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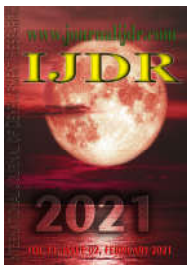

RESEARCH ARTICLE OPEN ACCESS

OROFACIAL MANIFESTATIONS OF IGG-4-RELATED DISEASE IN SALIVARY GLANDS: LITERATURE REVIEW

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ABSTRACT

Objective: An updated review about the immunoglobulin G4-related disease to clarify and assist the dental surgeon in the diagnosis and treatment of this condition. **Material and methods**: The descriptors "IgG4-related disease" and "salivary glands" were searched in the virtual databases of PubMed, CAPES, Medline, BBO, LILACS and Scielo, from January 2018 to December 2020. The data included sex, age, systemic impairment, signs and symptoms and treatment. **Results**: 35 articles were selected, of which 12 were original articles, 17 case reports and six literature reviews. **Conclusion:** The salivary glands are the second organ most commonly involved in immunoglobulin G4-related disease; often the affected patients present a diffuse increase in volume of these glands, usually bilaterally, painlessly and persistently, with varying degrees of mouth dryness. Although the diagnosis is still a challenge, the dental surgeon must be aware of this condition, making a differential diagnosis with other diseases such as Sjögren's syndrome and thus, helping in the correct diagnosis and treatment of comorbidities related to the disease.

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INTRODUCTION

The immunoglobulin G4-related disease (IgG4-RD) was initially described in 1995, after the identification of the condition called autoimmune pancreatitis (THOMPSON; WHYTE, 2018; YOSHIDA *et al*., 1995). Subsequently, there was an association with high serum levels of IgG4 and extra-pancreatic lesions (FUJITA, 2018; THOMPSON; WHYTE, 2018). Currently, this condition is considered to be a systemic, multifocal disease, tumefactive in nature, less commonly, infiltrative (THOMPSON; WHYTE, 2018). Clinically, it is histopathologically, by storiform fibrosis (an irregularly whorled pattern of fibrosis) and an intense lymphoplasmacytic inflammatory infiltrate, with abundant positive IgG4 cells (ARDILA-SUAREZ *et al*., 2017; THOMPSON; WHYTE, 2018). The etiological and pathophysiological mechanisms of the disease remain unclear, based on time, and effectiveness of steroid treatment and the histological characteristics common to the organs involved suggests that it is an autoimmune or infectious inflammatory condition (FUJITA, 2018).

The diagnosis of IgG4-RD is a challenge, not only due to the involvement of multiple organs, but also due its initial presentation; which may be nonspecific, mimicking or accompanying other inflammatory processes, such as autoimmune disorders, systemic vasculitis or neoplastic diseases (ARDILA-SUAREZ *et al*., 2017).

According to Umehara (2017), the diagnostic of IgG4RD is considered when all the criteria are present; as likely, when only clinical and histopathological criteria are recognized; and as possible when only clinical findings and high serum levels of IgG4 are found (Table 1). However, it is not well established whether serum levels of IgG4 above 135 mg/dL represent an absolute marker of the disease (FUJITA, 2018). This study is a narrative review of literature that aimed scientific support about the IgG4-RD in salivary glands to clarify and assist the dental surgeon in the diagnosis and treatment of this disease.

MATERIAL AND METHODS

Search strategies: A literature search was performed using the combination of descriptors "IgG4-related disease" and "salivary glands". The chosen descriptors were previously identified in articles published on the topic and are registered in the database of the Health Science Descriptors (DeCS). The virtual databases accessed for the research were: PubMed, Medline, BBO, LILACS and Scielo, from January 2018 to December 2020.

Inclusion and exclusion criteria: English-language publications in which the title and abstract were related to the topic were included. In total, 104 articles were selected and after reading, 69 were excluded for not meeting the requirements: Incomplete (n=8), language/not writing in English (n=12), studies on animals (n=3), inconsistent conclusions (n=9) and those that, when analyzed, did not fit to the proposed theme (n=37).

Data extraction: From the selected articles, information about sex, age, systemic impairment, signs and symptoms, diagnostic tests and treatment were extracted. For the introduction and discussion, literature reviews that mention IgG4-related disease in other regions, with or without salivary gland involvement, were also included.

