Probable Immunoglobulin Subtype—G4-Related Disease in the Head and Neck from Foreign Body Injection: A Case Report

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Abstract

Introduction Immunoglobulin subtype G4-related disease (IgG4-RD) is a fibroinflammatory disease of unknown etiology, with manifestations involving nearly every organ system. Its association with foreign bodies is not established. Here, we present a novel case of IgG4-RD in response to foreign body injection.

Case Description A 58-year-old woman presented with history of persistent left facial pain, xerophthalmia, blurred vision, and trismus. The patient's medical history was significant for left-sided temporomandibular joint (TMJ) reconstruction with silicone injection into the joint. Magnetic resonance imaging revealed a lesion in the left skull base. Biopsies demonstrated the cardinal histopathological features of IgG4-RD. The patient was treated with a tapering dose of prednisolone followed by rituximab, resulting in tumor shrinkage and resolution of her symptoms.

Discussion This is the first reported case of IgG4-RD potentially precipitated by a foreign body, in this case injected silicone into the TMJ. The pathogenesis and etiology of IgG4-RD is still not fully elucidated, but allergic and reactive inflammatory reactions have been implicated in the disease process. This case report should raise the idea of reactive foreign bodies as a causative agent for IgG4-RD.

Keywords

- immunoglobulin subtype
- G4-related disease
- foreign body injection
- head and neck

Introduction

Immunoglobulin subtype G4-related disease (IgG4-RD) is a fibroinflammatory disease of unknown etiology, which may present with a wide array of manifestations, with reported cases involving nearly every organ system. IgG4-RD is a diagnosis that is becoming increasingly recognized by the medical community. One of the most common and well-described manifestations is type 1 autoimmune pancreatitis. Additionally, over time, many previously described diseases have been recently reclassified. For example, Mikulicz syndrome, and Küttner tumor have been recognized as part of the spectrum of IgG4-RD.[1] Often with IgG4-RD, the presentations are so similar to that of a neoplasm that they are surgically managed as such. In the case of Küttner tumor, excision is fortunately both diagnostic and therapeutic. Delayed or missed diagnosis, however, can result in significant morbidity and mortality. This is evident when considering patients who have been diagnosed with type 1 autoimmune pancreatitis only after undergoing a Whipple procedure.

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Despite the wide array of presentations and locations of disease, there are clinical, laboratory, and histological characteristics that link the many disparate manifestations.[2] Clinically, the lesions are often tumefactive and have been described as arising in multiple sites across the body in both synchronous and metachronous patterns.[2] There is also often rapid clinical response to immunosuppression. This is typically achieved with corticosteroids, though concerns about long-term steroid use have prompted investigation into alternative therapies including the use of mycophenolate mofetil.[3]

In approximately 80% of patients with suspected IgG4-RD, laboratory testing reveals serum IgG4 levels greater than 135 mg/dL. Elevated serum IgG4 is not by itself sufficiently specific for a diagnosis of IgG4-RD as there can be elevated levels in other inflammatory diseases.[4] Conversely, some patients with classic histologic features have negative serum values, raising concerns about the sensitivity of this test. For example, in a case series of 11 patients, 6 had normal serum IgG4 levels; however out of these patients, 5 demonstrated positive IgG4 immunostaining.[5]

The diagnosis of IgG4-RD is primarily made with biopsy, demonstrating characteristic histopathological features and immunohistochemical staining. There are three histopathological findings which are highly suggestive of IgG4-RD, but could be found in other pathologies; these are dense lymphoplasmacytic infiltrate rich in IgG4, storiform pattern of fibrosis, and obliterative phlebitis.[2] Other potential features of disease include nonobliterative phlebitis and increased eosinophils, though these are neither sensitive nor specific in isolation.[2] It is important to ascertain the presence of granulomas, necrosis, giant cells, and neutrophils as these are suggestive of other underlying diseases such as granulomatosis with polyangiitis.[2]

In addition, specimens should be examined using immunohistochemistry. According to the diagnostic criterion presented by Pieringer et al, an IgG4/IgG ratio of greater than 40% is highly suggestive of IgG4-RD.[6] Visualization of more than 10 IgG4 cells in a high power field is also highly suggestive of IgG4-RD. The IgG4/IgG ratio is thought to be more useful as other inflammatory pathologies may present with increased IgG4 cells in a high power field due to the overall increase in plasma cells. Looking at the ratio is thus more specific to IgG4-RD.[2]

Material and Methods

This is a case report of a patient seen by our practice with suspected IgG4-RD of the head and neck. As well as a literature review utilizing PubMed.

Setting

The New York Head and Neck Institute (NYHNI) is a full-service otolaryngology department at Lenox Hill Hospital, part of the North Shore Long Island Jewish Health System. The NYHNI serves a diverse patient population with a wide range of head and neck diseases in a tertiary hospital setting.

