

ORIGINAL PAPER

**IGG4-RELATED DISEASE IN THE HEAD AND NECK REGION:
REPORT OF TWO CASES AND REVIEW OF THE LITERATURE**

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IgG4-related disease (IgG4-RD) is a rare immune-mediated condition characterized by extensive tissue fibrosis and infiltration by immunoglobulin G4 positive plasma cells in a single organ or systemic appearance. Two cases are presented including an unusual case of a 30-year-old man with IgG4-RD appearing simultaneously in the cervical lymph nodes, ethmoid, maxillary sinuses, and upper gingiva, with spontaneous loss of teeth. According to the literature, this is the first case with loss of teeth occurring in the course of the disease. The second case is a 46-year-old man suffering from IgG4-related chronic sclerosing sialadenitis of the right submandibular gland.

Key words: IgG4-related disease, head and neck, Küttner tumor, upper respiratory tract.

Introduction

IgG4-related disease (IgG4-RD) is an uncommon pathology of immunologic origin characterized by fibrosis and infiltration of IgG4-positive plasmacytes encountered in one organ or as systemic presentation. Clinical symptoms of IgG4-RD may mimic malignant neoplasm or infection [1, 2, 3]. IgG4-RD is diagnosed most commonly in the pancreas, followed by the head and neck region, particularly in the salivary glands, orbits, lymph nodes, thyroid, upper respiratory tract, and skin [1, 2, 4, 5].

This case report highlights two cases of IgG4-RD. The first case is a 30-year-old male patient with involvement of the cervical lymph nodes, upper gingiva, maxillary, and ethmoid sinuses. The second case is a 46-year-old male patient with Küttner tumor (IgG4-related chronic sclerosing sialadenitis) of the submandibular gland. A review of the literature is also presented.

Case 1

A 30-year-old male patient was admitted as an emergency case to the Department of Cranio-Maxillofacial Surgery. He had acute inflammatory infiltration of the eyelids of the left eye rapidly progressing for 2 days. His body temperature was normal. The patient reported spontaneous loss of teeth of the left maxilla occurring over the previous 2 years. Clinical examination revealed soft, painless swelling of the eyelids with redness of the skin, as well as ptosis of the upper eyelid. Enlarged cervical lymph nodes were also present on the left side, at neck levels I-III (Fig. 1).

Following spontaneous loss of teeth 25 and 26, the teeth sockets were filled with inflammatory granulation tissue. Loosening of tooth 24 was also found (Fig. 2). Ophthalmologic examination showed decreased visual acuity of the left eye (0.8). Motility of the eyeballs was within the normal range. Empiric



Fig. 1. 30-year-old patient with soft, painless swelling of the eyelids, ptosis of the upper eyelid, and cervical lymphadenopathy at neck levels I-III on the left side

antibiotic therapy was administered on admission and included Augmentin 3×1.2 g intravenously plus metronidazole 3×500 mg intravenously.

The CT scans showed thick soft tissues of the left frontal and supraorbital region, upper eyelid, and paranasal area. The superior oblique and the levator of the superior eyelid muscles were enlarged. A defect



Fig. 3. CT scan showing a defect of the alveolar part of the left maxilla with inflammation of the lining membrane of the maxillary and ethmoid sinuses

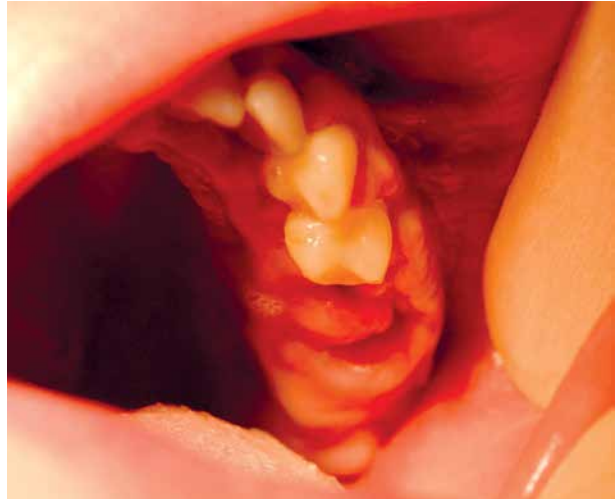


Fig. 2. Teeth sockets after spontaneous loss of teeth 25 and 26, filled with inflammatory granulation tissue

