



# Synchronous occurrence of IgG4-related sialadenitis and ductal carcinoma of the parotid gland: a case report

Angel Rollon-Mayordomo<sup>1</sup>, Ana Avellaneda-Camarena<sup>1</sup>, Alvaro Gutierrez-Domingo<sup>2</sup>,  
Elena Martinez-Carapeto<sup>1</sup>, Pedro Infante-Cossio<sup>3^</sup>

<sup>1</sup>Department of Oral and Maxillofacial Surgery, Virgen Macarena University Hospital, Seville, Spain; <sup>2</sup>Department of Pathology, Virgen Macarena University Hospital, Seville, Spain; <sup>3</sup>Department of Surgery, School of Medicine, University of Seville, Seville, Spain

*Correspondence to:* Pedro Infante-Cossio. Department of Surgery, School of Medicine, Avenida Dr. Fedriani s/n, 41009-Seville, Spain.  
Email: pinfante@us.es.

**Abstract:** Immunoglobulin G4-related disease (IgG4-RD) is a rare chronic systemic inflammatory pathology that poses a diagnostic challenge since it can simulate malignancy when it affects a salivary gland as a mass-like lesion. Here, the authors report an unusual clinical case of a 42-year-old man who presented with a painless, slow-growing swelling located in the right parotid gland with a 12-month evolution. Based on imaging tests and open biopsy, a diagnosis of chronic parotitis was presumed and oral methylprednisolone was prescribed. Due to poor response to medication, a total parotidectomy preserving the facial nerve was performed. The final pathology described a unilateral IgG4-related sialadenitis (IgG4-RS) in the parotid gland in combination with a poorly differentiated multifocal ductal carcinoma. The postoperative course was uneventful except for a temporary facial paresis (grade III according to the House-Brackmann classification system) that resolved completely within 5 months. There were no systemic manifestations on the whole-body 18F-FDG PET/CT. Adjuvant radiotherapy was administered without complications. Twenty-four months follow-up after surgery showed no recurrence or evidence of systemic involvement. This clinical report highlights the importance of considering the synchronous occurrence of a carcinoma underlying an isolated parotid gland mass in the context of IgG4-RS, especially if there is no response to prior steroid medication.

**Keywords:** Immunoglobulin G4-related disease (IgG4-RD); IgG4-related sialadenitis (IgG4-RS); parotid gland; head and neck; salivary duct carcinoma; case report

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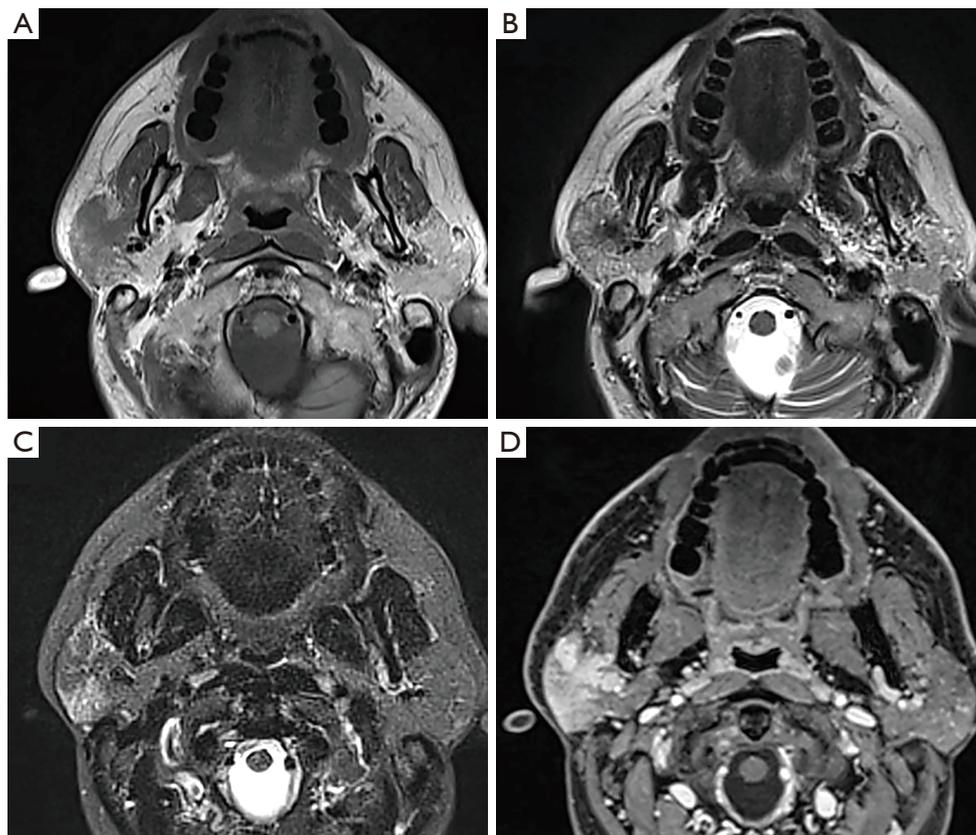
## Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a chronic systemic inflammatory disease of uncertain etiology described in the early years of the 21st century in the Asian population. It is considered an immune-mediated fibroinflammatory condition that can affect multiple organs showing mass-like lesions, elevated serum IgG4 concentrations, and typical pathological findings such as lymphoplasmacytic infiltration with IgG4-positive plasma cells, various degrees of fibrosis and obliterative phlebitis (1).

