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Case Report

IgG4-Related Disease: A Case Report of a Massive Presentation Leading to the Diagnosis of B-Cell Lymphoma

Solano Nicolás[1,2], Ramos Salomón[1,2], Rivera Ejusmar[1,2]* and Rios Elvia[1,2]

[1]*Oral and Maxillofacial Surgery Unit, Servicio Autónomo Hospital Universitario de Maracaibo, Venezuela*

[2]*Oral Surgery Postgraduate Residency Training Program, La Universidad Del Zulia, Maracaibo, Venezuela*

***Corresponding Author:** Rivera Ejusmar, Oral and Maxillofacial Surgery Unit, Servicio Autónomo Hospital Universitario de Maracaibo, Venezuela.

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Abstract

Immunoglobulin G4 related disease is a recently described entity with a broad spectrum of clinical manifestations. It is characterized for being a fibroinflammatory systemic condition involving a dense infiltrate of IgG4 rich-plasma cells. The organs most commonly affected by this pathology are the salivary and lacrimal glands. To establish the diagnosis, the clinician must follow certain criteria, such as a thorough physical examination in order to find the localized inflammatory characteristics in one or multiple organs, an hematologic test showing high levels of serum IgG4 (> 135 mg/dl) and a histopathological examination of the inflammatory lesions. Until now, glucocorticoids have been the main treatment for this condition due to its efficacy and affordability; however, if no positive response is found when using this treatment modality, it is indicative that the diagnosis may not be the correct one.

Keywords: IgG4; IgG4 Related Disease; Salivary Glands; B-Cell Lymphoma; Lacrimal Glands

Introduction

Immunoglobulin G4 related disease (IgG4-RD) is a recently described clinical-pathological entity with a broad spectrum of clinical manifestations that share a common histopathology. It is characterized by being a chronic bilateral fibroinflammatory systemic pathology with the presence of swelling, lymphadenopathy and a dense infiltrate containing plasma cells rich in IgG4 [1]. The most compromised organs are the salivary glands, lacrimal glands and, in some cases, the accessory salivary glands located in the hard palate and the tongue. This alteration can also compromise other organs such as the pancreas, lungs or liver, which can be affected at the same time or successively [2].

Mikulicz syndrome, previously considered as a phenotypic variant of Sjögren syndrome (SS) based on histopathological similarities, is now considered part of the IgG4-RD family [2,3]. The first descriptions of the pathological processes compatible with the disease date from 1892 by Johann von Mikulicz-Radecki. In 2004, the documentation of high levels of IgG4 in patients with Mikulicz disease established it definitively within the IgG4-RD spectrum. The current nomenclature of this condition was accepted in 2011 at the first international congress on IgG4-RD, held in Boston [4-6]. The purpose of this study was to present a clinical case of IgG4-related disease with unusual inflammatory characteristics which led to the diagnosis of B-cell lymphoma, as well as its management to achieve favorable remission.

This study was approved by the Servicio Autónomo Hospital Universitario de Maracaibo IRB and all participants signed an informed consent.

Case Report

A 69-year-old woman presented to the Oral and Maxillofacial Surgery Unit of the Servicio Autónomo Hospital Universitario de

Maracaibo, Venezuela, in August 2015, with the chief complaint of asymptomatic bilateral facial swelling with 1 year of progression. The patient's medical record was relevant for 20 years of smoking and recent weight loss. She denied any trauma to the region, along with any odontogenic pain or complications. She was noted to have xerophthalmia and slight xerostomia. The patient had been previously treated by other clinicians with NSAIDs therapy, without resolution. Clinical examination yielded a painless bilateral extensive swelling in the upper palpebral, parotid, submandibular and sublingual regions, indurated and fixated to deep planes, without any signs of acute inflammation (Figure 1 and 2). There was no impairment of ocular movement or diplopia, but her visual acuity was compromised due to the swelling in the area. Hematological tests were requested, including a serology study, resulting in: IgG 1891 mg/dl; IgM 100 mg/dl; IgG4: 924 mg/dl. Due to these findings, a decision was made to perform an incisional biopsy of the left parotid and upper palpebral lesions under general anesthesia and the specimens were submitted to histopathologic analysis. The following diagnosis was received: B-cell Lymphoma, confirmed by immunohistochemistry. Thus, the patient was remitted to the Oncology Service of the hospital and received adjuvant chemotherapy, consisting of a multicycle R-CHOP regime (rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisolone). Clinical examination at the 3-month follow-up revealed a well-healed site with almost no scar tissue and a complete resolution of the swelling in the upper palpebral, parotid and submandibular regions (Figure 3). After 2 years of being diagnosed, no recurrence of the facial swelling was observed; however the patient died due to lymphoma-related complications.

