The Journal of Laryngology & Otology (2010), ***124***, *1106–1110.*

doi:10.1017/S0022215110001143

Clinical Record

Immunoglobulin G4 related systemic sclerosing disease involving the temporal bone

L Masterson, M Martinez Del Pero, N Donnelly*, D A Moffat*, E Rytina†

Abstract

Objective: To report a rare condition affecting the temporal bone. Immunoglobulin G4 related systemic sclerosing disease is a recently described autoimmune condition with manifestations typically involving the pancreas, biliary system, salivary glands, lungs, kidneys and prostate. Histologically, it is characterised by T-cell infiltration, fibrosis and numerous immunoglobulin G4-positive plasma cells. This condition previously fell under the umbrella diagnosis of inflammatory pseudotumour and inflammatory myofibroblastic tumour.

Case report: We present the case of a 58-year-old woman with multiple inflammatory masses involving the pharynx, gall bladder, lungs, pelvis, omentum, eyes and left temporal bone, over a seven-year period. We describe this patient's unusual clinical course and pathological features, which resulted in a change of diagnosis from metastatic inflammatory myofibroblastic tumour to immunoglobulin G4 related systemic sclerosing disease. We also review the literature regarding the management of inflammatory pseudotumours of the temporal bone, and how this differs from the management of immunoglobulin G4 related systemic sclerosing disease.

Conclusion: We would recommend a full review of all histological specimens in patients with a diagnosis of temporal bone inflammatory pseudotumour or inflammatory myofibroblastic tumour. Consideration should be given to immunohistochemical analysis for anaplastic lymphoma kinase and immunoglobulin G4, with measurement of serum levels of the latter. Management of the condition is medical, with corticosteroids and immunosuppression, rather than surgical excision.

Key words: Temporal Bone; IgG4; Inflammatory Pseudotumor

Introduction

The term inflammatory pseudotumour was first used in 1954 to describe a lesion that follows the clinical and radiological pattern of a neoplasm.[1] It is not a single entity but rather a generic description applied to a non-specific, expanding, chronic inflammatory lesion. This broad definition has been used interchangeably with terms such as inflammatory myofibroblastic tumour, plasma cell granuloma, systemic fibrosis, xanthofibrogranulomatosis and multifocal fibrosclerosis.[2]

In 2001, Hamano *et al.* described an association between sclerosing pancreatitis and high levels of immunoglobulin (Ig) G4 complexes in the serum, compared with normal subjects and patients with chronic inflammatory conditions such as primary biliary cirrhosis.[3] This led to the proposal of a new entity characterised by extensive IgG4-positive plasma cell infiltration, together with cluster of differentiation 4 glycoprotein positive or cluster of differentiation 8 glycoprotein positive T lymphocytes, in the presence of sclerosing pancreatitis. Neild *et al.* conducted an extensive study on tissue from other organs with sclerosing disease, and found IgG4 present in serum and tissues.[2] This relatively new condition has been named IgG4-related systemic sclerosing disease or hyper IgG4 disease.

Immunoglobulin G4 is the least abundant of the IgG subclasses to be expressed, accounting for only 3–6 per cent of total IgG in normal serum. It has a low affinity for target antigens and cannot activate the classic complement pathway, but it appears to be part of the desensitisation pathway. Pathologically, it produces fibrosis and obstructive phlebitis, leading to autoimmune manifestations mainly in the pancreas, biliary system, salivary glands, lungs, kidneys and prostate. Histologically, it is characterised by T-cell infiltration, fibrosis and numerous IgG4-positive plasma cells.[4] The quantity of IgG4-positive plasma cells appears to correlate with disease activity.[2,5]

We present a case of IgG4-related systemic sclerosing disease involving the temporal bone, pharynx, gall bladder, lungs, pelvis, omentum and eyes over the course of seven years. We also review the unusual clinical course and unique pathological and radiological features of this disease, together with suggestions from the literature for the management of both temporal bone and systemic disease.

