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IgG4 disease of the ear: Report and review

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Abstract

In recent years, an immune-mediated disorder involving IgG4 has been described, which targets multiple organs and explains a number of disorders previously regarded as "idiopathic" or of unknown origin. Furthermore, the discovery of IgG4-related disease (IgG4-RD) has placed a number of pathologies within its spectrum, linking symptoms and conditions formerly considered isolated. Reports of the manifestations of IgG4-RD in the head and neck are scarce. Otological manifestations have been reported, but only a handful of cases are available in the literature. This is the first report of recalcitrant serous otitis media secondary to IgG4-RD, confirmed by immunohistopathology. A case of IgG4-RD of the middle ear is presented, manifesting itself as recalcitrant serous otitis media. The case is presented from an otolaryngological and histopathological perspective and briefly reviews this rare disorder. The importance of the awareness of IgG4-RD resides mainly in the fact that it is a treatable condition. This can potentially improve the quality of life of a number of patients, some of whom may not have had a clear diagnosis. A favorable response to glucocorticoids has been reported. In cases of persistent symptoms, immunosuppressive therapy has been used with success.

Keywords

IgG4-related disease, chronic otitis media, autoimmune ear pathology

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Introduction

IgG4-related disease (IgG4-RD) is a recently described, immune-mediated, multi-organ (in 60%–90% of cases)[1] condition. It has been misdiagnosed in the past due to its similarity to other pathologies and its widespread, unspecific, seemingly disjointed symptomatology. Its description has enabled the inclusion and connection of unspecific symptoms/disorders within its spectrum.[2] At present, the pancreas, salivary and lacrimal glands seem to be the most affected organs.[2–4] However, the numbers may be misleading, since many other forms of non-specific inflammation or autoimmune disorders may emerge in the future as new subclasses of IgG4-RD.

In otolaryngology, Mikulicz's disease (recurrent dacryoadenitis and enlargement of the major salivary glands) and Küttner's tumor (isolated, non-infectious, recurrent submandibular sialadenitis) are now widely recognized as part of the IgG4-RD spectrum because they share particular pathological, serological and clinical features (Table 1).[5] Still, other forms of diffuse inflammation potentially leading to permanent tissue disruption in the head and neck such as recurrent mastoiditis, some forms of thyroiditis and of laryngeal and tracheal stenosis, among others, are being linked to IgG4-RD.[10–12]

However, further research is still needed. True prevalence is still unknown, and possibly, lack of awareness has led to significant underdiagnoses. The condition has an equal sexual preponderance for the head and neck; however, there is a significant predominance among the

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Table 1. Previously described, now associated IgG4-related disorders in the head and neck.[2,5,6–9]

- Mikulicz's disease (IgG4-related dacryoadenitis and sialadenitis)
- Sclerosing sialadenitis (Küttner's tumor, IgG4-related submandibular gland disease)
- Inflammatory orbital pseudotumor (IgG4-related orbital inflammation or orbital inflammatory pseudotumor)
- Chronic sclerosing dacryoadenitis (lacrimal gland enlargement, IgG4-related dacryoadenitis)
- Riedel's thyroiditis
- IgG4-related thyroiditis
- IgG4-related hypophysitis
- IgG4-related pachymeningitis
- IgG4-related midline destructive disease
- IgG4-related serous otitis media[a]
- IgG4-related sclerosing mastoiditis and recurrent mastoiditis[a]
- IgG4-related facial nerve palsy[a]
- Fibrosing Hashimoto's thyroiditis[a]

[a]Unclear whether these can be included within the IgG4-RD spectrum; only some sporadic cases reported in the literature.