Figure 1: Clinical image of the patient on admission.

Figure 2: Intraoral view of the patient depicting the swelling in the floor of the mouth.

Figure 3: 3-month follow up after treatment. Swelling of the glands is no longer visible.

Discussion and Conclusion

IgG4 is the least common of the four IgG subtypes, only representing 3 - 6% in normal serum levels. The pathogenic and immunological mechanisms of IgG4-RD remain unclear. According to the literature, innate and adaptive immunity are involved; patients with IgG4-RD show a predominance of macrophage infiltration in multiple lesions, therefore it is believed that these play an important role in the generation of the inflammatory pathophysiology. Recently, CD4+ cytotoxic T lymphocytes have been identified as main actors in the inflammatory cascade that ends with fibrosis

in IgG4-RD. Complement C3 and C4 have also been shown to be decreased in 36% of IgG4-RD patients, suggesting that the complement cascade may be activated in the presence of IgG4 in these patients by an unknown mechanism, resulting in a controversial topic [3,7,8].

Kouwenberg., *et al*. [9] presented a 2:1 gender ratio (female/male), with an average age of onset between 50 - 70 years. However, IgG4-RD can affect any age group, including children, and the symptoms can vary depending on the location of their presentation, generally with predilection for the pancreas, liver, lungs and a strong propensity for the head and neck region, indicating that the symptoms associated with IgG4-RD were observed more frequently in the salivary, lacrimal, pituitary and thyroid glands. On the other hand, Zachary., *et al*. [10] in 2019, determined that the risk factors associated with the appearance of IgG4-RD are poorly understood, but it was recently discovered that exposure to tobacco and a history of malignancy may be a risk factor for the further development of the condition. These parameters and characteristics concur with our case.

The most common inflammatory manifestations associated with IgG4-RD are observed in the pancreas in 60% of cases. In the head and neck region, the main affected organs are the salivary glands in 34% of the cases, with a greater predominance for the submandibular glands, followed by the parotid, sublingual and labial glands. The inflammatory lesions of the lacrimal glands comprise only 22.5% of the reported cases. Inflammatory lesions may present in isolation in a single gland or affecting several groups of them. Also, the swellings can be found unilaterally or bilaterally, affecting the secretion of the affected glands [10,11]. In 2020, Yoh Zen [12] determined that inflammatory lesions in the pancreas predominate in men, while the salivary glands are mostly affected in women. Regarding the case presented in our study, the inflammatory characteristics associated with IgG4-RD were evidenced in all the head and neck glands simultaneously and bilaterally, being a chronic and massive presentation not previously reported in the literature.

The diagnosis of this alteration is complex and it results necessary to have a combination of clinical characteristics, where the glandular masses may appear as firm and painless swellings which persist for more than 3 months, in addition to laboratory tests and histopathological studies. Generally, the condition runs asymptomatic and its finding is incidental. When symptoms are present, this may be due to the important swelling caused by inflammatory lesions. In some cases, weight loss may occur in patients with IgG4-related autoimmune pancreatitis; on the other hand, fever is an atypical sign [1,2,10]. In 2018, Tsuchida., *et al*. [2] established that the diagnosis for IgG4-RD must follow certain criteria, including a physical examination in search of localized inflammatory characteristics or masses in one or multiple organs, a hematological examination that shows elevated serum IgG4 concentrations (> 135 mg/dl) and a histopathological examination of the inflammatory lesions. Biopsy of the salivary and lacrimal glands may result controversial due to the selection of the technique. Fine needle aspiration biopsies may not collect a sufficient number of cells for detailed immunostaining and the experience of the physician has an impact on the sample with this technique; in some cases it may show high specificity but low sensitivity for the diagnosis of IgG4-RD. Regarding the alterations evidenced in our case, we found serum IgG4 levels highly above the normal value and a 12-month period of asymptomatic swelling progression, non-responsive to conventional anti-inflammatory treatment. The literature recommends an incisional biopsy of the glands in order to reduce erroneous results despite the fact that this alternative is more invasive, justifying the selection of the technique used in the case presented [2,9].

