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ORIGINAL PAPER

Recurrent Mastoiditis Mimics IgG4 Related Disease: A Potential Diagnostic Pitfall

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Abstract IgG4-related disease (IgG4-RD) is a recently recognized entity that causes progressive fibrosis and formation of mass lesions. IgG4-RD can be diagnosed histologically by its hallmarks of storiform fibrosis, prominent lymphoplasmacytic infiltrate, and obliterative phlebitis, accompanied by the infiltration of excessive numbers of IgG4-positive plasma cells as well as elevations in serum IgG4 concentrations. A recent publication reported a case of IgG4-RD in the mastoid sinus, representing a new anatomic location for this disease. We report two additional cases of IgG4-RD occurring in the mastoid and causing clinical mastoiditis. The presenting symptoms were varied—tinnitus, hearing loss, and cranial nerve palsies. All three cases showed a dense lymphoplasmacytic infiltrate, storiform type fibrosis as well as elevated numbers of IgG4 positive plasma cells. The three patients responded to immunosuppressive therapy that included steroids and Rituximab. We further investigated 162 consecutive mastoiditis cases at our institution in order to determine the frequency of IgG4-RD as a previously unrecognized cause of mastoiditis. Within this latter cohort we identified nine cases of mastoiditis that had two of the histologic features of IgG4-RD, specifically storiform fibrosis and a dense lymphoplasmacytic infiltrate. Two of these cases showed >50 IgG4-positive plasma cells per high-power field with IgG4–IgG ratio of >40 %, thus fulfilling histological criteria for IgG4-RD. However, both were due to severe acute or chronic infection. In conclusion, we reaffirm IgG4 related mastoiditis as a distinct but uncommon cause of recurrent mastoiditis. The diagnosis of IgG4-related mastoiditis should be rendered with caution, and only after the exclusion of potential mimickers, particularly infection.

Keywords IgG4 related disease · Mastoiditis · IgG4

Introduction

IgG4 related disease (IgG4-RD) is a multi-system fibroinflammatory process that mimics both immune-mediated diseases and neoplastic processes. The disease is characterized by multiorgan involvement in which the organs can be affected synchronously [1–5]. Often, however, the pattern of disease involvement is metachronous, and the disease evolves over many years and even decades [1–3, 5]. IgG4-RD was initially recognized in the pancreas as a form of sclerosing pancreatitis, and elevated levels of serum and tissue IgG4 quickly became the hallmark of this disease [3, 5, 6]. Investigators have recognized subsequently, however, that neither elevated serum nor tissue levels of IgG4 are necessarily specific for IgG4-RD [7, 8]. Elevated serum IgG4 has been documented in a variety of unrelated inflammatory and neoplastic diseases [7, 8]. For the purposes of diagnosis, therefore, histopathology has emerged as the key-defining feature of IgG4-RD [9]. The critical histopathologic features of the disease are a dense inflammatory infiltrate, storiform fibrosis, and a unique form of vasculopathy known as obliterative phlebitis [5, 9].

Organ sites in the head and neck are among the most common anatomic locations of IgG4-RD, even though such manifestations have been characterized only recently [10–

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12]. The involvement of the submandibular, parotid, thyroid, and lacrimal glands are widely recognized, and the disease frequently affects cervical lymph nodes [13, 14]. More recently, diseases such as eosinophilic angiocentric fibrosis and Riedel's thyroiditis have been linked to IgG4-RD [15, 16]. Of particular interest to the findings presented here, a recent case report also documented the involvement of the mastoid by this disease [17]. In most instances, the identification of a sentinel case has led to the recognition of a substantial number of additional cases of IgG4-RD at that site—a paradigm that has resulted in establishing IgG4-RD as a systemic disease [5, 18, 19].