of the alveolar part of the left maxilla (19×15 mm) was found, along with inflammation of the lining membrane of the maxillary sinus (Fig. 3). On the left side of the neck, enlarged cervical lymph nodes (24×44 mm, 18×31 mm, 41×18 mm) were found under the sternocleidomastoid muscle, in the vicinity of the common carotid artery, and in the area of the mandibular angle. A chest X-ray and ultrasound of the abdomen showed no existing pathologies. Laboratory tests revealed an increased number of leucocytes ($12.56000/\mu\text{l}$) with neutrophilia ($8.22000/\mu\text{l}$) and monocytosis ($1.50000/\mu\text{l}$).

The initial diagnosis was lymphoma. However, in order to obtain histological verification, the enlarged cervical lymph nodes of neck level I were excised under general anesthesia. A biopsy was taken of the alveolar mucosa in the region of teeth 25 and 26, as well as an endoscopically assisted biopsy of the mu-

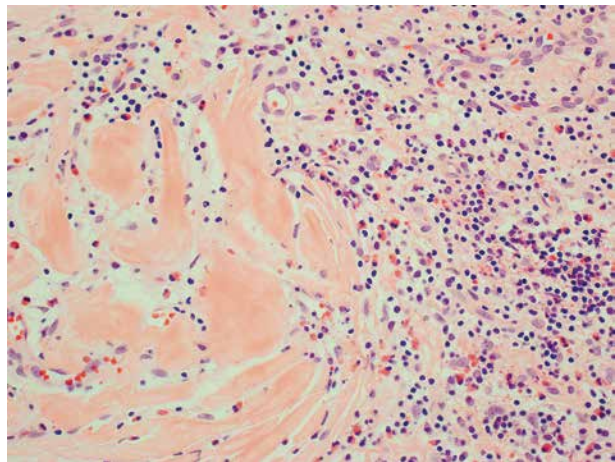


Fig. 4. Mucosa of ethmoid paranasal sinus with fibrosis, hyaline change, and inflammatory infiltration composed of plasma cells, eosinophils, and lymphocytes. HE, obj. magnification $40\times$

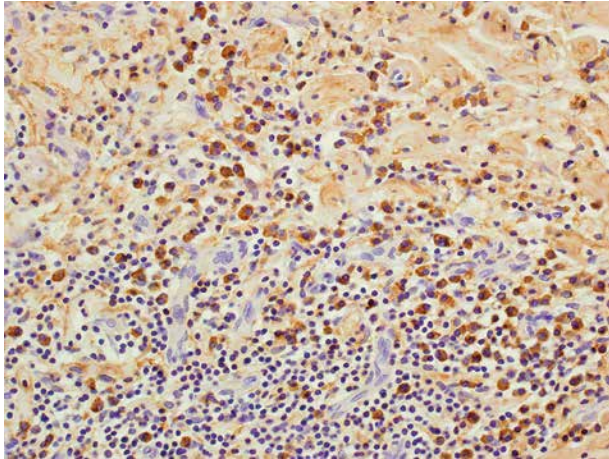


Fig. 5. Numerous IgG4-positive plasma cells in the lymph node with fibrotic and inflammatory changes. Immunohistochemical staining for IgG4, obj. magnification 40×

cosa of the middle nasal concha, and the left ethmoid sinus. Bacteriological examination of the specimen harvested from the sockets of teeth 25 and 26 revealed the presence of *Streptococcus oralis* sensitive to penicillin.

Histopathological examination of the surgical material from the ethmoid sinus revealed edematous mucosa occupied by the moderately abundant inflammatory infiltrate composed of lymphocytes, plasma cells, and many eosinophils. The walls of some of the small blood vessels were thickened, and focal non-obliterative phlebitis was found. In the mucosal stroma, scattered hyaline changes were also present (Fig. 4). In the removed lymph node (enlarged to 39 mm in the largest dimension), the architecture was generally restored with reactive changes (mainly follicular hyperplasia). It was blurred only in the small area where fibrosis and hyaline changes, focally storiform, were accompanied by dense inflammatory