All symptomatic patients with active IgG4-RD require treatment. Patients who are not given immunosuppressants are more likely to experience complications and are less likely to achieve remission. The administration of immunosuppressants prevents accumulation of IgG4 and reduces damage to the affected organs. Agazzoni., *et al*. [1] in a study carried out in 2017, stated that most of their patients responded to the use of glucocorticosteroids and more than 99% achieved clinical remission. Glucocorticoids have so far been the basis of IgG4 treatment due to their efficacy and affordability. Failure to respond to glucocorticoid therapy suggests that the diagnosis may be incorrect. Initial treatment may be prednisone 20 - 60 mg once per day, which can be adjusted according to the weight of the patient or the severity of the disease. After 2 to 4 weeks of treatment, the dose can be decreased slowly and sequentially, with the goal of totally suspending it after 3 months or even earlier. During this period, the patient must be monitored to detect the incidence and changes in the clinical presentation and symptoms, which are common especially in lower doses or when the medication is finished [10,13].

It should be noted that IgG4-RD may mimic a variety of inflammatory and neoplastic diseases [9]. These diseases have an unpredictable course in terms of patient evolution and therefore, the etiology, risk factors, treatment and prognosis depend on the underlying cause, which requires regular monitoring. Currently, there are very few reported cases of IgG4-RD associated with B-cell lymphoma. In the literature, the appearance of IgG4-related malignant neoplasia has been described with greater frequency associated with pancreatic lesions [13-15]. Sato., *et al*. [11] reported one case of B-cell lymphoma that produced IgG4 and presented with high serum concentrations and strong infiltration in the affected organs, therefore, they emphasize in having special consideration with the possibility of progression of the disease and the effect of the treatment in these patients. In relation to the case presented in our study, the transformation to malignancy could be related to the long history of evolution and progression of the IgG4-associated lesions without proper treatment, despite the fact that they were located only in the head and neck region.

Igawa., *et al*. [16] reflected that IgG4-RD may increase the probability of malignant tumors in the lung, colon and lymphomas. Due to the chronic inflammation produced, they can promote the development of B-cell lymphomas of the marginal zone. In such cases, numerous non-neoplastic IgG4-positive cells can be found among the malignant cells. Marginal zone lymphoma is considered to arise from mature B cells in the germinal center region as a result of chronic inflammatory conditions, infections and autoimmune diseases. It has also been described that a stimulated immune system with elevated levels of IL-4 and IL-10 due to unknown causes may be associated with the development of lymphomas in IgG4-RD. Therefore, it is important to note that some types of B-cell lymphomas are rare but important complications of IgG4-RD, although there is limited evidence in the literature on the frequency of malignant transformation of lymphocytes and thus, accurate diagnosis is critical to disease management [13].

In our case, once the diagnosis of B-cell lymphoma was confirmed, a multidisciplinary approach along with the Oncology service was applied and a chemotherapy regime was initiated, obtaining good results in the short and medium term. It is also remarkable to establish that, at the moment, there are no reported cases of this condition where the inflammatory manifestations were present simultaneously and bilaterally in all major salivary and lacrimal glands in such a massive way, adding the fact that it turned out to be associated with a B-cell lymphoma.

It is therefore of the utmost importance that Head and Neck Surgeons become aware of this condition and its course, in order to apply proper management, avoid complications and prolong the patient's life expectancy.

Funding

No funding was received for this study.

Conflicts of Interests

None.

Ethical Approval

This study was approved by the Servicio Autónomo Hospital Universitario de Maracaibo IRB.

Patient Consent

Written consent was obtained for publication.

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