RESULTS

The research resulted in 104 articles published between January 2018 and December 2020 in the PubMed, CAPES, Medline, BBO, LILACS and Scielo databases. After reading, 35 studies were selected, 12 original articles, 17 case reports and six literature reviews (Figure1). According to the studies, when the disease is related to salivary glands, men and women are affected in almost the same proportion. The organs commonly involved are pancreas, salivary and lacrimal glands, kidney, lung and retroperitoneum (FUJITA, 2018; IKEDA *et al*., 2019; LIU *et al*., 2020; NIWAMOTO *et al*., 2020; WANG *et al*., 2019). Salivary glands represent the second most commonly involved organ (FERNÁNDEZ-CODINA *et al*., 2015; LIU *et al*., 2020; MARTÍN-NARES *et al*., 2020; NIWAMOTO *et al*., 2020; PUXEDDU *et al*., 2018; WANG *et al*., 2019). The onset of general symptoms are slow and may vary from fatigue to systemic manifestations of inflammation, such as fever (PUXEDDU *et al*., 2018; THOMPSON; WHYTE, 2018). In the head and neck region, more specific symptoms include an increase in the diffuse volume of the salivary and lacrimal glands, often bilaterally and painlessly, persisting for more than three months (HONG *et al*., 2017; PUXEDDU *et al*., 2018). The involvement of regional lymph nodes is usually noticed (ARAKI *et al*., 2018; HIRATA *et al*., 2018; LI *et al*., 2015). Increased lip, neck and face region, vascular and skin involvement, with the presence of erythematous plaque and pain during eating were also reported. The first-line induction therapy for IgG4-RD is uniformly glucocorticoid administration. The table 2 summarizes organs involved, signs and symptoms, evolution time and treatment found in cases reports and table 3 summarizes data found in original studies and literature review.

Table 1. Diagnostic criteria for IgG4-RD. Modified from Umehara (2017) and Fujita (2018)

DIAGNOSTIC CRITERIA FOR IgG4-RD ACCORDING TO UMEHARA
1. Clinical examination showing a diffuse or localized increase in volume or organ masses. 2. High serum levels of IgG4 (≥ 135 mg/dL). 3. Histopathological findings, including intense lymphoplasmacytic infiltrate with fibrosis and infiltration of plasma IgG4 + cells with a proportion of IgG4 + / igG + cells greater than 40% and greater than 10 IgG4 + in plasma cells / field. Defined: meets all criteria (1), (2) and (3) Likely: meets (1) and (3). Possible: meets (1) and (2).

DISCUSSION

IgG4-RD is a chronic fibroinflammatory condition characterized by enlargement of the affected organs, elevated serum concentrations of IgG4, and infiltration of abundant IgG4-positive plasma cells into affected organs (ABOULENAIN *et al*., 2020; MARTÍN-NARES *et al*., 2020; MATSUI *et al*., 2016; NIWAMOTO *et al*., 2020; PEURAHARJU *et al*., 2019; THOMPSON; WHYTE, 2018). The etiology (autoimmune, infectious or paraneoplastic) of the disease remains uncertain (ABOULENAIN *et al*., 2020; ARDILA-SUAREZ *et al*., 2017; BLEDSOE *et al*., 2018; FUJITA, 2018; KARADENIZ; VAGLIO, 2020), as well as the existence of genetic predisposition and associated risk factors, such as smoking and asbestos exposure (WALLACE *et al*., 2019). Likewise, the pathological mechanisms of IgG4-RD remain unknown (LANZILLOTTA *et al*., 2020; WALLACE *et al*., 2019). Several types of lymphocytes and their cytokines such as T helper 2 (Th2) cells (ABOULENAIN *et al*., 2020; KARADENIZ; VAGLIO, 2020; PUXEDDU *et al*., 2018; YAMAMOTO *et al*., 2018), IL-4, IL-5 and IL-13; regulatory T (Treg) cells and cytokines IL-10 and TGFb; and follicular helper T (Tfh) cells, have been shown to contribute to the pathogenesis of the disease activating B lymphocyte, enhancing IgG4 class switch recombination, leading to development of ectopic germinal centers, and inducing fibrosis (LANZILLOTTA *et al*., 2020; PUXEDDU *et al*., 2018; TSUBOI *et al*., 2020). More than forty different sites can be affected by IgG4-RD (ZHANG *et al*., 2019), the main ones being pancreas, salivary and lacrimal glands, kidney, lung and retroperitoneum (IKEDA *et al*., 2019; KARADENIZ; VAGLIO, 2020; LIU *et al*., 2020; NIWAMOTO *et al*., 2020; WANG *et al*., 2019; YOO *et al*., 2020). Salivary glands represent the second organ most commonly involved, with changes observed in 16% to 68% of patients (FERNÁNDEZ-CODINA *et al*., 2015; LIU *et al*., 2020; MARTÍN-NARES *et al*., 2020; NIWAMOTO *et al*., 2020; PUXEDDU *et al*., 2018; WANG *et al*., 2019). The submandibular glands are the most affected, however, the parotid, sublingual and labial glands can also be involved (HONG *et al*., 2018). Former names of the condition were: Mikulicz's disease, when if affected in the head and neck region, with manifestations restricted to salivary and lacrimal glands bilaterally (ARDILA-SUAREZ *et al*., 2017; THOMPSON; WHYTE, 2018); Küttner'spseudotumor, with manifestations only in submandibular glands (FUJITA, 2018; LAKSHMANAN *et al*., 2019); and Riedel's thyroiditis (STAN *et al*., 2017). Nowadays, these three entities are recognized as manifestations of IgG4-RD (THOMPSON; WHYTE, 2018).