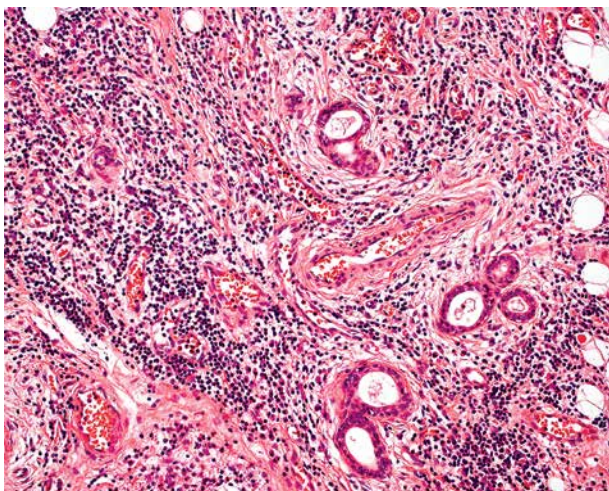


Fig. 6. Lymphoplasmacytic infiltrate in salivary gland parenchyma and non-necrotizing vasculitis. HE, obj. magnification 100×

infiltrate composed of many eosinophils, plasma cells, and lymphocytes. The histopathological features were highly suggestive of IgG4-RD, which led to appropriate immunohistochemical staining. This revealed a significant number of IgG4-positive plasma cells in the inflammatory infiltration. The IgG4+/IgG+ ratio was 80% (Fig. 5). An increased level of IgG4 +335 mg/dl was found in the patient's serum.

The patient was transferred to the Department of Immunology with a diagnosis of IgG4-RD, and received corticosteroids with good response.

Case 2

A 46-year-old male patient was admitted to our department for sialolithiasis of the right submandibular gland. The patient reported firm enlargement of the right submandibular gland and diminished secretion of the saliva for 7 months. Ultrasound showed an enlarged, heterogeneous submandibular gland and several calcified lesions that were 2-3 mm in diameter. The salivary duct was not widened, and an orthopantomogram showed no calcified lesions within the gland. On palpation, the right submandibular gland was painless and firm. A chest X-ray was normal and laboratory tests showed an increased level of glucose (5.7 mmol/l, n: 3.3-5.6).

Symptoms suggested cirrhosis of the submandibular gland caused by sialolithiasis. The patient received surgical treatment and excision of the right submandibular gland under general anesthesia. Macroscopically, histopathological examination revealed tumor-like changes of the enlarged gland (45 × 30 × 15 mm) section which showed a solid, firm, greyish mass. In the lumen of the three salivary ducts, sialoliths were found, ranging in size from 0.2 mm to 6 mm in diameter. Microscopically, the lobular architecture of the gland was preserved. Dense lymphoplasmacytic infiltrate with patchy distribution was accompanied by stromal fibrosis. The salivary ducts were surrounded by thick fibrous tissue and the epithelial lining was focally disrupted. Non-necrotizing inflammation of the veins was focally present (Fig. 6). Immunohistochemically, the infiltrate contained numerous IgG-positive plasmacytes with IgG4+/IgG+ ratio > 70% (Fig. 7). Laboratory tests showed a normal serum level of IgG4 + 87 mg/dl.

The patient was transferred to the Department of Immunology with a diagnosis of IgG4-RD (Küttner tumor), for further evaluation and treatment.

Discussion

IgG4-related disease is a disorder of immunologic origin. It is relatively uncommon and not often recognized in its early stages. IgG4-RD combines many pathologies of uncertain etiology into one syn-

drome. The head and neck presentation of IgG4-RD is equally common in male and female patients, with an average age of 64 years [5]. Both cases presented here occurred in younger, adult men aged 30 and 46 years old.

IgG4-RD can be diagnosed in any organ, and symptoms of the disease are characteristic for a specific localization [1, 2]. Due to massive infiltration of IgG4-positive plasmacytes, dysfunction of the affected organ is most commonly observed. Local symptoms in the subacute course of the disease may suggest a neoplasm [1, 2]; thus, histologic examination is critical in the diagnosis of IgG4-RD. According to Deshpande *et al.* [6], histological appearance includes three main features: marked infiltrate of polyclonal lymphocytes and plasmacytes, storiform fibrosis, and obliterative phlebitis. Multiple authors have identified the criteria necessary for a definitive diagnosis of IgG4-RD, including: a) enlargement of affected organ, presence of a tumor or dysfunction of the organ; b) increased serum level of IgG4 (> 135 mg/dl); and c) the presence of more than 10 IgG4-positive plasma cells/high power field (HPF), and IgG4+/IgG+ ratio higher than 40%, during histological examination [7, 8].