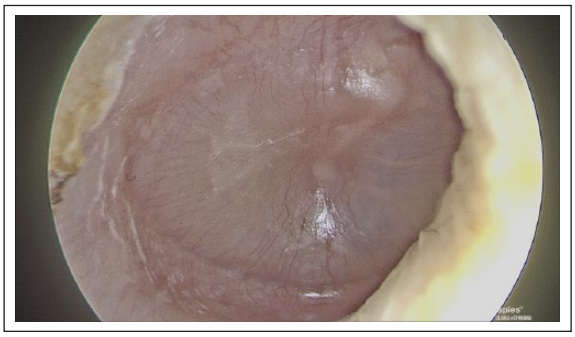

Figure 1. Right ear. Opacification and discrete bulging, mainly evident in the posterior and inferior quadrants of the tympanic membrane.

middle-aged male population when abdominal and retroperitoneal organs are affected.[2]

Case report

A 56-year-old male, with past medical history of idiopathic hypertension, presented with a 1-month history of right aural fullness and subjective hearing loss. The presence of a conductive hearing loss secondary to otitis media with effusion was confirmed through an audiogram and examination (Figure 1). During placement of a ventilation tube, otitis media with effusion was noted. The effusion was thick, viscous with a red and yellow hue.

A computed tomography (CT) scan revealed partial opacification of both the middle ear space and the mastoid cavity. Incidentally, the scan also demonstrated findings suggestive of chronic rhinosinusitis (CR). Eustachian tube dysfunction secondary to CR was suspected as the cause for the patient's symptoms. However, nasal endoscopy was unremarkable, and his nasal symptoms despite being permanent were not significant.

The patient experienced temporary relief; however, the otorrhea persisted. A swab of the secretion was negative and a biopsy showed unspecific inflammation of the postnasal space. A second grommet was required following spontaneous extrusion of the first tube. A larger internal diameter Microgel® tube was used on this occasion (Medtronic©), but symptoms persisted over time due to constant blockage, without improvement.

Magnetic resonance imaging (MRI) of the brain, internal auditory canal and eustachian tubes with gadolinium revealed on the right side a large T2 hyperintense and T1 hypointense middle ear cavity and mastoid effusion (Figure 2). Contrast administration revealed a patchy enhancement of the mucosal lining of the mastoid and middle ear suggesting mucosal inflammation. The edematous thickening with increased enhancement extended to the eustachian tube, nasopharynx and sinonasal cavity. The overly persistent middle ear effusion and the extensive, diffuse inflammation of the ear, with a cobblestone appearance, evidenced during endoscopic myringotomy, which extended through the upper respiratory tract, in conjunction with an absence of a clear history of atopy,[2] or other obvious cause, raised the suspicion for an autoimmune disorder.

Blood analysis targeting autoimmune causes for chronic diffuse inflammation revealed normal RF (rheumatoid factor), ANCA (anti-neutrophil cytoplasmic antibodies), ANA (antinuclear antibodies), serum IgE, CCP (cyclic citrullinated peptide), renal and liver function and ESR (erythrocyte sedimentation rate). Remarkable results included elevated ACE (angiotensin-converting enzyme) test and elevated IgG (IgG = 16.21 g/L, normal range 6.2–14.4). An abnormal ACE test can indicate the presence of sarcoidosis; therefore, a chest X-Ray was ordered to rule out lung involvement and a QuantiFERON Gold test was ordered to rule out tuberculosis; both were unremarkable. Sequential ACE tests showed normalization.

A request for serum IgG subclasses revealed elevated IgG4 levels (IgG4 = 2.29 g/L, normal range 0.02–2.01), with other subclasses of IgG within the normal range.

While awaiting the results of these tests, the patient was prescribed a course of oral prednisone, as well as clarithromycin and nasonex to treat the underlying CR. The course of