Conditions other than IgG4-RD are now known to display some of the hallmark features of IgG4-RD, leading to misdiagnosis. Sites such as the aorta, lung, and sinuses in which infections are more likely than IgG4-RD are potentially problematic in this regard because the overdiagnosis of IgG4-RD can lead to inappropriate treatment [20–22]. Infection of the aortic wall with a gram-positive organism has been associated with high tissue concentrations of IgG4-positive plasma cells, but the histologic features of storiform fibrosis and obliterative phlebitis were not present [22]. To minimize the possibility of IgG4-RD misdiagnosis, consensus guidelines emphasize the presence of both characteristic histopathologic features and elevated numbers of IgG4-positive plasma cells [9]: both parameters are seldom seen outside the context of IgG4-RD.

This study was undertaken with the hypothesis that IgG4-RD of the mastoid is an underdiagnosed entity and that careful evaluation of retrospective material may reveal other examples of this disease. Our secondary goal was to attempt to identify mimics of IgG4-related mastoid disease.

Materials and Methods

In addition to the cases identified in the Massachusetts General Hospital (MGH) pathology archives, we received three cases of IgG4 related mastoiditis in consultation. The records on clinical, radiologic, and therapeutic aspects of the disease were recorded. Two of these patients were subsequently treated at this institution. The hematoxylin and eosin stained slides were reviewed for the presence of storiform fibrosis and obliterative phlebitis. The definition of storiform fibrosis is as defined by a recently published consensus document [9]. The pathology archives of the MGH were interrogated for all cases of mastoiditis/chronic otitis media identified between 2008 and 2011. We identified 162 cases in which the cause of the otitis media/mastoiditis was not clearly attributable to another cause (such as a cholesteatoma). All 162 cases were reviewed for histologic evidence of IgG4-RD; namely, a dense lymphoplasmacytic infiltrate with at least one of these two additional findings: (1) storiform fibrosis, or (2) obliterative phlebitis. Immunohistochemistry for IgG4 and IgG expression was performed on cases that met the histologic criteria for a diagnosis of IgG4-RD [9].

The rationale for this algorithm is that the diagnosis of true IgG4-RD requires at least two histological features as well as elevated numbers of IgG4-positive plasma cells [9]. The mere presence of elevated numbers of IgG4-positive plasma cells is not sufficiently specific for the diagnosis.

The tissue specimens were processed via routine fixation in buffered formalin and embedded in paraffin for histological evaluation using hematoxylin and eosin staining. Immunohistochemistry for IgG4 and IgG was also performed as described previously [23]. In brief, immunohistochemical studies using antibodies to IgG4 (MRQ-44, Cell Marque, 1:25 dilution) and IgG (Dako, 1:3000) were carried out. Antigen retrieval was performed using protease digestion, and antigen detection was carried out using UltraView diaminobenzidine chromogen (Ventana Medical Systems, AZ). Three HPFs (area = 0.2375 mm^2) with the highest number of IgG4-positive cells were identified and the average was recorded. The number of positive plasma cells on the corresponding three HPFs on the IgG preparation were computed and an IgG4–IgG ratio derived.

Results

Clinical Features: IgG4-RD Cases

All three cases with IgG4 related mastoiditis affected women and the mean age was 48 years. They presented with a wide range of symptoms related to middle ear disease, including tinnitus and hearing loss (see Table 1). In addition, two patients showed clinical symptoms of facial nerve palsy. On imaging, all three patients showed mass-like lesions with erosion of the adjacent bones. The serum IgG4 levels were elevated in both cases in which this parameter was evaluated (Table 1). A mastoidectomy was performed in each case. Cultures were negative for microorganisms. Enzyme immunoassay for anti-neutrophil cytoplasmic antibodies (ANCA) were also negative.

The disease in all three cases was found to extend beyond the middle ear and mastoid cavity. In case number 1, the recurrence involved the region of the right pterygopalatine fossa, the inferior and superior orbital fissures, and the right foramen rotundum. A small, mass-like enhancement also developed in the nasopharynx. In case number 2, on MR imaging, disease was identified in the pachymeninges as well as the adjacent brain. In case number 3, cerebritis was detected on MRI.