When the disease is related to salivary glands, men and women are affected in almost the same proportion (IKEDA *et al*., 2019; MARTÍN-NARES *et al*., 2020; PEURAHARJU *et al*., 2019; YAMAMOTO *et al*., 2018) and although does exists reports of the disease in children (JORDAN *et al*., 2018; WALLACE *et al*., 2019), the age at diagnosis ranges from 50 to 70 years in most cases (ABOULENAIN *et al*., 2020; BLEDSOE *et al*., 2018; WALLACE *et al*., 2019). This condition is also associated with high frequency of allergies and autoimmune pancreatitis (LANZILLOTTA *et al*., 2020; NIWAMOTO *et al*., 2020; TACHIBANA *et al*., 2020). IgG4-RD occurs in a subacute manner in most patients (PUXEDDU *et al*., 2018; ROOS *et al*., 2019; THOMPSON; WHYTE, 2018). Thus, the onset of general symptoms is slow and there seldom is weight loss (ABOULENAIN *et al*., 2020; WALLACE *et al*., 2019), night sweats, fatigue, elevation of acute phase markers and other systemic manifestations of inflammation, such as fever (PUXEDDU *et al*., 2018; THOMPSON; WHYTE, 2018; YOO *et al*., 2020). In the head and neck region, more specific signs include an increase in the diffuse volume of the salivary and lacrimal glands, often bilaterally (MARTÍN-NARES *et al*., 2020) and painlessly, persisting for more than three months (HONG *et al*., 2017; PUXEDDU *et al*., 2018). The involvement of regional lymph nodes is usually noticed (ARAKI *et al*., 2018; HIRATA *et al*., 2018; LI *et al*., 2015). Increased lip, neck and face region, vascular and skin involvement, with the presence of erythematous plaque and pain during eating were also reported (Table 2).

Table 2. Results of case reports with information on gender, organs involved, signs and symptoms, evolution and treatment.