Case Review

Here, we present a case of a 58-year-old woman who presented to our practice in 2011 with persistent left face pain, xerophthalmia, and blurred vision. She also had left proptosis, left periorbital edema, and trismus. These symptoms were believed to be caused by a chronically expanding mass in her infratemporal fossa with some orbital involvement. She is morbidly obese (body mass index > 40) and has a history of hypertension and diabetes mellitus type II as well as temporomandibular joint (TMJ) dysfunction. Notably, the patient underwent TMJ reconstruction and received silicone injections to the left TMJ in 2000.

In 2007, the patient began manifesting symptoms of left periorbital edema and proptosis. It is suspected that the lesion is a reaction to the silicone injection given the location and timing. On imaging (►**Fig. 1**), a lesion in the left infratemporal fossa, masticator, and buccal space with extension into the maxillary sinus and orbit is noted. The largest margin of the mass measures 5 cm. The mass had been biopsied in 2008 and showed chronic granulation tissue. The lesion decreased in size in response to treatment with prednisone. Over the next several years, this mass was monitored closely, including several biopsies.

Histology strongly suggested an underlying inflammatory etiology; however, for several years the pathology reports had trouble identifying the exact inflammatory modulators. Clinical correlation suggested an inflammatory cause of symptoms as it manifested in the area, where the patient received the silicone injection, the tumor took up 18F-fluorodeoxyglucose, the tumor responded to acute treatment with prednisone, and all of the pathology reports showed fibrotic tissue with lymphoplasmacytic infiltrate.

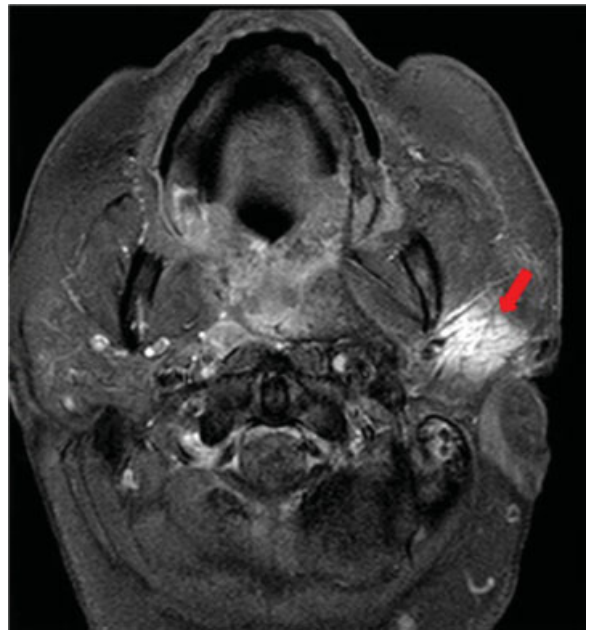

Fig. 1 A transverse T2-weighted MRI of the skull base showing the lesion expressed as the region of high signal intensity in the left infratemporal fossa (red arrow). MRI, magnetic resonance imaging.

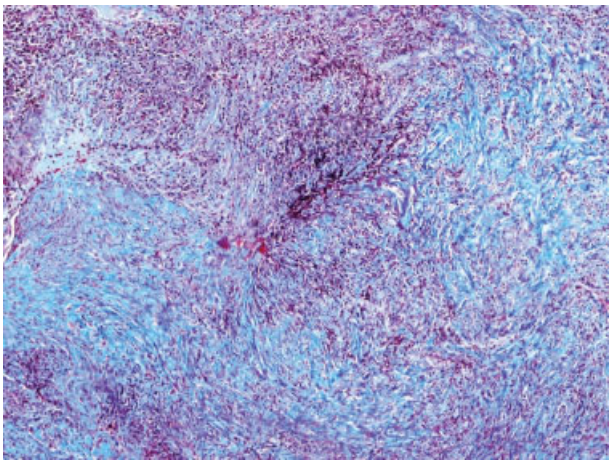

Fig. 2 A high-power Mallory trichrome stain demonstrates storiform fibrosis.

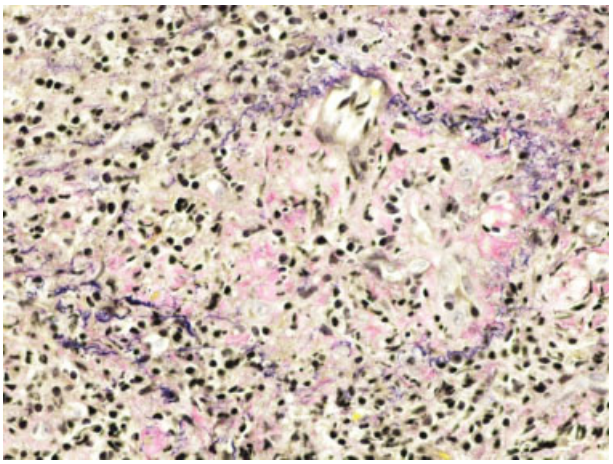

Fig. 4 High-power Verhoeff elastic staining, demonstrating obliterative phlebitis.