Case report

A 58-year-old woman presented to the ENT clinic in 2008 with a five-month history of left-sided deafness and intermittent vertigo. Over the course of the previous seven years, she had undergone several operations for inflammatory masses thought to be due to inflammatory pseudotumour.

From the Department of Otolaryngology, Norfolk and Norwich University Hospital, and the Departments of *Skull Base Surgery, and †Histopathology, Cambridge University Hospital, UK.
Accepted for publication: 22 February 2010. First published online 2 June 2010.

The initial presentation in 2001 had been to the ENT department, with a mass in the right parapharyngeal space centred on the tonsil. The mass had extended from the nasopharynx to the hypopharynx, causing airway obstruction, and had had an associated enlarged jugulodigastric lymph node. Clinically, it had been thought to be due to carcinoma or lymphoma, but histological analysis had shown chronic inflammation. On further biopsy, the patient had developed airway obstruction requiring an emergency tracheostomy. Following this, the patient had been treated with oral steroids for six months. The inflammation had subsided and the patient had been decannulated. A diagnosis of inflammatory pseudotumour had been made, based on histological examination and the response to steroids.

In 2002, the patient had undergone cholecystectomy for symptoms of cholecystitis. A pre-operative chest X-ray had revealed a mass in the left upper lobe of the lung. A biopsy had demonstrated recurrence of the 'pseudotumour'. Surgical management had been the preferred option. The operation had been complicated by excessive bleeding, leading to a left pneumonectomy (in 2003). Histological examination of resected tissue had revealed pseudotumour infiltrating blood vessels within the pleura, and satellite lesions within the lung.

Around the same time, an ophthalmological review for poor eyesight had revealed macular oedema. This had settled spontaneously over five months.

In 2004, the patient had developed a pelvic mass, treated surgically with a salpingo-oophorectomy and omentectomy. The histological report had described an inflammatory myofibroblastic tumour.

Over the course of the seven years, the patient had complained of intermittent hearing loss and tinnitus. She had had one set of grommets inserted for middle-ear effusion; this subsequently recurred and was treated conservatively. In 2008, she became acutely deaf and vertiginous. Examination revealed a mildly erythematous tympanic membrane and profound sensorineural hearing loss on the left side. She had a positive left fistula sign and rotated to the left with Unterberger's stepping test. A computed tomography scan showed a completely opacified left middle-ear cleft and mastoid. The tegmen and ossicular chain appeared intact; however, there was evidence of erosion of the mastoid air cells and a lateral semicircular canal fistula (Figure 1). A clinical diagnosis of cholesteatoma was made.

A mastoid exploration revealed an extensive, firm, vascular mass filling the middle ear and mastoid. A large fistula was seen in the lateral semicircular canal, and the majority of the horizontal segment of the facial nerve canal was dehiscent. The stapes was absent over an open oval window. Remnants of the head of the malleus and the body of the incus were present. A modified radical mastoidectomy was performed to excise the lesion; however, complete excision was not possible. The initial histological examination suggested an inflammatory myofibroblastic tumour.

The patient was referred to the regional skull base multidisciplinary team. Histological review of the mastoid specimen revealed a diffuse infiltrate that did not correspond entirely to a diagnosis of inflammatory myofibroblastic tumour. The histology samples from previous resections were requested and analysed in detail by the histopathologist named in this paper (ER). This analysis revealed the same diffuse appearance in these specimens (Figure 2). Positive staining for IgG4 (Figure 3) led to the diagnosis of IgG4-related systemic sclerosing disease. This was confirmed by serum sample positivity for IgG4.