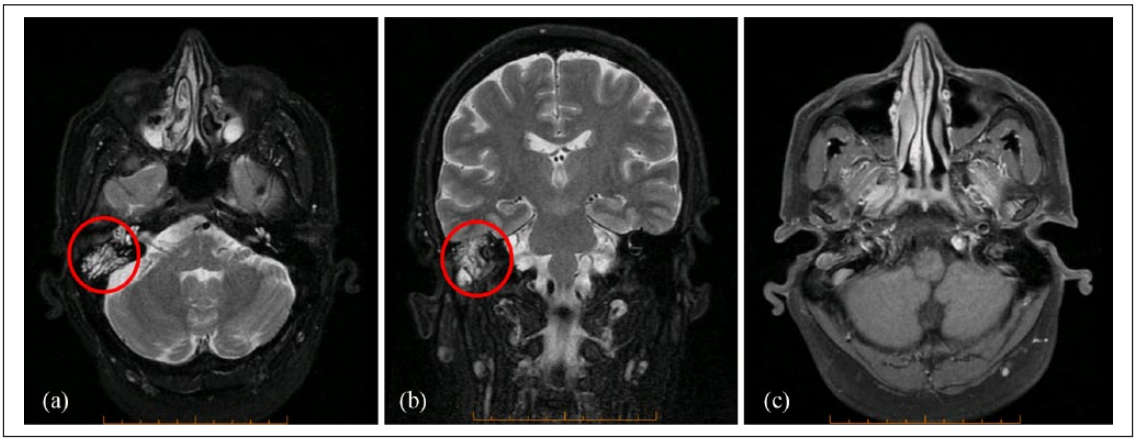

Figure 2. (a and b) MRI T2-weighted images demonstrating hyperintensity of the right mastoid and middle ear cavities due to fluid occupancy (red circle). (c) MRI T1-weighted images post-gadolinium administration demonstrating diffuse inflammation of the nasal lining, nasopharynx and eustachian tubes bilaterally.

prednisone (50, 25 and 10 mg/5 days) resulted in marked improvement of the otological symptoms.

Biopsy of the middle ear mucosa was undertaken endoscopically by elevating a tympanomeatal flap. A considerable amount of granulation tissue was removed and sent for analysis. Endoscopic vision allowed safe dissection and denudation of middle ear mucosa.

Histopathology showed a small portion of inflamed fibrous tissue lined by seromucinous epithelium and containing glands in keeping with middle ear mucosa. There was active and stromal inflammation consisting of numerous lymphocytes and plasma cells, as well as histiocytes. No eosinophils were observed. No granulomas or foreign body material were included. There was no storiform fibrosis or obliterative phlebitis. Immunohistochemistry demonstrated abundant plasma cells with IgG and IgG4 staining, with elevated absolute numbers of IgG4 cells (over 50 per high-power field (HPF)) and an increased IgG4 to IgG ratio greater than 40%. There were increased numbers of IgA cells whose significance is uncertain and no increase in IgD- or IgM-positive cells.

The features of the immunohistopathological analysis, together with an elevated IgG4 serum level, suggest that an IgG4-RD would explain the patient's findings and symptoms. In addition, the favorable response to glucocorticoids supports this diagnosis.

Discussion

IgG4-RD is a great mimicker due to its unspecific and disjointed clinical findings. Frequently, patients feel well aside from the organ-specific symptoms, unless important multi-organ involvement exists.[13]

Diagnosis is based on correlation of clinical findings, serology, imaging and immunohistopathology. Clinically, enlargement of the affected organ(s) secondary to chronic fibro-inflammation is common.[5] In the head and neck, the condition can display both allergic and autoimmune features. Although unconfirmed, it is believed that the function of IgG4 may be related to the regulation of the response to allergens and pathogens. It is unknown whether these antibodies are intrinsically pathogenic or whether its deleterious effects are the result of the downregulation of certain normal processes.[14] Given this, and in addition to the unfamiliarity of clinicians with this disease, manifestations in ENT can be overlooked as purely allergic. Further diagnostic confusion can arise from the concurrence of IgG4-RD with asthma, rhinitis, mild eosinophilia and elevated serum IgE, which is present in a subset of IgG4-RD patients.[2,5,4] In view of this, the presence of perennial and diffuse inflammation of the upper respiratory tract and ears emphasizes the need to rule out an autoimmune condition.[2]

