enlargement (often symmetrical) of the lacrimal, parotid, submandibular, and occasionally sublingual salivary glands.

Fig. 4 IgG4 related sialadenitis (a). Note the dense lymphoplasmacytic infiltrate and storiform type fibrosis in the interlobular septum. Chronic sialadenitis—not otherwise specified (b). Note the relatively

acellular interlobular stroma. However, increased numbers of IgG4 positive plasma cells are noted, in isolation, a relatively non-specific feature (inset)

The disease was originally described in the late 18th century by Mikulicz-Radecki, a Polish-Austrian surgeon. In the 1950s Benjamin Castleman, a Boston based pathologist, provided a modern interpretation of the disease [19]. Based on Castleman's observations, it was concluded that MD is an atypical manifestation of Sjögren's syndrome, and the term MD, for the most part, was erased from the English literature. The term was resurrected in Japan, where examples of MD were associated with elevated levels of serum IgG4 [20]. It is now widely recognized that the majority of patients diagnosed with MD represent IgG4 related disease. This paradigm of reclassifying inflammatory diseases (many with eponymous terms) and gathering them under the IgG4 related disease 'umbrella' has played out in virtually every organ.

Clinically, MD closely mimics Sjögren's syndrome—patients present with dry eye and dry mouth [20]. However, bilateral and symmetrical enlargement of the parotid glands is distinctly uncommon in Sjögren's syndrome, offering the first clue that the disease represents a variant of IgG4 related disease. This distinction is of vital clinical importance: Sjögren's syndrome shows no response to immunosuppressive therapy, while IgG4 related disease shows swift and virtually complete response to steroids, and other forms of immunosuppressive therapy.

While the histologic changes within the submandibular salivary gland are virtually identical to those described earlier in this review, the parotid and the orbital manifestations may not show one or more of the morphologic changes associated with IgG4 related disease. Of note, typical storiform-type fibrosis and/or obliterative phlebitis are often absent in the orbit and the parotid gland. The diagnosis, thus, relies significantly on demonstrating elevated numbers of IgG4 positive plasma cells as well as an elevated IgG4 to IgG ratio. Fortunately, the clinical

appearance is highly characteristic, and in this context the presence of elevated numbers of IgG4 positive plasma cells may be sufficient to clinch the diagnosis. Lip biopsies from individuals with Sjögren's syndrome are negative (or show rare positive cells) for IgG4 plasma cells, while those with MD generally show both fibrosis as well as increased numbers of IgG4 positive plasma cells.

Eosinophilic Angiocentric Fibrosis

Eosinophilic angiocentric fibrosis (EAF) is an uncommon and enigmatic disease that affects the lacrimal gland, nasal cavity, nasal sinuses, and lower respiratory tract. Histologically, the disease is characterized by the presence of numerous small vascular channels that are surrounded by concentric layers of fibrosis. Interestingly, the perivascular concentric fibrosis is occasionally seen in other forms of IgG4 related disease. The intervening stroma is infiltrated by substantial numbers of eosinophils, as well as lymphocytes and plasma cells. While histologically, this entity does not fit the prototypic description of IgG4 related disease, the majority of these cases show elevated numbers of IgG4 positive plasma cells, an elevated IgG4 to IgG ratio, as well as elevated serum IgG4 [21]. The current standard of therapy is surgical extirpation of the lesion, although they may also respond to immunosuppression.

IgG4 Related Orbital Disease

Patients with IgG4 related orbital disease show a slight male predominance and affect middle aged to elderly patients [22]. The lacrimal gland is the most commonly involved structure (62 %) [22]. However, extra lacrimal

involvement is common, and the sites affected include the soft tissue of the orbit, and occasionally the orbital muscles, as well as the branches of the trigeminal nerve.

Unlike the submandibular manifestation of the disease, the majority of these cases lack obliterative phlebitis, and storiform type fibrosis is not universally identified. Thus, many cases show only a dense lymphoplasmacytic infiltrate—large reactive germinal centers are commonly found. Focal areas of ‘patternless’ fibrosis are frequently identified. Thus, the diagnosis relies considerably (and sometimes exclusively) on the presence of elevated numbers of IgG4 positive plasma cells—and an IgG4 to IgG ratio of >40 %.

IgG4 Related Disease of the Thyroid

Over the last decade, a fascinating and rapidly evolving association between IgG4 and Hashimoto’s thyroiditis has emerged. Some groups now believe that a significant proportion of cases of fibrosing Hashimoto’s thyroiditis, and a minority of cases with classic Hashimoto’s thyroiditis belong to the spectrum of IgG4 related disease [3, 4, 23–26]. However, unlike most other manifestations of the disease, both forms of thyroiditis (now termed IgG4 related thyroiditis) remain confined to the thyroid, and systemic manifestations have not been recognized [3, 4, 23, 24]. Nonetheless, a significant proportion of patients with autoimmune pancreatitis and IgG4 related disease show evidence of hypothyroidism, thus arguing for an association between this thyroid disease and IgG4 related disease [27]. In contrast, RT, now firmly considered an IgG4 related disease variant, has had a long association with systemic fibrosclerosing diseases, many of which are now included within the IgG4 related disease spectrum [28].