In 2014, the patient was diagnosed with probable IgG4-RD based on a confluence of clinical presentation and biopsy, including histology. The biopsy revealed a lymphoplasmacytic infiltrate, storiform fibrosis (►**Fig. 2** and **3**), obliterative phlebitis (►**Fig. 4**), and an IgG4/IgG ratio of greater than 30% in plasma cells (►**Fig. 5**), which are the hallmarks of IgG4-RD. It is important to correlate these findings to the clinical and hematological markers, because focally many disease entities may mimic IgG4-RD. Even in the presence of pathognomonic histological features, blood levels of IgG4 should be evaluated. While other disease entities can resemble IgG4-RD on isolated sections, when these histologic findings are found in the setting of elevated serum IgG4, a diagnosis of probable IgG4-RD can be made. The patient did not have elevated serum IgG4 levels; however, as per the criteria proposed by Pieringer et al (►**Fig. 6**), she has probable IgG4-RD despite normal serum IgG4 levels.

The established treatment of IgG4-RD, like most inflammatory diseases, is corticosteroids. The patient received a tapering dose of prednisolone. Long-term corticosteroid usage presents a multitude of problems, including Cushing syndrome and Cushing-like presentations. As a result, prednisolone is administered via a tapering dose. The prednisolone did not significantly shrink the lesion as much as we had hoped and thus the patient was also started on rituximab. She received one dose every month and responded well with significant tumor shrinkage and resolution of her complaints. Currently, the patient is receiving one dose every 2 months. Rituximab is a monoclonal antibody toward CD-20, a marker present on B-cells precursors as well as mature B-lymphocytes. The function is to inhibit the further production of antibodies such as IgG4.

Discussion

When clinical course suggests potential IgG4-RD yet serum levels are normal, biopsy criterion should be evaluated as they are considered a more powerful measure than serum levels.[2] Patients with IgG4-RD typically demonstrate IgG4/IgG ratios of $> 40\%$. These must be correlated with overall sample IgG4 cells per high powered field. Our patient demonstrated the three cardinal histopathological features of

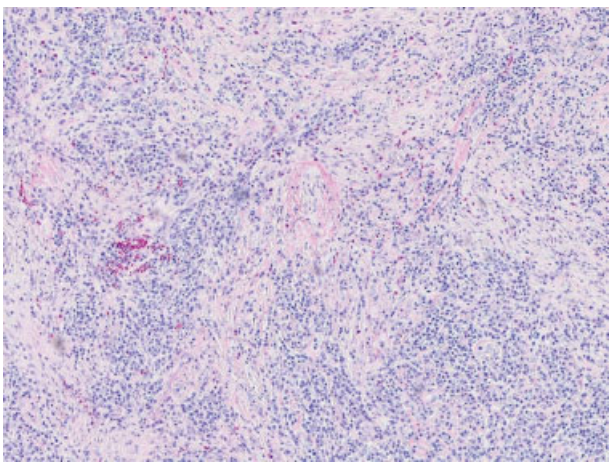

Fig. 3 A high power H&E image from our patient showing storiform fibrosis and pale staining plasma cells. H&E, hematoxylin and eosin.

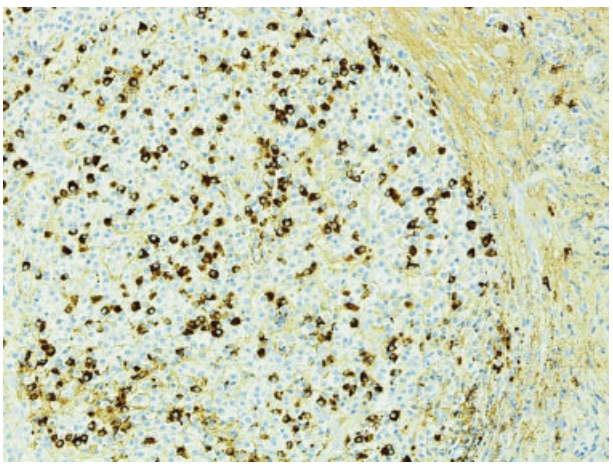

Fig. 5 A high-power IgG4 stain, which demonstrates more than 30% of plasma cells have IgG4. IgG4, immunoglobulin subtype G4.