In the head and neck region, IgG4-RD can be observed as tumefactive enlargement as part of the systemic disease or in isolation, with the orbit and the salivary and lacrimal glands being the most frequently affected sites (2).

Salivary gland involvement, known as IgG4-related sialadenitis (IgG4-RS), is a rare condition that is currently considered part of the spectrum associated with IgG4-RD (3). IgG4-RS is found in 27% to 53% of IgG4-RD patients (4), mainly in the submandibular gland (5). Histologically, IgG4-RS is distinguished by an infiltration of IgG4-bearing

<sup>^</sup> ORCID: 0000-0002-2770-8573.



**Figure 1** Magnetic resonance imaging. (A) Right parotid gland superficial lobe infiltration, hypointense on T1. (B) Low to intermediate signal intensity in T2-weighted images. (C) High signal intensity with some areas of low signal intensity on STIR. (D) Marked homogeneous enhancement after gadolinium-enhanced T1-weighted images. STIR, short time inversion recovery.

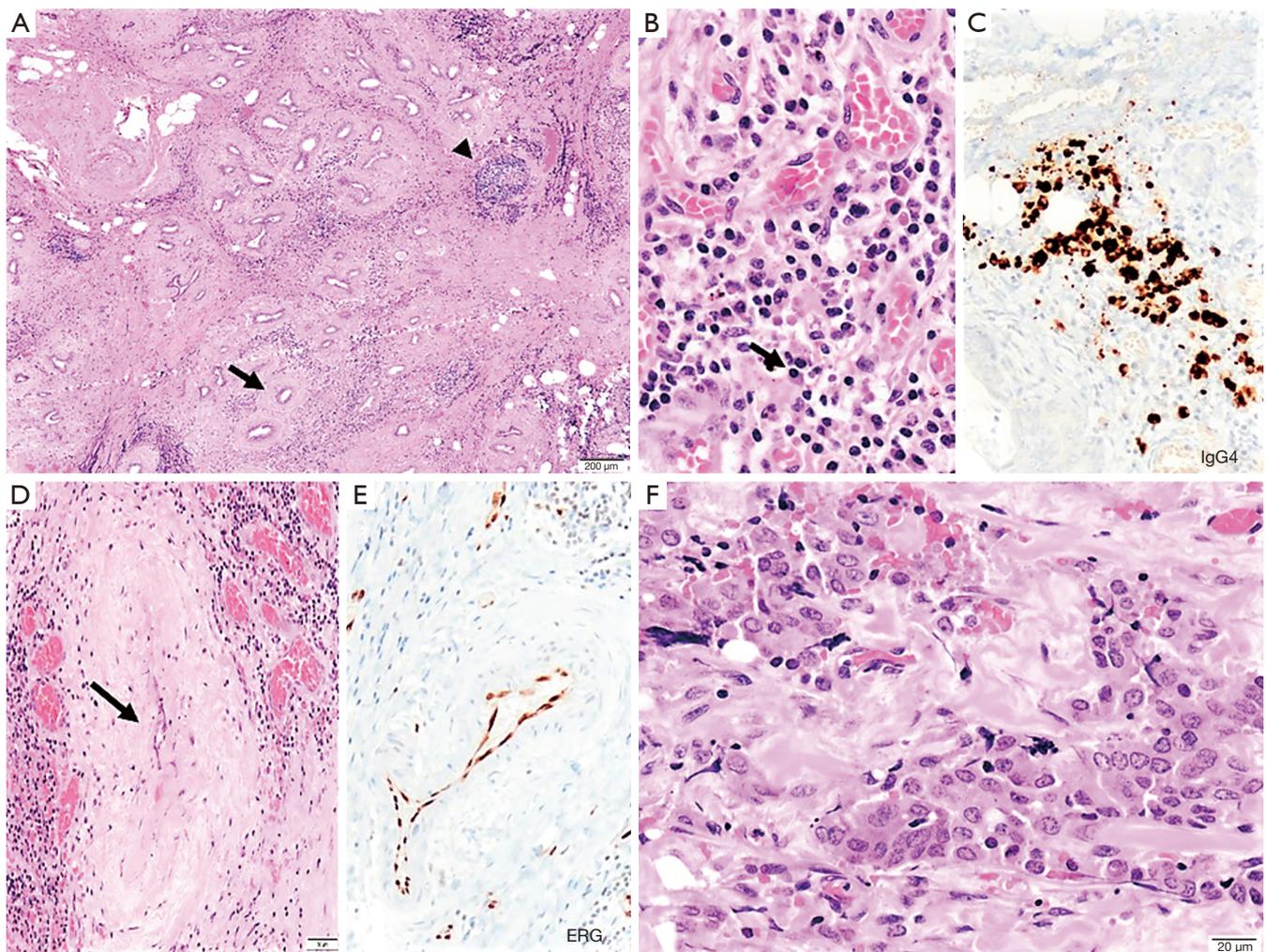
plasma cells into salivary gland tissue. Clinically, it presents as a swollen, painless mass in either major or minor salivary gland, unilateral or bilateral, which poses a diagnostic challenge for the clinician and pathologist since, at times, can simulate a malignancy. Furthermore, not only is the diagnosis of IgG4-RS difficult to establish, which can lead to a misdiagnosis of malignancy, but there is also a range of malignancies associated with this condition. However, very few cases of IgG4-RS and salivary gland carcinoma have been reported. Isolated cases of marginal zone B-cell lymphoma and salivary duct carcinoma have been notified, as well as one case of adenoid cystic carcinoma arising in the context of this disease (6-8). Here, the authors report an unusual clinical case of a patient with unilaterally located IgG4-RS in the parotid gland who underwent a parotidectomy revealing a simultaneous adjacent ductal carcinoma.