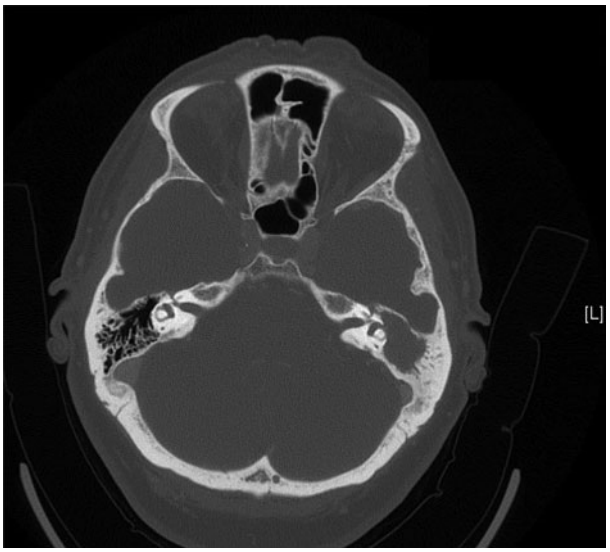

FIG. 1

Axial computed tomography image showing left lateral semicircular canal dehiscence with total opacification of the left otomastoid cavity. L = left

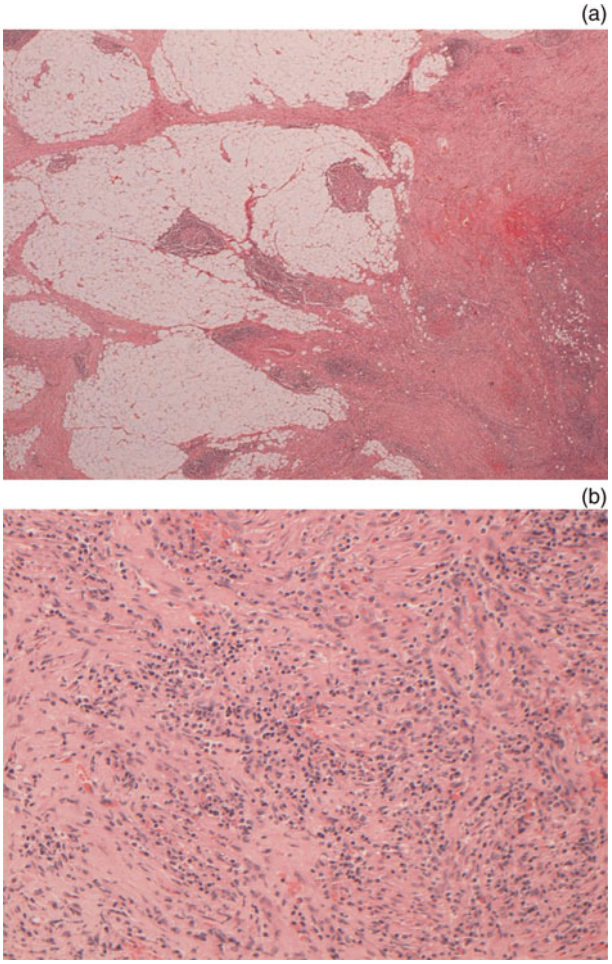

FIG. 2

(a) Low power photomicrograph of omentum showing the poorly circumscribed, infiltrative nature of the lesion (H&E; ×10). (b) Medium power photomicrograph of temporal bone biopsy demonstrating fibrosis identical to that seen elsewhere, with an infiltrate of lymphocytes and plasma cells (H&E; ×20).

https://doi.org/10.1017/S0022215110001143 Published online by Cambridge University Press

This new diagnosis prompted a referral to the immunology team of the same institution. Systemic immunosuppressive treatment was initiated, in the form of mycophenolate mofetil and low dose prednisolone.

One year later, the patient remained well and in remission. The residual mass around the left jugular bulb was being reviewed at six-monthly intervals by magnetic resonance imaging (MRI) scanning. Serial imaging demonstrated a reduction in size and vascularity of the tumour, compared to its appearance prior to commencement of immunosuppressive treatment (Figure 4).