The first patient (Case 1) met all diagnostic criteria identified above. The second patient (Case 2), however, met only two of the three criteria, (a) and (c), which is characteristic for a probable diagnosis. In general, the IgG4 serum level is considered an unreliable diagnostic criterion. This is due to the fact that almost 40% of patients with a histologically confirmed IgG4-RD serum level of IgG4 fall within the normal range, particularly in cases where the disease is localized in one organ, as happened in the second case [9, 10]. Conversely, in patients meeting criteria (a) and (b), a possible diagnosis of IgG4-RD can be made [7, 8].

The most common sites of presentation of IgG4-RD in the head and neck region are the salivary glands and lymph nodes. Upper respiratory tract presentation of the disease is rare (Table I) [3, 8, 9, 11, 12, 13, 14, 15, 16]. A review of the available literature showed only single cases of IgG4-RD of the oral cavity with presentation in the palate, tongue, floor of the mouth, and upper and lower gingiva [3, 8, 9].

In the current article, the authors present the case of the youngest patient with manifestation of IgG4-RD in the upper gingiva with subsequent spontaneous loss of teeth. According to the literature, this is only the sixth case of IgG4-RD in the oral cavity, and the first case with loss of teeth occurring in the course of the disease.

Enlargement of the submandibular gland is a fairly common presentation for maxillofacial and ear, nose, and throat surgeons. It is typically caused by chronic sialadenitis connected with sialolithiasis [17,

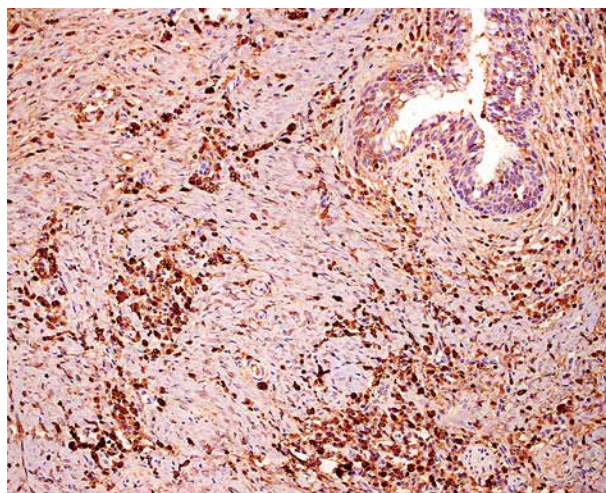


Fig. 7. IgG4-positive cells predominate in the inflammatory infiltrate. Immunohistochemical staining for IgG4, obj. magnification 100×

18, 19]. Firm enlargement of the salivary gland is characteristic of chronic sclerosing sialadenitis, which can suggest the presence of the neoplasm, and, as a result, another name for this condition is Küttner tumor [10]. Furukawa *et al.* [19] suggested that patients with Küttner tumor do not have sialolithiasis; however, during histological examination of the specimen, dense infiltrate of IgG4+ plasmacytes/HPF was present and the serum level of IgG4+/IgG+ was higher than 40%, which is specific for IgG4-RD. Küttner tumor can also be observed bilaterally, either synchronously or metachronously [19]. In addition, because it is a systemic disease, it may involve organs other than the submandibular gland [10, 19]. According to the available literature, only Laco *et al.* have described Küttner tumor with a 4 mm sialolith, which was similar to our case [18]. Sialoliths found in the course of IgG4-RD are likely formed secondary to sialadenitis and diminished secretion of saliva.

In the majority of studies with IgG4-related chronic sclerosing sialadenitis, patients were from either Japan or the United States [10, 19, 20]. Rare occurrences of the disease in Europe were confirmed in two retrospective studies evaluating the frequency of IgG4-RD in removed submandibular glands. In the United Kingdom, Harrison and Rodriguez-Justo reviewed 129 postoperative specimens and found no cases that met IgG4-RD criteria [17]. In the Czech Republic, Laco and colleagues were able to confirm diagnosis of IgG4-RD in only 6 (5.7%) of 105 treated cases [18].

The mean age of patients with IgG4-related chronic sclerosing sialadenitis, according to various published series, ranges from 57 to 64.5 years [10, 18, 19, 20]. The patient presented in Case 2 was younger, although Melo *et al.* presented a case of IgG4-RD of the submandibular gland in an 11-year-old boy [21].