Post-surgical disease recurrence in all three cases necessitated additional therapy. Case no. 1 was treated with

Table 1 Clinical and histologic features of cases with IgG4-related mastoiditis

	Gender	Age	Presenting symptoms	Imaging results	Surgical intervention	Histology	Serum IgG4 (normal <140 mg/dL)	Cultures	Recurrences	Treatment	Clinical outcome
1	F	43	Pulsatile tinnitus	Inflammatory pseudotumor, subsequent mass-like enhancement in nasopharynx	Mastoidectomy x2, temporal bone resection	Lymphoplasmacytic infiltrate, storiform fibrosis, IgG4 200 per HPF; IgG4:IgG cell ratio >50 %	191 mg/dL	Negative	X2	Postoperative radiation, methylprednisolone and prednisone, followed by Rituximab	Disease stabilization with symptom resolution
2	F	52	Headaches, multiple right-sided cranial nerve palsies, ipsilateral hearing loss	Pachymeningitis and mastoiditis	Cortical mastoidectomy	Lymphoplasmacytic infiltrate, storiform fibrosis, IgG4 110 per HPF; IgG4:IgG cell ratio 35 %		Negative	X1	Rituximab	Disease stabilization with symptom resolution
3	F	50	Recurrent mastoiditis complicated by serous otitis media, facial paresis, cerebritis, barotitis, hearing loss, and pain	Erosive lesion involving the retrofacial space	Myringotomy tube, modified radical mastoidectomy, surgical debulking	Lymphoplasmacytic infiltrate, storiform fibrosis, IgG4 210 per HPF; IgG4:IgG cell ratio >50 %	213 mg/dL	Negative	X3	Prednisone	Disease stabilization with symptom resolution

postoperative radiation therapy. Although the disease in case no. 1 responded favorably to steroids, a further recurrence prompted the use of rituximab therapy and in this case and well as case no. 2, rituximab resulted in stabilization of the disease, as well as resolution of symptoms. In one case (case 3), steroids were used following the third recurrence, and proved sufficient to ameliorate disease symptoms. Following rituximab/steroid therapy, no further evidence of recurrence has been identified.

Clinical Features: Consecutive Series of 162 Cases of Mastoiditis

Of the 162 biopsies from patients at our institution with mastoiditis and/or otitis media not readily attributable to other causes, we identified 9 (5.5 %) cases with storiform-type fibrosis and a dense lymphoplasmacytic infiltrate—the minimal requirement for the diagnosis of IgG4 related disease. The nine patients (see Table 2) all presented for surgical mastoidectomy secondary to mastoiditis, with all but one having a history of either chronic otitis media, prior surgery in of the ear/mastoid region, or both. The patients were predominantly male (7/9) with an average age of 39.4 years (range 6–72 years), and three suffered from co-morbid diabetes mellitus type II. Clinically active infection was favored at the time of surgery in seven cases, and five of these also suffered from chronic otitis media/mastoiditis. Infectious organisms, both Gram-positive cocci were identified via culture in two cases—culture performed at the most recent surgical procedure: *Streptococcus pneumoniae* and coagulase-negative *Staphylococcus aureus*). One third of the patients had a history of myringotomy without the placement of tympanostomy tubes, while another third had myringotomy with tube placement. Two patients had undergone prior mastoidectomy and one of these had been diagnosed with a cholesteatoma following an earlier biopsy. Serum IgG4 was not available on these cases.