Author	Gender	Age	Organs involved	Signs and symptoms	Evolution time	Treatment
Araki *et. al*.(2018)	Female	65	Liver (Autoimmune Hepatitis), hepatic hilar lymph nodes, cervical vertebra, salivary gland, lips, gingiva, and stomach wall	Cutaneous pruritus and swelling of the lips	Not reported	Oral prednisolone administration at 50 mg/day (0.8 mg/kg/day)
Hirata *et. al*. (2018)	Male	61	Optic nerves, lacrimal glands, submandibular glands, mediastinal hilar lymph node, bronchial tubes, pancreas, aorta and prostate	Decreased visual acuity, blepharoedema, conjunctival injection, exophthalmos, diplopia, and blurred vision.	21 years	Steroid pulse therapy and 40 mg/day oral prednisolone to 10 mg/day
Mizuma *et. al*. (2018)	Male	82	Mononeuritis multiplex, bilateral lacrimal and salivary glands (Mikulicz's disease).	Gait disturbance, pain and swelling of the left hand and right toe. These symptoms were progressive and made it difficult for him to walk	1 year	40 mg/day of oral prednisolone
Murai *et. al.* (2018)	Female	68	Lacrimal and salivary glands (Mikulicz's disease)	Bilateral palpebral swelling and difficulty opening her eyes	Not reported	8 weeks of treatment with prednisolone.
Narayan *et. al.* (2018)	Male	56	Pancreas and submandibular glands	Acute painless jaundice, neck swelling with dry mouth sensation, particularly at night	4-5 months	Corticosteroids
Pomponio *et. al*. (2018)	Female	50	Bilateral parotid gland, bilateral periorbital and lung	Eyelid xanthelasmas, adult-onset asthma and salivary and lacrimal glands enlargement with sicca syndrome and slight pain	18 months	1 cycle of 2 g rituximab - 1000 mg each 15 days apart together with methylprednisolone 100 mg single shot premedication
Tous-Romero *et. al*.(2018)	Male	40	Skin, masseter muscle, right submaxillary gland and lung	Erythematous plaque in the right paramandibular region	4 months	Methylprednisolone 40 mg/ day
Dong *et. al*. (2019)	Male	51	Bilateral orbits, salivary glands, submandibular glands, lymph nodes, and prostate (Mikulicz's disease)	Bilateral exophthalmos, reduced vision, and weight loss	2 years	Surgery and 40 mg of oral methylprednisolone
Ikeoka *et. al*. (2019)	Male	64	Vascular and skin involvement, bilateral salivary glands (Mikulicz's disease)	Repetitive critical upper and lower limb ischemia owing to occlusive disease of multiple small arteries and bilaterally swollen salivary glands	Not reported	The patient was administered low-dose steroid (prednisolone, 0.1 mg/kg/d) to prevent bypass artery occlusion
Jinkala *et. al*. (2019)	Female	51	Salivary gland, lacrimal gland, lymph node and kidney	bilateral neck swellings, left lateral eyelid swelling and axillary lymphadenopathy	1 year	Oral prednisolone 1mg/ KBW/day for 4 weeks
Lakshmanan *et. al*.(2019)	Female	33	Submandibular gland (Kuttner's tumour)	Pain and swelling in the right submandibular region. Her symptoms aggravated more during mealtime	15 days	Antibiotics and analgesics for a week. Right Wharton's duct marsupialization followed by stone removal
Li *et. al*. (2018)	Male	48	Lymph nodes, bilateral lacrimal and parotid glands (Mikulicz's disease)	Enlarged lacrimal and parotid glands, dry mouth and thrombocytopenia	3 years	Intravenous 40 mg methylprednisolone for seven days
Roos *et. al*. (2019)	Male	37	Bilateral parotid	Left-sided facial swelling with local and upper body itch and seven years later, right parotid swelling	2 years	Radiotherapy (30 Gy in 15 fractions daily over 3 weeks using a direct 16-MeV electron field)
Yang and Tsai (2019)	Female	39	Minor salivary glandular	Hard mass on right cheek	3 months	Glucocorticoid therapy, starting with prednisolone 30 mg/day for 4 months
Okamoto *et al.* (2020)	Male	64	Submandibular gland	Mild right back pain and swelling in the bilateral submandibular glands	6 months	Oral prednisolone 30 mg/day for 2 weeks and gradually tapered by 10% every 2–4 weeks
Tachibana *et al*. (2020)	Female	51	Bilateral submandibular gland	Bilateral submandibular nodules	1 month	Oral prednisolone 30 mg/day for 4 months
Aboulenain *et al*. (2020)	Male	46	Bilateral submandibular and parotid glands	Bilateral submandibular and parotid glands swelling, bilateral eyelid swelling, excessive lacrimation and diplopia	6 months	Prednisone 20 mg/12 hours