Discussion

Immunoglobulin G4 related sclerosing disease is a new systemic entity and is commonly known to involve the pancreas and other retroperitoneal organs. Head and neck involvement has been described in the major salivary glands, the thyroid gland and ophthalmic region, but not, to date, in the temporal bone or larynx.[2]

Initially, this patient was thought to suffer from a systemic inflammatory pseudotumour, later relabelled as a multifocal inflammatory myofibroblastic tumour. The term inflammatory pseudotumour has been used to describe a pattern of bland fibroblastic and myofibroblastic spindle cell proliferation with prominent inflammation, particularly with plasma cells.[6] This probably represents a number of reactive entities. A proportion of these lesions have been shown to be true neoplasms – inflammatory myofibroblastic tumours.[7] Both diagnoses were used interchangeably in this case. However, these conditions usually present in the abdomen, retroperitoneum or lung, and tend toward local rather than distant or multifocal recurrence.[8,9] Inflammatory myofibroblastic tumour typically occurs in children and young adults.

In the presented patient, the definitive diagnosis of IgG4-related systemic sclerosing disease was made after retrospective review of all histology specimens. The histological cellular constituents of this condition are identical to inflammatory pseudotumour and inflammatory myofibroblastic tumour, characteristically occurring together with obliterative phlebitis and, in the pancreas, periductal fibrosis plus a predominance of IgG4-positive plasma cells. However, when all our patient's biopsies were reviewed together, an infiltrative growth pattern with partial preservation of tissue architecture was observed, rather than the well defined mass seen in inflammatory myofibroblastic tumour. Additionally, there were more IgG4-positive plasma cells, eosinophils and lymphoid follicles than is typical for inflammatory myofibroblastic tumour. The spindle cells were anaplastic lymphoma kinase negative on immunohistochemical analysis, whereas up to 60 per cent of inflammatory myofibroblastic tumours are positive in this regard.[10]

The recommended treatment of IgG4-related systemic sclerosing disease is corticosteroids.[2,3,11] This treatment has been advocated by Hamano and colleagues, who first described the disease, and by Neild *et al.*, who found a significant reduction of plasma cells and absence of IgG4

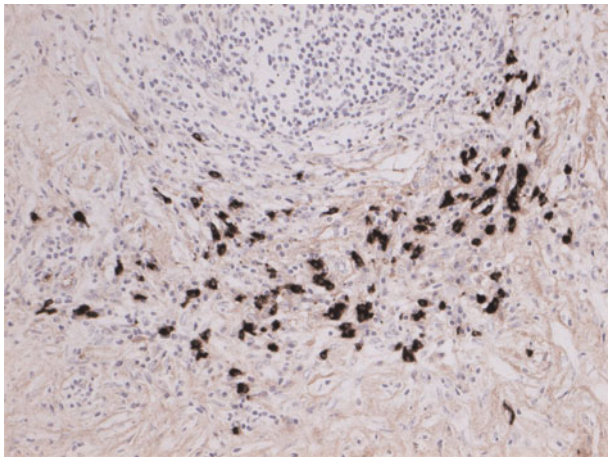

FIG. 3

Photomicrograph of omentum showing immunohistochemical positivity for immunoglobulin (Ig) G4 in plasma cells, strong evidence for IgG4-related fibrosclerosing disease. A correlation with a raised serum IgG4 level during the active phase of disease would be diagnostic (×20).