We present the following case in accordance with the

CARE reporting checklist (available at <https://dx.doi.org/10.21037/gs-21-90>).

### Case presentation

A 42-year-old man presented with a painless, slow-growing swelling located in the right parotid gland with a 12-month evolution. Physical examination revealed a 4 cm mass in the preauricular area without skin infiltration or evidence of facial nerve dysfunction. On palpation, there was a firm, smooth-surfaced and poorly defined tumor. The patient did not present other associated symptoms and was otherwise healthy. MRI imaging showed an ill-delineated infiltration with predominantly involvement of parotid gland superficial lobe, hypointense on T1 (*Figure 1*). The contrast highlighted a homogeneous enhancement with some scattered dilated cystic areas and ductus that were better appreciated on T2 weighted images. Fine needle aspiration



**Figure 2** Histopathological examination. (A) Parotid gland with totally distorted architecture with disappearance of serous acini due to predominantly severe periductal fibrosis (arrow) and associated inflammatory process. Some germinal centers are shown (arrowhead) (hematoxylin-eosin, 40 $\times$ ). (B) Inflammatory infiltrate with plasma cells predominance (arrow) (hematoxylin-eosin, 400 $\times$ ). (C) Immunohistochemical study showing abundant IgG4 plasma cells (more than 10 cells per high-power field with IgG4/IgG ratio greater than 40%) (IgG4, 400 $\times$ ). (D) Image of obliterative phlebitis due to lymphoplasmacytic infiltration of venule walls that obliterates the lumen of the vessel (arrow) (hematoxylin-eosin, 100 $\times$ ). (E) ERG immunohistochemical expression confirmed obliterative phlebitis (ERG, 100 $\times$ ). (F) Multifocally, a ductal carcinoma composed of a small tumor nest with cells with atypia and evident nucleolus is observed (hematoxylin-eosin, 200 $\times$ ). IgG4, immunoglobulin G4; ERG, erythroblast-transformation-specific related gene.

cytology (FNAC) and open biopsy were nonconclusive in determining the origin of the lesion, reporting that the mass contained a heterogeneous lymphoid population with minimal inflammatory changes. No histological evidence of malignancy was found.