Biopsy of the affected tissue is the diagnostic gold standard,[15] and it is virtually unequivocal when it displays three main histopathological features: lymphoplasmacytic infiltration, obliterative phlebitis (which affects medium-sized veins) and storiform fibrosis (characterized by centrifugally arranged collagen fibers, fibroblasts and inflammatory cells). Storiform fibrosis is such a unique pattern to IgG4-RD that the presence of other types of fibrosis virtually excludes this diagnosis.[2,15] In long-standing disease, histopathological confirmation may be difficult because the fibrosis may be quite extensive and predominate over the other histological features. Notably, abundant fibrosis is also linked to a lesser response to glucocorticoid treatment. Necrosis, discrete granulomata and xanthogranulomatous changes are atypical and when present suggest that other diagnoses should be considered.[2] Nonetheless, in the head and neck region, storiform fibrosis and obliterative phlebitis may not always be present.[2] In the biopsy of the case at hand, there was no obliterative phlebitis or storiform fibrosis, possibly because the specimen was small and superficial or because the biopsy was performed at an early stage of the process. There was mixed inflammation without eosinophils or granulomas,

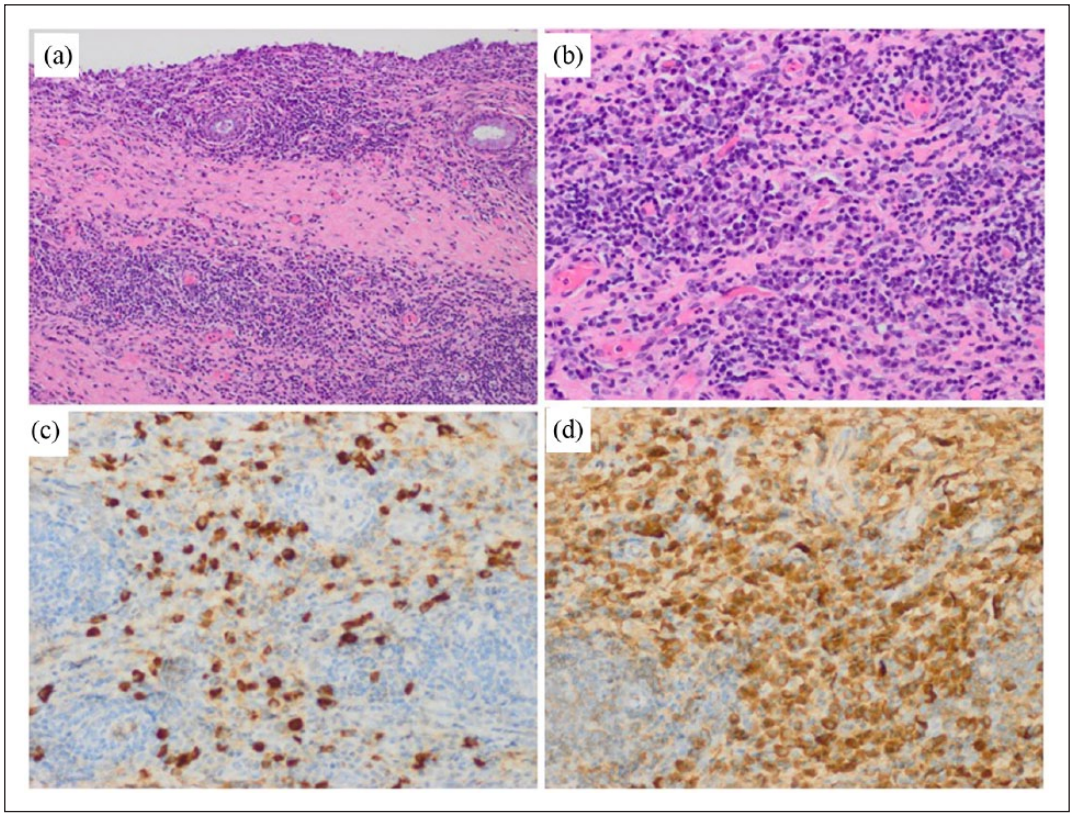

Figure 3. (a and b) Superficial middle ear mucosa with lymphoplasmacytic infiltrate (hematoxylin and eosin staining: (a) ×100, (b) ×200). (c) Immunohistochemistry showing IgG4-positive cells (×200) and (d) immunohistochemistry showing IgG-positive cells (×200).

raising the possibility of infection but that was excluded clinically, prior to commencing therapy.