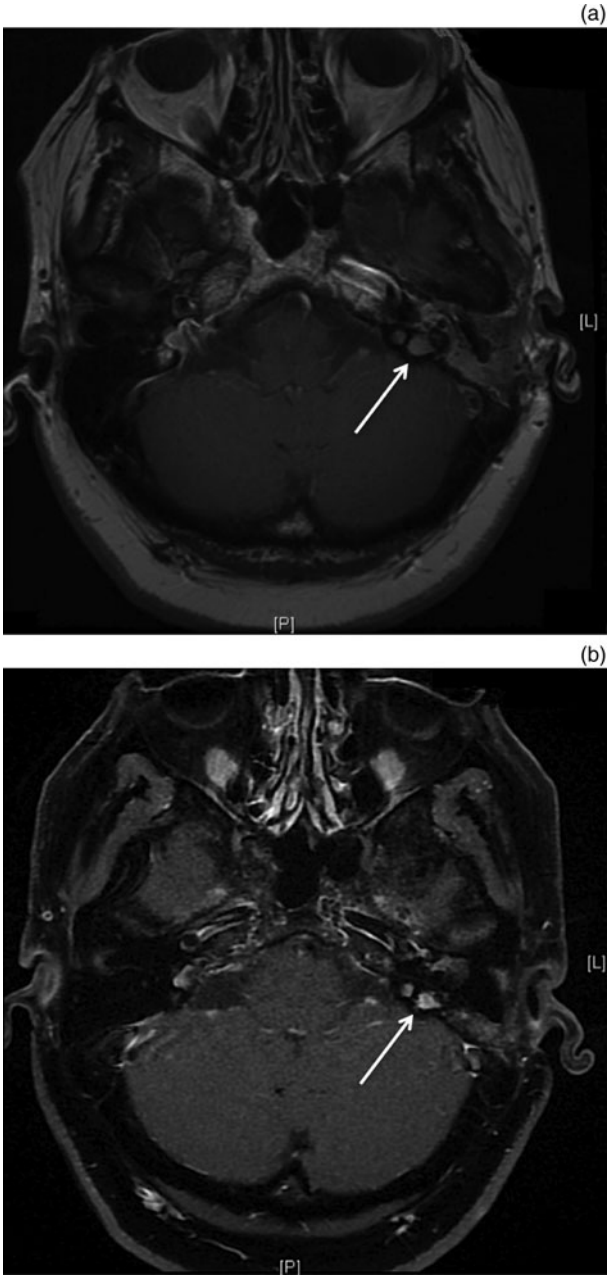

FIG. 4

Interval, T1-weighted magnetic resonance imaging scans with gadolinium of temporal bones. (a) demonstrates disease (arrow) adjacent to left jugular bulb prior to treatment. (b) demonstrates decrease in the size of residual disease following six months of immunosuppressive treatment. L = left; P = posterior

https://doi.org/10.1017/S0022215110001143 Published online by Cambridge University Press

TABLE I

REPORTED HEAD AND NECK MANIFESTATIONS OF IGG4-RELATED DISEASE

H&N region or process	Associated involvement	Treatment
Submandibular gland	Pancreas[12]	Steroids
Parotid	Pancreas[13]	Steroids
Sjögren's syndrome	Pancreas[13] or RPF[14]	Steroids
Maculopathy	MFF[15]	Steroids or local resection
Uveitis	Renal[16]	Steroids
Lacrimal	Salivary gland[17]	Steroids, immunosuppression or local resection
Hashimoto's disease or Graves' disease	RPF[18]	Steroids

Ig = immunoglobulin; H&N = head and neck; RPF = retroperitoneal fibrosis; MFF = multifocal fibrosis

expression in tissues after treatment of patients with corticosteroids.[2,3,5] Some authors have favoured the use of cytotoxic immunosuppression as an adjunct to steroid therapy when the head and neck region is affected (Table I). Surgical management is rarely indicated for extensive disease.

Inflammatory pseudotumour affecting the temporal bone is rare, and as such the treatment strategy has not been established. Surgical resection is the treatment of choice in most reports due to the aggressive and unpredictable course.[19–23] In one of the larger case series, Williamson *et al.* described complete surgical excision in eight cases and subtotal excision in one. Corticosteroids were administered to one patient with residual microscopic tumour, and external beam radiotherapy was used for residual or recurrent disease in another case.[21] No long-term follow up exists for all treatment modalities. However, a review of two cases undergoing extensive surgical resection for erosive disease showed no recurrence at eight and 10 years, variously.[20]

Inflammatory pseudotumour can behave aggressively in the temporal bone, in contrast to the orbital region.[21] Computed tomography and MRI are required to assess the extent of bone destruction and the inherent structure of the lesion. The recognised pattern is of a soft tissue mass characterised by low signal intensity on T2-weighted images and marked contrast enhancement. The tissue mass is often seen to spare the inner ear and the ossicles.[24] In the case described, the radiological and surgical findings demonstrated a more aggressive process.