Table 3. Data found in the original studies and literature review

Author	TS*	Goals	Sample size	Results
Min *et. al*. (2020)	OS	Detect the changes of tight junctions in submandibular glands derived from IgG4-RS patients, and analyze the relationship and possible mechanism between this and the progression of IgG4-RS.	22 patients (10 male and 12 female) / Mean age 54.73 ± 12.54 years	The integrity of tight junctions complex of SMGs is impaired and might contribute to hyposalivation of IgG4-RS patients
Niwamoto *et. al*. (2020)	OS	Classify IgG4-RD and identify the clinical features, including the comorbidities of each subgroup	73 patients had salivary gland lesion	IgG4-RD can be classified into subgroups according to the pattern of affected organs. Mikulicz's disease may have frequent complications with allergies and malignancies
Ikeda *et. al*. (2020)	OS	Analyze the incidence, types and details in the clinical course of malignancies in patients with IgG4-RD in head and neck regions	26 patients had head and neck lesion (25 in salivary gland) / The mean age 60.6 ± 11.6 years	Two patients (7.7%) developed life-threatening malignancies (salivary duct carcinoma in the submandibular gland and lymphoma in the orbital tissue)
Sakamoto *et. al*. (2020)	OS	Investigate the diagnostic utility sonography and labial salivary gland biopsy as a less invasive procedure for diagnosing IgG4-RD dacryoadenitis and sialadenitis (IgG4-DS)	68 patients with suspected IgG4-DS before biopsy (32 men and 36 women; mean age, 59.4 ± 16.0 years)	Submandibular gland sonography is sufficient for the diagnosis of IgG4-DS, especially when combined with serologic analysis
Hong *et. al.* (2019)	OS	Explore the role of TNF-α in acinar cell injury in IgG4-RS, with a possible mechanism involved in the regulation of autophagic flux	33 patients (20–74 years old; 21 men)	TNF-α induces acinar cell injury in IgG4-RS and raises the possibility that treatments targeting TNF-α could be beneficial for patients
Yamamoto *et. al.* (2018)	OS	Verify clinical stages of IgG4-RD (that they assumed) using serum cytokine levels in the groups classified by lesion distribution	55 patients (29 males and 26 females) / The mean age 58.3±12.8 years	The serum IL-5 level was significantly increased in the groups with a poor prognosis than in the good prognosis group
Liu *et. al*. (2020)	OS	Compare detailed demographic, clinical and laboratory characteristics of IgG4-RD patients with salivary gland lesions (IgG4-RD SG+) and salivary-gland-free IgG4-RD (IgG4-RD SG-) in a large cohort	249 cases had IgG4-RD SG+, and 179 cases IgG4-RD SG-	IgG4-RD SG+ patients showed younger age at disease onset and diagnosis, and a longer interval between symptom onset and diagnosis. This group involved more female patients, and allergic diseases were more common. In terms of organ involvement, the IgG4-RD SG+ group were more frequently presented with lacrimal gland involvement
Hong *et. al*. (2018)	OS	Determine the short-term and long-term outcomes of IgG4-RS patients treated with glucocorticoids and steroid-sparing immunosuppressive agents	Glucocorticoids were used in all 43 patients and steroid-sparing immunosuppressive agents in 38 patients / The mean age 51.8 ± 14.4 years	The combination of glucocorticoid and steroid-sparing agents could be effective for treating IgG4-RS and restoring salivary gland function
Martín-Nares *et. al.* (2020)	OS	Evaluate if major salivary gland enlargement in patients with IgG4-RD is associated with systemic involvement	47 patients, 25 men with a mean age of 50.8 ± 14.2 years	Patients with major salivary gland involvement had a higher number of affected organs, a higher prevalence of lacrimal glands, lymph nodes, and lung involvement, rheumatoid factor positivity