Microscopic Pathology

IgG4 Related Disease

The pathology findings on the two cases reported here were remarkably similar to the recently published report on IgG4-related mastoiditis (Table 1) [14]. All three biopsies were characterized by a dense lymphoplasmacytic infiltrate and eosinophils were virtually absent (Fig. 1). Sheets of mature plasma cells were found in all three cases. The tissue was also dominated by fibrosis, and the fibrosis was organized into a storiform pattern. An evaluation at high power also revealed spindle-shaped cells that

Table 2 Clinicopathologic features of nine cases with histologic features suggestive of IgG4 related disease

Case	Age at surgery	Gender	Prior myringotomy with tubes	Prior myringotomy w/o tubes	Prior mastoidectomy	Prior cholesteatoma	Chronic OM	Acute infection	Culture results	Co-morbid conditions	IgG4 + cells/hpf IgG4/IgG ratio
#4	33	M	Y	N	N	N	Y	Y	Negative	DMII	52 52%
#5	68	M	N	N	N	N	N	Y	*Streptococcus pneumoniae*	Alcoholism	51 84%
#6	41	M	Y	N	Y	N	Y	Y	Negative	DMII, hypothyroid	4
#7	20	M	N	Y	N	N	N	Y	Coagulase negative staphylococcus	None	14
#8	12	M	N	N	Y	Y	N	N	n/a	None	2
#9	53	M	N	N	N	N	Y	Y	Negative	Asthma	5
#10	72	M	Y	N	N	N	Y	N	n/a	DMII, prostate cancer	9
#11	50	F	N	Y	N	N	Y	Y	Negative	None	11
#12	6	F	N	Y	N	N	Y	Y	Negative	None	8

Key: *DM* Diabetes mellitis, *Y* Yes, *N* No, *M* Male, *F* Female, *n/a* Not available

were morphologically compatible with fibroblasts. The inflammatory infiltrate was seen to extend into bone. However, osteonecrosis was not observed and only minimal amounts of woven bone were identified. There was no obliterative phlebitis or evidence of vasculitis.

Immunohistochemistry: The plasma cells were polyclonal in all cases. Elevated numbers of IgG4-positive plasma cells were identified in the mastoid biopsies. Greater than 50 IgG4 positive cells were identified in all three cases. The IgG4–IgG ratio was >40 % in cases #1 and #3 but measured <40 % in case 2. However, immunohistochemical staining of the original dural biopsy in case 2 revealed 161 IgG4-positive plasma cells/HPF and an IgG4+–IgG+ ratio of 51 % .

Consecutive Series of 162 Cases of Mastoiditis

Re-examination of the histology showed extensive lymphoplasmacytic infiltrate, as well as storiform fibrosis (Fig. 2). In two cases, >50 IgG4 positive plasma cells were identified per HPF. The ratio in these two cases was measured at 52 and 84 %, respectively. The remaining seven cases showed fewer IgG4 positive plasma cells (range 4–14/HPF). Both cases with elevated numbers of IgG4 positive plasma cells responded to antibiotic medications.

Discussion

The three cases of IgG4-RD involving the mastoid and middle ear showed characteristic histological features of IgG4 related disease: storiform fibrosis, elevated numbers of IgG4-positive plasma cells, and an elevated IgG4–IgG ratio. All three patients reported long standing disease at this site as well as multiple surgical interventions and recurrences. The disease extended to the meninges and caused cerebritis in two cases. In spite of this long standing nature of the disease, therapy with steroids and/or rituximab in two cases resulted in stabilization of the disease and resolution of symptoms.

There are several pieces of evidence that support the contention that these three cases represent IgG4 related disease. The histologic features are strongly supportive of IgG4-RD: storiform type fibrosis and a dense lymphoplasmacytic infiltrate. Although obliterative phlebitis was not identified, this feature is seldom seen in the head and neck manifestations of the disease. All three cases showed greater than 100 IgG4 positive plasma cells per HPF as well as a ratio of >40 % (although the ratio was lower in case no. 2, the pachymeningeal biopsy in this patients showed a ratio of >40 %). Furthermore, multiple recurrences, as in these cases, are a common theme in patients