Hashimoto’s Thyroiditis

In a series of elegant papers, Kakudo identified a variant of Hashimoto’s thyroiditis (IgG4 related thyroiditis) that showed elevated numbers of IgG4 positive plasma cells—defined as greater than 20 IgG4 positive plasma cells per HPF, and an IgG4 to IgG ratio of greater than 30 % [3, 23]. There were significant differences between patients with IgG4 positive thyroiditis and IgG4 negative thyroiditis. IgG4 related thyroiditis patients tended to be younger, male, and were more likely to have a shorter duration of disease, higher anti-thyroglobulin, and anti-thyroid peroxidase antibody titres. Furthermore, on ultrasound, the IgG4 positive group showed diffuse low echogenicity [3, 23].

Histologically, the 2 variants of the disease were also distinct: IgG4 positive group revealed severe

Fig. 5 IgG4 related disease involving the nasal cavity paranasal sinuses. Note the storiform pattern. Virtually all the plasma cells were positive for IgG4 (image not shown)

lymphoplasmacytic infiltration, fibrosis, follicular cell degeneration and numerous microfollicles, as well as the presence of occasional giant cells and histiocytes [3, 23]. Although these features were also seen in the IgG4 negative cohort, these parameters were far more prominent in the IgG4 positive group. In fact, a significant number of IgG4 positive thyroiditis cases could be categorized as fibrosing variant of Hashimoto’s thyroiditis, a variant of thyroiditis first characterized by Austin Vickery, a pathologist from the authors’ institution. In a more contemporary series from Boston, 90 % of cases classified as fibrosing variant of Hashimoto’s thyroiditis were associated with high IgG4 levels [4].

Riedel Thyroiditis

Riedel thyroiditis is a form of chronic thyroiditis characterized by a fibrosing inflammatory process that extends beyond the capsule into the surrounding tissue.

Riedel thyroiditis shows several features that justify its inclusion into the spectrum of IgG4 related disease. Foremost among them are the fibroinflammatory nature of the infiltrate, the presence of obliterative phlebitis, and its association with other forms of fibrosclerosis including sclerosing cholangitis, and retroperitoneal fibrosis, among others [29]. In fact, one-third of patients with RT develop fibrosing disorders in other organs. In 2010, our group showed that RT is an IgG4 related disease [28]. This argument was supported by the fact that RT showed elevated numbers of IgG4 positive plasma cells as well as the morphologic features of IgG4 related disease.

Even prior to its association with IgG4 related disease, immunosuppressive therapy (mainly prednisone) was used successfully in the management of patients with RT.

However, unlike most other forms of the disease, RT demonstrates broad zones of acellular fibrosis, making total/near total response unlikely, as is commonly seen in other forms of IgG4 related disease.

Clinical Significance of IgG4 Related Thyroiditis

The clinical significance of a diagnosis of IgG4 related disease remains uncertain. With the exception of Riedel's thyroiditis, these patients do not progress to systemic IgG4 related disease. However, patients with IgG4 related thyroiditis progress more rapidly to a hypothyroid state. The firm and relatively quickly growing thyroid raises concern for malignancy. One potential (although unproven) application of diagnosing IgG4 related thyroiditis early in its course (potentially on a fine needle aspirate and flow cytometry) is to intervene early to prevent destruction of the thyroid and thus hypothyroidism.

Other Sites of Disease

IgG4 related disease also involves the nasal sinuses, the nasal cavity, the nasopharynx, as well as the tracheobronchial tree and larynx [30, 31]. These patients generally present with a mass-forming lesion. The disease at these sites may perforate the craniofacial skeleton [6]. It is likely that many of the so-called “inflammatory pseudotumors” of the head and neck region, in retrospect, represent IgG4 related disease. The histologic changes are generally similar to those seen in the submandibular salivary gland. However, biopsy samples from these sites are typically small, and hence obliterative phlebitis is seldom seen. Nevertheless, the presence of fibrosis, particularly storiform fibrosis as well as the elevated numbers of IgG4 positive plasma cells (and an IgG4 to IgG ratio >40 %), in the appropriate clinical context, represent sufficient evidence for IgG4 related disease (Fig. 5).

Conclusion

Since the disease has been recognized only over the last decade, there continues to be under-recognition of IgG4-RD by both clinicians and pathologists. In our experience many of these patients are subjected to multiple biopsies, often prompted by a clinical appearance that mimics a malignancy. More recently, over-diagnosis of this entity has emerged—driven primarily by an over reliance on the IgG4 stain. The latter pitfall is relatively easily avoided by requiring both the appropriate histologic appearance as well as the presence of increased numbers of IgG4 positive cells.

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