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Wang *et. al*. (2019)	OS	Study the impact of sex on the clinical presentation of IgG4-RD	403 IgG4-RD patients, consisting of 150 females and 253 males	Allergy history, Mikulicz's disease and thyroiditis were more common in female patients, while autoimmune pancreatitis, sclerosing cholangitis and retroperitoneal fibrosis were more common in male patients
Peuraharju *et. al*. (2019)	OS	Determine whether chronic sclerosingsialadenitis always presents as IgG4-RD or associates with autoimmune diseases	21 patients (26 male and 25 female) / The mean age 57.6 years	Non-sclerosing chronic sialadenitis and chronic sclerosingsialadenitis remain difficult to distinguish histologically. Thus, it is possible that they represent a continuum progressing from the former to the latter over time
Yoo *et al*. (2020)	OS	Investigate the clinical and imaging features predicting the histopathological diagnosis of IgG4-RD in patients with suspected IgG4RD on computed tomography (CT).	178 patients (67 male) / The mean age was 64 years	Elevated IgG4 level, renal involvement, and swelling pattern on CT are associated with histopathological diagnosis of IgG4RD. The clinical and imaging features might help to decide further evaluation in patients with clinically suspected IgG4RD
Bledsoe *et. al.* (2018)	LR	Summarize the histopathologic and clinical features of IgG4-RD with detailed discussion of the histopathologic characteristics of the most commonly involved anatomic sites	-	A core set of histopathologic features has been established – including storiform fibrosis, increased IgG4+ plasma cells with an increased IgG4/IgG plasma cell ratio, and obliterative phlebitis
Fujita (2018)	LR	Discuss the details of SjS and IgG4-RD	-	IgG4-RD typically shows both multiglandular and localized involvement, which is often difficult to differentiate from malignancies such as lymphoma or salivary gland carcinoma.
Puxeddu *et. al.* (2018)	LR	Discuss new insights in the pathogenesis of IgG4-RD, focusing on its clinical aspects and the tools that are currently available for a correct differential diagnosis when the salivary glands are involved	-	Biopsy of affected organs remains so far the gold standard for diagnosis. Therapy is presently based on the use of steroids and immunosuppressants, but recent insights into pathogenic mechanisms forecast new more disease-tailored therapeutic approaches
Thompson & Whyte (2018)	LR	Discuss the recent evolution of IgG4-RD with respect to the recognition, nomenclature, diagnosis, postulated aetiology, pathogenesis and treatment	-	The radiologist should be aware of the systemic nature of IgG4-RD, potential manifestations at each head and neck subsite and relevant differential diagnoses. MALT lymphoma has similar imaging findings and always requires exclusion; it can also occur secondary to IgG4-RD within the salivary glands
Lanzillota *et al*. (2020)	LR	Discuss the advances in the diagnosis and management of IgG4-RD	-	The optimal management of patients with IgG4-RD has to be grounded in careful clinical-pathological correlation and the continued follow-up is crucial. IgG4-RD is highly treatable and responds promptly to glucocorticoids.
Karadeniz & Vaglio (2020)	LR	Present a review of recent advances in clinico-pathological characteristics, diagnosis and treatment of IgG4-RD	-	The etiology, prevalence and epidemiologic knowledge is quite limited. IgG4-RD is diagnosed based on the combination of clinical, radiological and histopathological findings. Glucocorticoids lead to rapid clinical response. It is prudent to monitor patients for the symptoms of malignant diseases.