Inflammatory pseudotumour of the temporal bone has been mostly treated surgically, followed by corticosteroids.[20–23] However, there are cases of patients being treated with corticosteroids alone, with good results.[6,11,25,26] Schaeffer *et al.* reported a case of recurrence following tapering reduction of corticosteroids, therefore supporting the need for surgery.[6] This case could also support an argument for the use of other immunosuppressive agents. None of the literature concerning pseudotumours in the temporal bone reported IgG4 staining. If performed, and in the absence of end-organ damage, this could have guided management strategies towards a more conservative approach. We would recommend a full review of all histological specimens in patients with a diagnosis of inflammatory pseudotumour or inflammatory myofibroblastic tumour. Consideration should be given to staining for IgG4, together with measurement of serum levels, especially in patients with unusual clinical or histological features such as multifocal distribution, poor circumscription with infiltrative margins, or non-typical constituent inflammatory cells.

- **Immunoglobulin (Ig) G4 related systemic sclerosing disease is a multisystem, autoimmune inflammatory condition**
- **It closely resembles inflammatory pseudotumours and inflammatory myofibroblastic tumours**
- **The diagnosis is confirmed by immunohistochemical identification of IgG4-positive plasma cells, absence of anaplastic lymphoma kinase, and raised serum levels of IgG4**
- **Management is non-surgical, with corticosteroids and immunosuppressive agents**

Our patient presented a diagnostic challenge, and underwent multiple operations under different specialties for various manifestations of the same disease. Her previous diagnosis of inflammatory pseudotumour, and latterly inflammatory myofibroblastic tumour, was replaced with a diagnosis of IgG4-related systemic sclerosing disease. The diagnosis of this autoimmune condition enabled the multidisciplinary team to avoid further surgery and to treat the patient with appropriate corticosteroids and immunosuppressive agents.

References

1 Umiker WO, Iverson L. Postinflammatory tumors of the lung; report of four cases simulating xanthoma, fibroma, or plasma cell tumor. *J Thorac Surg* 1954;**28**:55–63
2 Neild GH, Rodriguez-Justo M, Wall C, Connolly JO. Hyper-IgG4 disease: report and characterisation of a new disease. *BMC Medicine* 2006;**4**:23
3 Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T *et al.* High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001; **344**:732–8
4 Kamisawa T, Okamoto A. IgG4-related sclerosing disease. *World J Gastroenterol* 2008;**14**:3948–55
5 Hamano H, Kawa S, Ochi Y, Unno H, Shiba N, Wajiki M *et al.* Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet* 2002;**359**:1403–4
6 Schaeffer CJ, Minai OA, Sharma N, Kanne JP, Mohammed TL. Inflammatory myofibroblastic tumor of the lung: recurrence after steroid treatment. *J Thorac Imaging* 2008;**23**: 191–3
7 Coffin CM, Watterson J, Priest JR, Dehner LP. Extrapulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumour). A clinicopathological and immunohistochemical study of 84 cases. *Am J Surg Pathol* 1995;**19**:859–72
8 Gleason BC, Hornick JL. Inflammatory myofibroblastic tumours: where are we now? *J Clin Pathol* 2008;**61**:428–37
9 Meis JM, Enzinger FM. Inflammatory fibrosarcoma of the mesentery and retroperitoneum. A tumor closely simulating inflammatory pseudotumor. *Am J Surg Pathol* 1991; **15**:1146–56
10 Cook JR, Dehner LP, Collins MH, Ma Z, Morris SW, Coffin CM *et al.* Anaplastic lymphoma kinase (ALK) expression in the inflammatory myofibroblastic tumor: a comparative immunohistochemical study. *Am J Surg Pathol* 2001;**25**: 1364–71
11 Tsuboi H, Inokuma S, Setoguchi K, Shuji S, Hagino N, Tanaka Y *et al.* Inflammatory pseudotumors in multiple organs associated with elevated serum IgG4 level: recovery by only a small replacement dose of steroid. *Intern Med* 2008;**47**:1139–42
12 Taguchi M, Aridome G, Abe S, Kume K, Tashiro M, Yamamoto M *et al.* Autoimmune pancreatitis with IgG4-