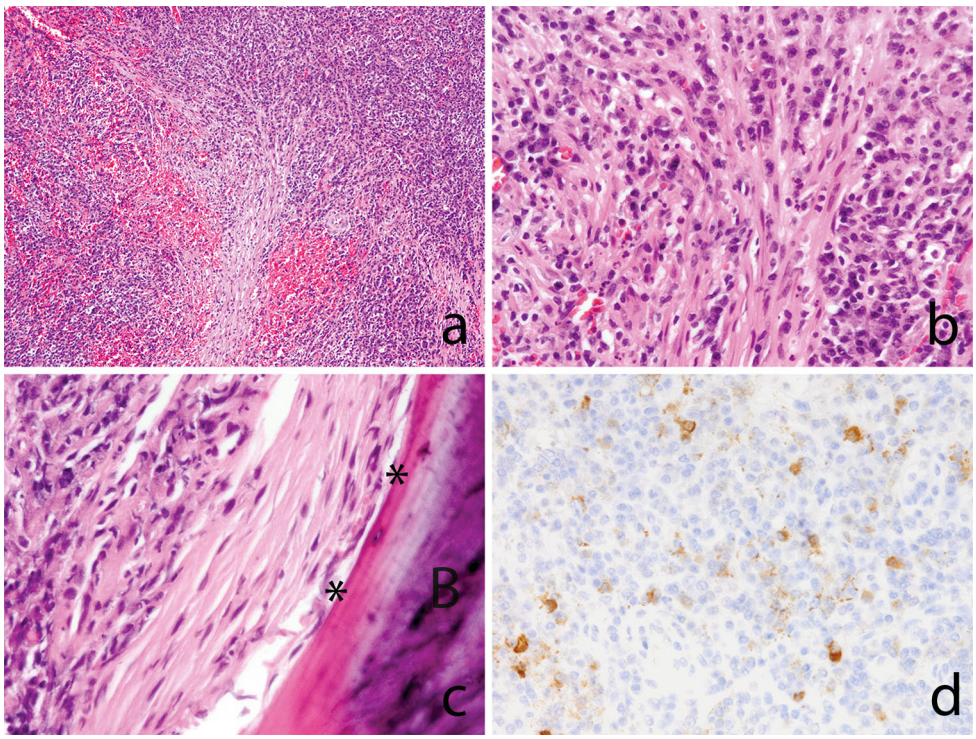

Fig. 1 Case 1: IgG4 related mastoiditis. Dense lymphoplasmacytic infiltrate with storiform type fibrosis (**a**, **b**). The infiltrate involves the bone (**c**). Arrow indicates lamellar bone and the periosteum is marked with an *asterisk*. An immunohistochemical stain for IgG4 shows elevated numbers of IgG4 positive plasma cells (**d**)

with IgG4 related disease. These individuals were treated with multiple cycles of antibiotics, with little or no response. Instead, all three cases showed resolution of disease with immunosuppressive therapy. In two cases, rituximab resulted in long-term disease stabilization. IgG4-RD responds dramatically and swiftly to rituximab [24]. Response to an anti-CD20 antibody is an unexpected phenomenon, given that the disease is dominated by the presence of plasma cells. Nevertheless, it is believed that the IgG4 positive plasmablasts (short-lived cells) fuel the production of IgG4 positive plasma cells [25]. These IgG4 positive plasmablasts bear CD20, and hence are responsive to rituximab [24]. Finally, like other forms of IgG4-RD, recurrences were identified outside the primary site, the nasopharyngeal lesion in one case, and the pachymeninges in case 2—although both recurrences were in the vicinity of the primary disease.