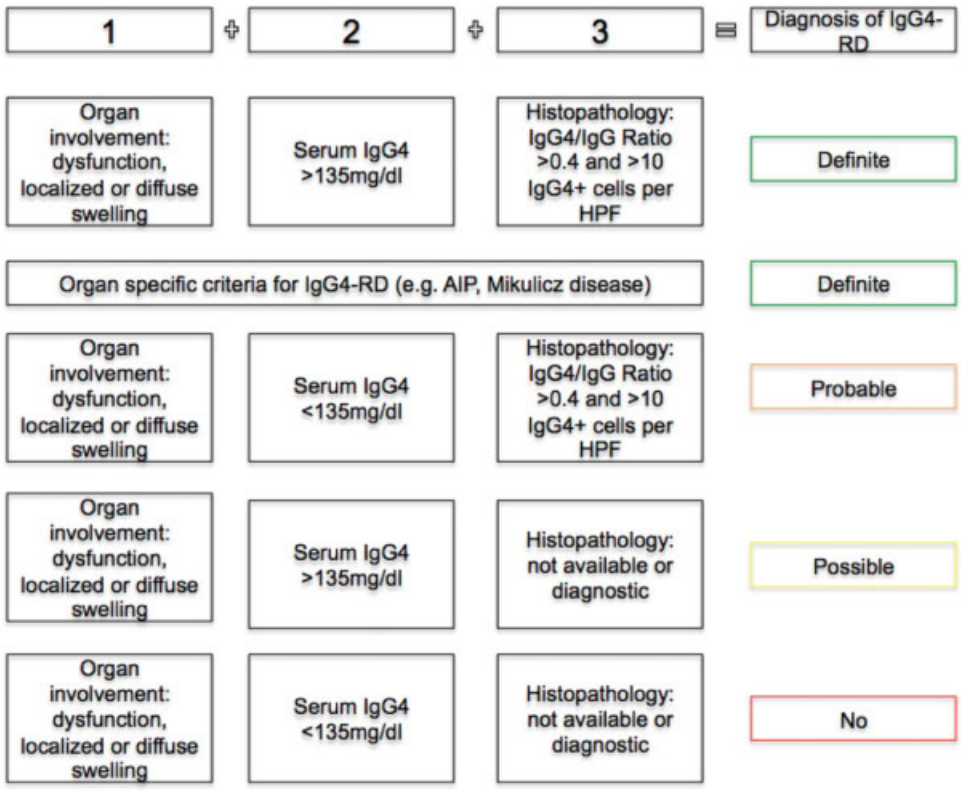

Fig. 6 IgG4-related disease: an orphan disease with many faces. (Reprinted with permission from Pieringer et al.)[6] IgG4, immunoglobulin subtype G4-related disease.

IgG4-RD: (1) lymphoplasmacytic infiltrate, (2) obliterative phlebitis, and (3) storiform fibrosis. However, her IgG4 + / IgG ratio was > 30%, making her a borderline patient.

Clinical and histopathological correlation must be made to differentiate from other immune-mediated diseases such as rheumatoid arthritis and Castleman disease. It is important when considering a diagnosis of IgG4-RD, particularly in a patient with an atypical presentation, to rule out immune-modulated inflammatory diseases, low-grade lymphoma, and organ-specific malignancies. Our patient underwent a bone marrow biopsy to rule out plasma cell dyscrasia. Elevated plasma cells were noted, but the levels of less than 10% indicated that there was no amyloid reaction.

To date, there is limited published data on head and neck manifestations of IgG4-RD. The majority of cases reported concern lacrimal glands, salivary glands, and isolated or concurrent cervical lymph node involvement; however, case reports involving disease in the sinonasal cavity and skull base are beginning to emerge as the disease is becoming better known. These are more likely than other manifestations of the disease to lack the typical histologic patterns of storiform fibrosis and obliterative phlebitis. Rarely, IgG4-RD can present as a tumor in the head and neck.[7–11]

Conclusion

Given the appropriate clinical picture, histological findings, and serum levels may point us in the direction of IgG4-RD. The diagnosis of this disease is very important as it can eliminate the need for risky unnecessary surgeries, which are associated with substantial morbidity. For example, autoimmune pancreatitis is often not diagnosed until the patient has undergone a Whipple surgery, which greatly increases morbidity and mortality over the treatment with prednisone.

In the past, diagnosis has been delayed as not much was understood about IgG4-RD. Hopefully with the gained understanding, patients can be diagnosed earlier to prevent subsequent surgeries, like in our patient who underwent many biopsies before the ultimate diagnosis.

While difficult to prove, it is conceivable that the patient experienced IgG4-RD in response to her silicone injection. Injectables have been known to cause an inflammatory response and other injectables have been indicated in IgG4-RD; however, this would be the first case of silicone as a causative agent.

Taking together the imaging, history of disease, and histopathological results, this case report should raise the clinical possibility of reactive foreign bodies as a causative agent for IgG4-RD. This case report should be informative for the head and neck surgeon as this disease entity is becoming increasingly recognized.

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