https://doi.org/10.1017/S0022215110001143 Published online by Cambridge University Press

positive plasma cell infiltration in salivary glands and biliary tract. *World J Gastroenterol* 2005;**11**:5577–81
13 Pickartz T, Pickartz H, Lochs H, Ockenga J. Overlap syndrome of autoimmune pancreatitis and cholangitis associated with secondary Sjogren's syndrome. *Eur J Gastroenterol Hepatol* 2004;**16**:1295–9
14 Fukui T, Okazaki K, Yoshizawa H, Ohashi S, Tamaki H, Kawasaki K *et al*. A case of autoimmune pancreatitis associated with sclerosing cholangitis, retroperitoneal fibrosis and Sjogren's syndrome. *Pancreatology* 2005;**5**:86–91
15 Brazier DJ, Sanders MD. Multifocal fibrosclerosis associated with suprasellar and macular lesions. *Br J Ophthalmol* 1983;**67**:292–6
16 Sugimoto T, Tanaka Y, Morita Y, Kume S, Uzu T, Kashiwagi A *et al*. Is tubulointerstitial nephritis and uveitis syndrome associated with IgG4-related systemic disease? *Nephrology* 2008;**13**:89
17 Sato Y, Ohshima K, Ichimura K, Sato M, Yamadori I, Tanaka T *et al*. Ocular adnexal IgG4-related disease has uniform clinicopathology. *Pathol Int* 2008;**58**:465–70
18 Armigliato M, Paolini R, Bianchini E, Monesi G, Zamboni S, D'Andrea EA *et al*. Hashimoto's thyroiditis and Graves' disease associated with retroperitoneal fibrosis. *Thyroid* 2002;**12**:829–31
19 Schonermark M, Issing P, Stover T, Ruhand S, Lenarz T. Fibroinflammatory pseudotumor of the temporal bone. *Skull Base* 1998;**8**:45–50
20 Strasnick B, Vaughan A. Inflammatory pseudotumor of the temporal bone: a case series. *Skull Base* 2008;**18**:49–52
21 Williamson RA, Paueksakon P, Coker NJ. Inflammatory pseudotumor of temporal bone. *Otol Neurotol* 2003;**24**: 818–22
22 Goh BS, Tan SP, Husain S, Rose IM, Saim L. Metachronous inflammatory myofibroblastic tumour in the temporal bone: case report. *J Laryngol Otol* 2009;**123**:1184–7
23 Lee JH, Jung MK, Song CE, Yeo SW, Lee HK, Pang PS *et al*. Concomitant inflammatory pseudotumor of the temporal bone and lung: a case report. *Ear Nose Throat J* 2007;**86**:614–16
24 Gasparotti R, Zanetti D, Bolzoni A, Gamba P, Morassi ML, Ungari M *et al*. Inflammatory myofibroblastic tumor of the temporal bone. *Am J Neuroradiol* 2003;**24**:2092–6
25 Kasliwal MK, Suri A, Gupta DK, Suri V, Rishi A, Sharma BS. Sphenoid wing inflammatory pseudotumor mimicking a clinoidal meningioma: case report and review of the literature. *Surg Neurol* 2008;**70**:509–13
26 Coulson C, George A, Biswas A, Phelan C, De R. Pseudotumour of the temporal bone: an unusual cause of otorrhoea and facial palsy. *Eur Arch Otorhinolaryngol* 2008;**265**:713–15

Address for correspondence:
Mr Neil Donnelly,
Department of Skull Base Surgery,
Cambridge University Hospitals,
Hills Road, Cambridge CB2 0QQ, UK.

E-mail: neil.donnelly@addenbrookes.nhs.uk

Mr N Donnelly takes responsibility for the integrity of the content of the paper.
Competing interests: None declared