Over a three-year period at our institution, we were unable to identify any additional examples of IgG4-related mastoid/middle ear disease. Rather, the two cases (cases #4 and 5) that displayed morphological and immunohistochemical features compatible with IgG4-RD showed clinical features that are more keeping with a diagnosis of recurrent middle ear infections. Although only one of these two cases showed microorganisms on culture, both patients responded to the surgical intervention and post operative antibiotic therapy. Seven additional cases showed dense chronic inflammation as well as fibrosis, however, these showed only a minimal increase in IgG4 positive plasma cells. While bacterial organisms were identified on culture in only a minority of cases (likely as a result of multiple prior cycles of antibiotics), the clinical context was highly suggestive of infection. Most significantly, the disease responded favorably to antibiotic therapy, arguing against the possibility that patients #4 and 5 represent some unusual form of IgG4 related disease.

Histology has emerged as the gold standard for the diagnosis of IgG4-RD. The histologic diagnosis of IgG4-RD requires: (1) characteristic morphological changes; and, (2) elevated IgG4-positive plasma cells [17]. The requirement for both morphological appearance as well as immunohistochemical evidence is driven by the understanding that the complete spectrum of histologic changes are not observed in all IgG4-RD cases. In fact, obliterative phlebitis is infrequently observed in the head and neck manifestations of the disease [11, 12]. In addition, elevated numbers of IgG4-positive plasma cells are seen in a variety of diseases entirely unrelated to IgG4-RD [8]. However, the only other disease that consistently shows both storiform fibrosis and elevated numbers of IgG4-positive plasma cells is granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis) [20]. Fortunately, GPA is often readily distinguishable from IgG4-RD because it is associated with serum anti-neutrophil cytoplasmic antibodies directed against either proteinase-3 (most often) or myeloperoxidase.

This study uncovered an additional mimic of IgG4-related mastoiditis: long-standing or severe bacterial

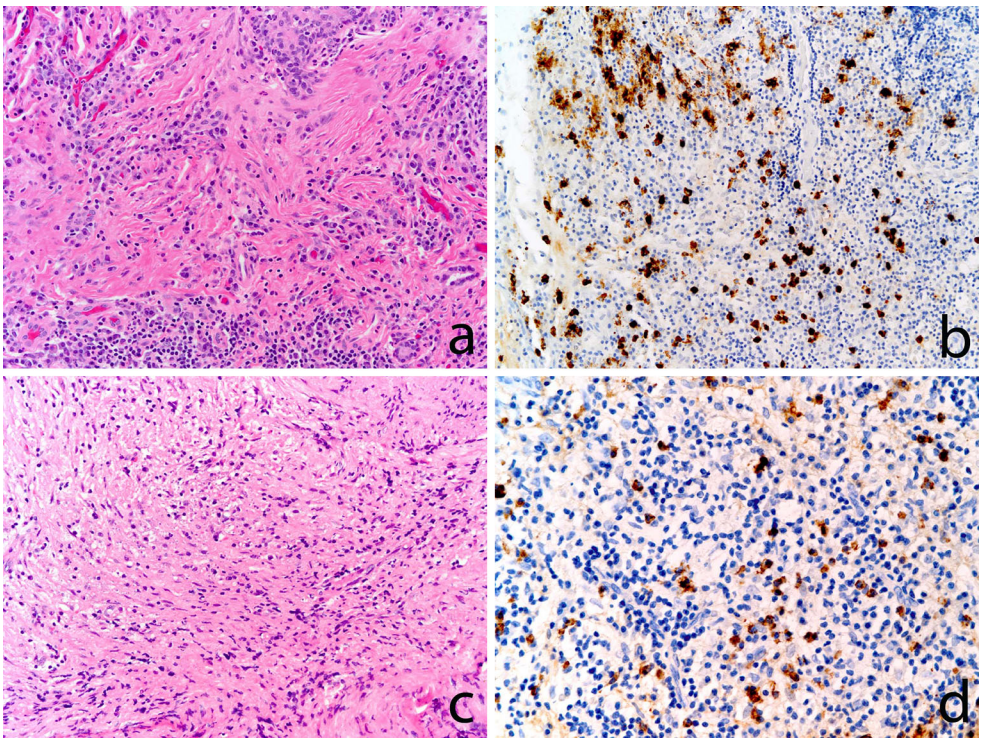

Fig. 2 Infectious mastoiditis mimicking IgG4 related mastoiditis. The storiform type fibrosis is more apparent in case 4 (**a**) than case 5 (**c**). However, both cases show markedly increased numbers of IgG4 positive plasma cells (**b**, **d**)