With the presumed diagnosis of chronic parotitis, oral methylprednisolone was prescribed at 30 mg/day for three weeks along with conventional measures such as

hydration and glandular massage. Due to poor response to medication, a total parotidectomy preserving the facial nerve was performed to remove the lesion and establish the diagnosis. The histological examination described a consistent morphologic appearance of diffuse IgG4-RS in combination with a poorly differentiated multifocal ductal carcinoma (pT2N0Mx, stage II) with perineural invasion and without vascular or lymphatic invasion (*Figure 2*). The

**Table 1** Timeline table of case report

Date	Summaries from initial and follow-up visits	Diagnosis testing	Interventions
July 2018	Evaluated for a mass in the parotid gland	MRI: poorly defined infiltration predominantly in the superficial lobe FNAC: heterogeneous lymphoid population	
October 2018	Admission to hospital for open biopsy under general anaesthesia	Open biopsy: glandular tissue with minimal inflammatory changes	Methylprednisolone 30 mg/day for three weeks
November 2018	No response to corticosteroids. Office visit for surgical consultation: recommendation for excision		
November 2018	Admission to hospital for surgical intervention. Uncomplicated operation		Parotidectomy
December 2018	Follow-up consultation	Pathology: diffuse IgG4-RS in combination with a poorly differentiated multifocal ductal carcinoma Serological test including IgG subtypes: normal Whole-body 18F-FDG PET/CT: no systemic manifestations	
January 2019	Consultation with the multidisciplinary head and neck cancer tumour board		Starts radiation therapy
January 2021	Follow-up consultation. The patient was in good condition two years after surgery		Reviews every two months

MRI, Magnetic Resonance Imaging; FNAC, Fine Needle Aspiration Cytology; IgG4-RS, IgG4-related Sialadenitis; 18F-FDG PET/CT, 18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography.

immunohistochemical study identified abundant IgG4 plasma cells (more than 10 cells per high-power field with an IgG4/IgG ratio greater than 40%) and an obliterative phlebitis image due to lymphoplasmacytic infiltration of the venule walls. Subsequent serological examination, including IgG subtypes, was normal. There were no systemic manifestations on the whole-body 18F-FDG PET/CT. In accordance with the above, the diagnosis of IgG4-RS synchronous to infiltrating ductal carcinoma of the parotid gland was suggested. The postoperative course was uneventful except for a temporary facial paresis (grade III according to the House-Brackmann classification system) that resolved completely within 5 months. Adjuvant radiotherapy with a total dose of 67.5 Gy on the tumoral bed and 54 Gy on levels I-II-III of the neck in 5 weekly fractions for 6 consecutive weeks was recommended by the multidisciplinary head and neck tumour board of our institution. The patient showed good tolerance, without the need for interruption. At 24 months of follow-up, the patient was doing well with no recurrence or evidence of

systemic involvement.

A timeline concisely showed the medical procedure of our unusual case (*Table 1*).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

### *Patient perspective*

Our patient reported the following about his experience: *“Throughout the process of my clinical care, I was informed about the concerns, doubts and problems that raised the diagnosis and treatment of my disease. I was aware of the risks of the surgical procedure, especially of facial nerve damage. Although during the first postoperative months I was concerned about the difficulty in moving my facial muscles, over time I have recovered normal*

*facial mobility. Currently I can do my usual activity without any problem. However, I perceive a slight hollow in the preauricular area, but I am happy with the result obtained.”*

## Discussion

Few reports have described the association between IgG4-RS and synchronous development of malignancies appearing in a background of IgG4-RD. To the best of our knowledge, this report is the first documented case of IgG4-RS with unilateral involvement of the parotid gland that occurred simultaneously with an infiltrating ductal carcinoma of the adjacent tissue in the same gland.

IgG4-RS diagnosis is based on a set of clinical-radiological, serological, and histopathological criteria, none of which are pathognomonic (9,10). Diagnosis can sometimes be complex due to the number of overlapping and similar clinical conditions that can affect the parotid glands. In our clinical case, the clinical presentation as persistent glandular swelling, imaging tests and pathological findings were compatible but not conclusive with those of chronic parotitis described by other authors (5,11). FNAC was a limited tool to obtain a valid and conclusive sample to evaluate IgG4 positive plasma cells. Therefore, it is very important that the surgeon can obtain an adequate biopsy sample with enough tissue to carry out a correct pathological evaluation (12). However, the incisional biopsy performed was unable to initially diagnose the presence of an occult tumor foci that was hidden within IgG4-RS involvement. Percutaneous core needle biopsy under ultrasound guidance is an alternative tool to FNAC for the preoperative evaluation of patients with lesions of the salivary glands, but we ruled it out due to the risk of bleeding and possible damage to hypervascularized intraparotid vessels.