Salivary flow can be normal (ABOULENAIN *et al*., 2020; FUJITA, 2018), or slightly reduced, and mouth dryness is present in 30% of patients, being less frequent than in Sjögren's syndrome (SSj) (PUXEDDU *et al*., 2018). Secretory impairment, when present, is more severe in the submandibular glands and improves with early steroid treatment (FUJITA, 2018; PUXEDDU *et al*., 2018). This improvement was justified by recent studies that demonstrated the accumulation of immune cells and their released cytokines, culminating in acinar cell injury and fibrosis (HONG *et al*., 2019; MIN *et al*., 2020; PUXEDDU *et al*., 2018). SSj makes a differential diagnosis with IgG4-RD, sharing clinical and laboratory aspects, such as increased glandular volume, Sicca syndrome, arthralgias, hypergammaglobulinemia, hypocomplementemia, and the presence of antinuclear antibodies (ANA) (PUXEDDU *et al*., 2018). However, the glandular increase in IgG4-RD is persistent, while in SSj, it is frequently recurrent and of short duration (HONG *et al*., 2017; THOMPSON; WHYTE, 2018). Regarding laboratory tests, they are distinguished by the presence of anti-Ro / SSA and anti-La / SSB antibodies in the vast majority of patients with SSj, and by the infiltration of plasma IgG4+ cells (KARADENIZ; VAGLIO, 2020; PUXEDDU *et al*., 2018; TACHIBANA *et al*., 2020; THOMPSON; WHYTE, 2018). Furthermore, only IgG4-RD responds to steroids (PUXEDDU *et al*., 2018). In addition, Baer *et al*. (2013) reported that only one in 2594 patients in a research record for SSj had histopathological and clinical findings consistent with the diagnosis of IgG4-RD. Other entities makes differential diagnosis with IgG4-RS amongst them Castleman disease, eosinophilic granulomatosis with poliangiitis, sarcoidosis, and the Heerfordt syndrome, characterized by extrapulmonary manifestations, in which salivary glands and cervical lymph nodes are involved, and uveitis and facial nerve palsy can be present (PUXEDDU *et al*., 2018). In 2017, Umehara *et al*. (2017) proposed diagnostic criteria for IgG4-RD based on the clinical aspect, IgG4 serum concentrations and, histopathologically, on the marked lymphoplasmacytic infiltration. For the confirmation of the disease, it is necessary that three diagnostic criteria are met; if not, the disease is considered possible or probable. Although IgG4 serum concentrations can be an important data for the diagnosis of the lesion, other conditions may also present high IgG4 serum concentration such as chronic sinusitis and recurrent pneumonia (CARRUTHERS *et al*., 2015; KARADENIZ; VAGLIO, 2020; LANZILLOTTA *et al*., 2020; YOO *et al*., 2020). Likewise, patients with IgG4-RD may have normal levels of IgG4 (CARRUTHERS *et al*., 2015; KARADENIZ; VAGLIO, 2020; LAKSHMANAN *et al*., 2019; WALLACE *et al*., 2015). In addition, several diseases, including pemphigus (LAFFITTE *et al*., 2001), rheumatoid arthritis (ASANO; SATO, 2012; CHEN *et al*., 2014) and salivary carcinomas (GILL *et al*., 2009) exhibit infiltration of plasma IgG4+ cells in local lesions.

Tissue biopsy of the affected organ is the gold standard for diagnosing IgG4-RD (FUJITA, 2018; LANZILLOTTA *et al*., 2020; PUXEDDU *et al*., 2018; TACHIBANA *et al*., 2020) and the histopathologic diagnosis of IgG4-RD include two or more characteristic features: a dense lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis, an increased number of IgG4+ plasma cells/HPF, and an IgG4+/IgG+ plasma cell ratio of >40% (BLEDSOE *et al*., 2018; KARADENIZ; VAGLIO, 2020; LAKSHMANAN *et al*., 2019; OKAMOTO *et al*., 2020; TACHIBANA *et al*., 2020). The inflammatory infiltrate of IgG4-RD is composed of frequent mature-appearing plasma cells and small lymphocytes, with a variable number of eosinophils (BLEDSOE *et al*., 2018). Histiocytes, although present, are not prominent (BLEDSOE *et al*., 2018; KARADENIZ; VAGLIO, 2020). Image exams are important to reach and clarify a correct diagnosis (ABOULENAIN *et al*., 2020; YOO *et al*., 2020). The magnetic resonance imaging demonstrates diffuse swelling of the salivary glands and most lesions are well-defined and demonstrate relatively homogeneous signal intensity (ABOULENAIN *et al*., 2020; FUJITA, 2018). However, these findings are not specific for IgG4-RD (FUJITA, 2018; YOO *et al*., 2020) and have some limitations (PUXEDDU *et al*., 2018).