Lymphoplasmacytic infiltration is typically seen histologically.[2] In the present case, the classic histological feature of a lymphoplasmacytic infiltrate was supported by immunohistochemistry with elevated numbers of IgG4-positive plasma cells as well as an increased IgG4 to IgG ratio of greater than 40% (Figure 3). These findings may be seen even in the absence of elevated serum IgG4.

The histological criteria for IgG4-RD with respect to absolute numbers of IgG4 plasma cells does vary between organs and papers,[5,10] but overall, the case at hand fulfills the currently accepted criteria originally proposed by Umehara et al.[3] for an IgG4-RD definite diagnosis: (1) positive localized organ involvement—this was evidenced in the otoscopic and radiological findings, (2) serum IgG4 of >135 mg/dL—the case presented has a serum IgG4 of 229 mg/dL, (3) histopathological findings of >10 IgG4 cells/HPF and an IgG4 fl/IgG fl cell ratio >40%—the biopsy in this case displays elevated absolute numbers of IgG4 cells (over 50 per HPF) and an increased ratio of IgG4 to IgG ratio of greater than 40%.

Imaging of IgG4-RD–affected tissue will present as diffuse inflammation, like in the present case, but it can also display mass-forming or infiltrative lesions. All of these features are non-specific and are linked to many differentials. However, some authors suggest that when the lymphoplasmacytic infiltration is significant, it may impact in a characteristic way the intensity in T2-weighted images (WI) and diffusion-weighted images (DWI) in MRI.[16] However, a pathognomonic radiological pattern has not been clearly described. Notwithstanding the limited knowledge regarding IgG4-RD radiological features, MRI and positron emission tomography (PET) modalities are becoming an integral part in managing IgG4-RD, to evaluate involved organs and presence of multifocal disease.[17]

Ear involvement has been scarcely reported to date. Takagi et al. performed a retrospective analysis of 39 patients with confirmed IgG4-RD in organs outside of the head and neck and found otological symptoms in five of them. The findings included serous otitis media (n=2), eosinophilic otitis media (n=2) and sensorineural hearing loss (n=1).[18] However, unlike in our case, histopathological confirmation in the ear was not made, and thus, the findings could have been circumstantial. Histopathologic confirmation of IgG4-RD of the ear was found in the literature review in two occasions. These cases were reported as sclerosing middle ear disease[16] and recurrent mastoiditis,[6] respectively. In both cases, damage was significantly greater than that in our patient, involving bone erosion and damage to the facial nerve, presumably because the diagnosis was made at a later stage.

The patient responded well to steroids which may have been helped by the absence of established storiform fibrosis.

Glucocorticoids normally provide a good clinical response, in particular prednisone, but recurrence is expected once the effect wears off. Administration of either immunomodulators or immunosuppressants may be required. Of these, rituximab offers targeted effect that lowers the levels IgG4-producing cells specifically. However, in the absence of a randomized controlled trial, it is still considered an off-label use for rituximab.[19]

Conclusion

The IgG4-RD spectrum encompasses a multitude of disorders, some of which were previously deemed untreatable. Its description offers objective explanations and correlation between a number of rare disorders and symptoms, as well as new therapeutic options. The involvement of the ear within this spectrum has only been described in few occasions. The present report highlights IgG4-RD in the diagnostic armamentarium of otolaryngologists.

Declaration of conflicting interests

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

Verbal informed consent was obtained, before the construction of this paper, from the patient for the anonymized information to be published in this article. We have retrospectively obtained written informed consent from the patient to publish this article, for the purpose of this application.

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