The diagnosis of IgG4-RS in our patient was established according to the Okazaki *et al.* (13) and Umehara *et al.* (14) criteria: (I) persistent inflammation (>3 months) of single or multiple major salivary glands; (II) histopathological and immunohistochemical examination showing a marked lymphocyte and plasmacyte infiltration of IgG4 plasma cells ratio of IgG4/IgG cells >40% and >10 IgG4 plasma cells per high-power field; (III) obliterative phlebitis; and (IV) exclusion of other diseases that present with glandular swellings. The total serum IgG and IgG4 concentration was normal, which is consistent with up to 30–50% of IgG4-RD cases (15). These normal levels of IgG4 in peripheral blood can be explained by the fact that our patient had

mainly an infiltration component located in a single gland without excessive active inflammation, and by the previous corticosteroids that had been administered (16).

Given the finding of an isolated parotid gland mass in the context of parotid IgG4-RS, the first mandatory key point is to exclude a primary salivary gland tumor and other neoplasms such as lymphoma or metastatic tumors (8). Next, the differential diagnoses closest to IgG4-RS include chronic sialadenitis and Sjogren's syndrome (17). Chronic sialadenitis typically affects the submandibular gland and has no characteristic pattern with marked lymphocyte and plasmacyte infiltration of IgG4 plasma cells or obliterative phlebitis. Sjogren's syndrome is associated with xerostomia, xerophthalmia and glandular destruction accompanied by an increase in related antinuclear antibodies (anti-SSA). Among other entities that could mimic an IgG4-RS are granulomatous disorders and storage diseases such as sarcoidosis or amyloidosis, Castleman's disease, eosinophilic granulomatosis with polyangiitis, and Heerfordt syndrome (18).

The treatment indicated in symptomatic patients with IgG4-RD is corticosteroids with an initial prednisolone dose of 30 mg/d, tapered in 5-mg reductions every 2 weeks (1,10). However, this approach was not effective in our patient, probably due to 12-month delay in consultation, the relatively large mass with isolated involvement that was very difficult to reduce with medication, or the underlying synchronous ductal carcinoma. Although we performed a total parotidectomy to ensure the histological diagnosis and rule out other pathologies, IgG4-RS would not usually require such radical surgery, since in case of residual disease or recurrence it could be easily treated with corticosteroids (16). On the other hand, there is no general agreement on the best therapeutic approach for infiltrating ductal carcinoma, but a total parotidectomy is usually recommended, even in T1 tumors, because local recurrence regularly has a very poor prognosis (19). In cases of apparent involvement of the facial nerve and locoregional extension, a surgical resection with wide margins should be considered. Postoperative radiotherapy is recommended when extraparotid extension, positive surgical margins, neck lymph node metastasis, or perineural invasion is found (19). In our clinical case, the multidisciplinary head and neck tumour board proposed postoperative radiotherapy to the tumoral bed and elective radiotherapy to the neck since the histopathological diagnosis was made after parotidectomy (20).

A higher incidence of various neoplasms has been

reported in association with IgG4-RD, including solid tumors located in the pancreas, gastrointestinal tract, lung and prostate, and also lymphomas (21,22). Recently, a prospective cohort study showed that IgG4-DR Chinese patients have a 2.78-fold increased risk of metachronous malignancy over a median 61.4-month follow-up, with the gastrointestinal tract being the most common site of malignancy (23). The etiopathogenesis of this event is unknown. Long-lasting chronic inflammation appears to play a fundamental role in cancer development through the carcinogenesis process associated with inflammation (23), although it has also been speculated that IgG4-RD could be considered a type of paraneoplastic syndrome (14). The risk of association between IgG4-RD and a synchronous tumor has not yet been elucidated, nor is its pathogenic relationship. Our case report stands out the difficulties involved in the clinical diagnosis of this rare condition insofar as it could only be established through a histopathological evaluation after performing a parotidectomy.

In conclusion, this rare case report adds to the growing literature describing salivary gland involvement in patients with IgG4-RD. Considering the low occurrence of IgG4-RS located in the parotid gland, the clinician must be aware of this condition to establish a correct differential diagnosis, ensure its proper management, and carry out long-term follow-up to eventually detect the involvement of additional sites and organs at one or more parts in the body. Furthermore, this report highlights the importance of considering the possibility of an underlying carcinoma in the presence of a single parotid gland mass in the context of IgG4-RS and the management problems that can arise when both conditions occur synchronously. Discarding local or distant synchronous or metachronous malignancies is especially relevant if, as in the case presented, the diagnostic difficulty increases because there was no clear response to prior steroids medication.

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### Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at <https://dx.doi.org/10.21037/gs-21-90>

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this Case report and any accompanying images.

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