Ultrasonography plays an important role in the assessment of dacrioadenitis and sialoadenitis related to IgG4-RD (THOMPSON; WHYTE, 2018). Sakamoto *et al*. (2020) proposed the use of ultrasound as an alternative to biopsy in the investigation of IgG4-RD in submandibular glands, since they found that ultrasound combined with IgG4 serum measurement exhibits sensitivity, specificity and precision similar to biopsy. However, although the assessment of clinical, serological, radiological and pathological characteristics contributes to the classification of IgG4-RD, none of these approaches alone provide definitive evidence for the precise classification of patients (SAKAMOTO *et al*., 2020). Proper categorization requires data integration for all tests due to the multiorgan nature of the disease (SAKAMOTO *et al*., 2020).
Thus, it highlights the importance of performing biopsies of lesions with enlarged volume to definitively diagnose the disease (SAKAMOTO *et al*., 2020). The accumulation of 18F-fluoro-2-deoxy-D-glucose (18F-FDG) seen on positron emission tomography (PET), which is widely used for the diagnosis of malignant diseases with glucose metabolism, however, has also been observed organ labeling with IgG4-RD (ARAKI *et al*., 2018; LANZILLOTTA *et al*., 2020) and used as a complementary exam for the diagnosis and assessment of response to the treatment of IgG4-RD (ARAKI *et al*., 2018; DONG *et al*.2019; HIRATA *et al*., 2018; LI *et al*., 2018b; POMPONIO *et al*., 2018; PUXEDDU *et al*., 2018).

Despite the possibility of spontaneous remission (HONG *et al*., 2018), the involvement of several organs requires the administration of systemic medications and sometimes the gland is removed for therapeutic purposes and for definitive, like when localized diseases such as submandibular gland (LAKSHMANAN *et al*., 2019). Glucocorticoids should be used as first line therapy (KARADENIZ; VAGLIO, 2020; LANZILLOTTA *et al*., 2020). The goal of treatment is to maintain remission of the disease, in order to prevent the progression of fibrosis with destruction of affected organs (KARADENIZ; VAGLIO, 2020; LAKSHMANAN *et al*., 2019; PUXEDDU *et al*., 2018). The discontinuing steroid therapy is very difficult and only 4.7% of patients attained drug-free remission, and half of the IgG4-DS patients presented with relapse within seven years from initial treatment (YAMAMOTO *et al*., 2018).

Conventional steroid-sparing agents can be considered a second line of therapeutic action, such as rituximab, a monoclonal antibody against the CD20 antigen (BLEDSOE *et al*., 2018; LANZILLOTTA *et al*., 2020; PUXEDDU *et al*., 2018). Its mechanism of action seems to be linked to the elimination of autoantibody-producing cells, and it is a medication that has few side effects, in general, due to allergic reactions (BLEDSOE *et al*., 2018). However, the application of steroid-sparing immunosuppressive seems to be controversial and Hong *et al*. (2018) did not found difference between the groups treated with or without steroid-sparing agents; and the combination of glucocorticoid and steroid-sparing agents could be effective for treating IgG4-RS and restoring salivary gland function.

In addition to the well-established treatments, Roos *et al*. (2019) reported a case of IgG4-RD treated with an intermediate dose of radiotherapy (30 Gy in 15 daily fractions for 3 weeks using a direct 16-MeV electronic field), which resulted in remission of the parotid swelling. Despite the promising result, the authors themselves report that this therapy can be controversial, particularly due to the heterogeneous histological characteristics in the different sites affected by the disease. Regarding malignancy, besides IgG4-RD mimics many malignant disorders (ABOULENAIN *et al*., 2020; FUJITA, 2018; TACHIBANA *et al*., 2020; YOO *et al*., 2020), such as lymphoma (JINKALA *et al*., 2019; PUXEDDU *et al*., 2018), Ikeda et. al. (2019) found malignancies (lymphoma and salivary duct carcinoma) in only 7.7% head and neck IgG4-RD patients, with high levels of IgG4/IgG and multiple lesions. Niwamoto *et al*. (2020) demonstrated that 11% of the sample of 108 cases of IgG4-RD presented reports of malignancy after diagnosis, in which only one of these patients developed tongue cancer.

CONCLUSION

The diagnosis of IgG4-RD remains a challenge. The salivary glands are the second most commonly involved organ in IgG4-RD; as such, the affected patients often present a diffuse increase in volume of these glands, usually bilaterally, painlessly and persistently, with varying degrees of mouth dryness. Thus, the dentist must be aware of these manifestations, making a differential diagnosis of IgG4-RD with other diseases such as SSj and, thus, assist in diagnosis and treatment of comorbidities related to the disease. Moreover, it is necessary to keep in the mind the possible coexistence of malignancies in patients with IgG4-RD at the time of diagnosis and during long-term follow-up.

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