Table I. IgG4-related disease of the upper respiratory tract

AUTHOR	GENDER/AGE (YEARS)	LOCALIZATION URT*	IgG4/HPF †	IgG4/IgG RATIO	SERUM IgG4 LEVEL (G/L)	OTHER INVOLVED ORGANS
Ishida <i>et al.</i> [11]	M/73	Nasal septum Maxillary sinus	“Diffuse”	0.72-0.86	0.63	Parotid gland
Ikeda <i>et al.</i> [12]	F/50	Ethmoid sinus Maxillary sinus	39	0.77	2.58	Pleura
Pace <i>et al.</i> [13]	M/73	Maxillary sinus	N/A‡	0.20	“normal”	None
Khurram <i>et al.</i> [3]	F/45	Palatine tonsil Tongue	“Dense”	0.65	3.52	Cervical lymphadenopathy
Lindau <i>et al.</i> [14]	M/69	Ethmoid sinus Maxillary sinus Sphenoid sinus	>30	N/A	0.75	Orbit
Andrew <i>et al.</i> [9]	F/71	Hard palate of the oral cavity	280	0.80	30.31	Lacrimal glands Parotid glands
Khoo <i>et al.</i> [15]	M/62	Supraglottic portion of the larynx	>50	N/A	1.52	None
Morris <i>et al.</i> [16]	M/34	Nasal cavity	>50	>0.40	2,3	None
Laco <i>et al.</i> [8]	F/59	Floor of mouth	103	0.68	1.85	None
Laco <i>et al.</i> [8]	M/79	Lower alveolar mucosa	139	0.72	1.65	None
Laco <i>et al.</i> [8]	M/74	Upper alveolar mucosa	66	0.71	N/A	None
Gontarz <i>et al.</i>	M/30	Upper alveolar mucosa Ethmoid sinus Maxillary sinus	75	0.80	3.35	Cervical lymphadenopathy

*URT – upper respiratory tract

†HPF – high power field

‡N/A – not available

In patients with confirmed IgG4-RD, involvement of other organs should be excluded [9, 10]. Patients with systemic IgG4-RD require a multidisciplinary approach that includes rheumatologists, gastroenterologists, pathologists, radiologists, and surgeons [22]. When treating IgG4-RD, corticosteroid therapy is the method of choice for the majority of patients.

To date, there are no randomized studies available that provide guidelines on the appropriate treatment of IgG4-RD. Reviewed articles were mainly retro-

spective analyses of patients who were treated with prednisolone [1, 23]. Management with corticosteroids leads to decreased serum levels of IgG4 and remission of clinical and radiological symptoms. In the majority of patients, clinical results are obtained quickly, and the response to treatment depends upon the length of time of the disease and the degree of fibrosis of the affected organ [1, 2, 4].

The diagnosis of IgG4-RD requires both an appropriate histological appearance and an increased number of IgG4+ plasma cells in the tissue specimen.

The three major histopathological features are dense lymphoplasmacytic infiltrate, fibrosis of storiform pattern (at least focally), and obliterative phlebitis. Other features include phlebitis without lumen obliteration (this phenomenon was seen in our second case) and an increased number of eosinophils. IgG4 immunostaining is an essential test for the pathological diagnosis of IgG4-RD; however, IgG4+/IgG+ plasma cell ratio is a more powerful tool than IgG4+ plasma cell count in establishing the diagnosis. It is well documented that many other diseases can be associated with an increased number of IgG4+ plasmacytes in the tissue (primary sclerosing cholangitis, rheumatoid arthritis, and inflammatory bowel disease). Thus, the diagnosis of IgG4-RD requires the presence of at least two of three histological features, as well as collaboration between the pathologist and the physician.

In the differential diagnosis of head and neck pathologies, IgG4-RD should be considered. Early diagnosis and treatment of this disease can prevent severe dysfunction of organs caused by progressive fibrosis. Elimination of a malignant neoplasm is mandatory in every case diagnosed as IgG4-RD. Patients require a multidisciplinary approach in order to exclude systemic presentation of the disease. Finally, long-term observation of the patient is strongly advocated in order to assess the dynamics of the disease and the effectiveness of treatment.

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The authors declare no conflict of interest.

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