infections. Two cases of chronic infectious otitis media and mastoiditis in this study demonstrated a dense lymphoplasmacytic infiltrate, storiform fibrosis, and more than 50 IgG4-positive plasma cells/HPF accompanied by increased IgG4–IgG ratio (45 and 84 %, respectively) [9]. In most settings, these findings would serve as strong evidence for the diagnosis of IgG4-RD.

Misinterpreting a chronic infectious disease as IgG4-RD has major clinical consequences: the introduction of long-term glucocorticoid use and potentially rituximab in long-standing middle ear infections/mastoiditis may be associated with acceleration of this disease as well as enhancing the potential for extension of the infection into the meninges and brain parenchyma. Although our study was confined to the middle ear and mastoid, it is conceivable, if not likely, that chronic bacterial infections at other sites can also be associated with elevated numbers of IgG4-positive plasma cells, elevated IgG4–IgG ratios, and histopathologic features suggestive of IgG4-RD. Indeed, IgG4-positive plasma cell infiltrates have been reported to be associated with chronic infectious aortitis due to Gram-positive bacteria, but neither of these two examples of aortitis showed characteristic histologic features of IgG4-RD [22]. Thus, in organs commonly affected by chronic bacterial infections, elevated numbers of IgG4-positive cells are more likely to be encountered as a consequence of the infection rather than as a manifestation of IgG4-RD. The possibility that a fibro-inflammatory mass lesion with storiform fibrosis and elevated numbers of IgG4 positive plasma cells represents a reaction to chronic bacterial infection should therefore be excluded prior to embarking on immunosuppressive therapy.

The presence of elevated numbers of IgG4 positive plasma cells in a chronic bacterial infection is not entirely a surprise; some precedent exists in the contexts of other types of infection. CD4 positive cells, an essential component of cell-mediated immunity, can polarize towards Th1, Th2 or Th17 pathways, each of which is characterized by typical cytokine responses [26]. The cytokine response in IgG4 related disease is skewed in the direction of the Th2 pathway. In contrast, intracellular organisms and most bacterial infections typically trigger a predominantly Th1 cytokine response. Th2 cytokine responses, particularly those driven by interleukin-4 and interleukin-10, mediate B cell class switching to IgG4 [2]. The presence of IgG4-positive plasma cells provides indirect support for the hypothesis that the two individuals in this report (cases 4 and 5) mounted a robust Th2 response to chronic or severe middle ear infections.

These cases underscore the importance of correlating histopathological features with other clinical, serological, and radiologic findings. While the presence of storiform

fibrosis is highly suggestive of IgG4–RD, this criterion is not infallible. The recent consensus effort sets a high threshold for the number of IgG4-positive cells, but there are nevertheless occasional cases of other diseases that may reach these thresholds [9]. The Comprehensive Diagnostic Criteria (CDC) for IgG4, developed by a group from Japan, require presence of only 10 IgG4-expressing plasma cells/HPF with an IgG4/IgG ratio of 40 % [27]. In our experience, these thresholds would result in a substantial number of cases inappropriately classified as IgG4-RD and potentially lead to inappropriate or harmful treatments.

In conclusion, IgG4-RD involving the middle ear and mastoid is an uncommon manifestation of the disease, and may be mimicked by infectious diseases at this site. Biopsies from individuals with chronic infectious mastoiditis may fulfill histologic criteria for IgG4-RD. The diagnosis at this site should be deliberated on by a multidisciplinary group, with every effort being made to exclude an infectious etiology, before embarking on immunosuppressive therapy.

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