*The Journal of Laryngology & Otology (2015)*, ***129***, *226–231*.

doi:10.1017/S0022215115000195

**REVIEW ARTICLE**

# Immunoglobulin G4 related chronic sclerosing sialadenitis

E L CULVER[1], A HUNT[2], E CREWE[2], K A SHAH[3], P MARTINEZ-DEVESA[2]

[1]*Translational Gastroenterology Unit, John Radcliffe Hospital and Oxford University, and Departments of* [2]*Otorhinolaryngology – Head and Neck Surgery, and* [3]*Cellular Pathology, John Radcliffe Hospital, Oxford, UK*

## Abstract

*Background*: ENT surgeons may be the first specialists to encounter and diagnose patients with salivary gland disease. A new entity involving the salivary glands has recently been described of which ENT surgeons need to be aware: immunoglobulin G4 related chronic sclerosing sialadenitis.

*Method*: A literature search of Medline, Embase and Cochrane Library databases was performed, using the search terms 'IgG4', 'hyperIgG4 syndrome' and 'IgG4 related chronic sclerosing sialadenitis'.

*Results*: Knowledge concerning immunoglobulin G4 related chronic sclerosing sialadenitis is rapidly increasing. This new entity is part of a fibro-inflammatory corticosteroid-responsive systemic disease (immunoglobulin G4 related disease) and has been described in almost every organ. Biopsy of the submandibular gland can be diagnostic. However, the diagnosis can easily be overlooked if: clinical suspicion is not high, one is unaware of the classical morphology and/or immunoglobulin G4 staining is not performed. This paper presents a summary of the current understanding of the disease and its management.

*Conclusion*: ENT surgeons should be aware of this new disease entity. Patients with systemic disease should be managed under a multidisciplinary team, with input from clinicians who have an interest in such diseases (such as gastroenterologists and rheumatologists), and input from histopathologists and radiologists.

**Key words:** Submandibular Gland; IgG4; IgG4-Related Disease; Chronic Sclerosing Sialadenitis; Küttner's Tumor; Sjogren's Syndrome; Sialadenitis

## Introduction

An enlarged submandibular gland is a common presentation to the ENT surgeon, with a variety of possible diagnoses. Recently, a new entity has been described: immunoglobulin G4 (IgG4) related chronic sclerosing sialadenitis. As ENT surgeons may be the first specialists to see patients with salivary gland disease, it is important to highlight this newly described disease.

The association between increased levels of IgG4 and sclerosing inflammatory disease was first described as occurring in the pancreas in 2001.[1] Over the last 10 years, it has become apparent that IgG4-related inflammatory fibrosis can manifest in many organs as part of a systemic IgG4-related disease, including the pancreas, bile ducts, liver, retroperitoneum, lymph nodes, kidneys, lungs, orbital tissues, pituitary gland, aorta, parotid and salivary glands.[2] There is a wide spectrum of disease, and clinical presentation usually depends on the organ involved. The disease can be confined to a single organ or involve multiple organs at any one time, although not all are clinically apparent. It has many mimics including malignancy, and inflammatory, infective and other immune-mediated diseases.[3]

In 2010, the relationship between chronic sclerosing sialadenitis and IgG4 was described in the Western population.[4] Geyer *et al*. reported elevated tissue IgG4-positive plasma cells in patients with Sjögren's syndrome, chronic sclerosing inflammatory fibrosis and sialadenitis; the authors found a lymphoplasmacytic infiltrate with increased numbers of IgG4-positive plasma cells in the chronic sclerosing inflammatory fibrosis group.[4] A link was proposed between chronic sclerosing sialadenitis and IgG4, and this new disease entity was distinguished as separate from Sjögren's syndrome, sialadenitis or lymphoproliferative disease.

We present a review of the current understanding regarding the presentation, diagnosis and management of IgG4-related chronic sclerosing sialadenitis, with the aim of highlighting this new disease to ENT surgeons. We propose a diagnostic pathway to aid management of these cases.

Accepted for publication 13 July 2014

## Materials and methods

A computer literature search of Medline, Embase and Cochrane Library databases was performed (by E Crewe) to identify all studies on the subject of interest. For this purpose, the search terms used were: 'IgG4', 'hyperIgG4 syndrome' and 'IgG4 related chronic sclerosing sialadenitis'. The abstracts of the identified manuscripts were inspected and irrelevant studies were excluded. The full text of relevant studies was then examined.

## Disease presentation

Patients usually present with IgG4-related chronic sclerosing sialadenitis in the sixth decade of life and there is a male preponderance (similar to other organ manifestations of IgG4-related disease), although one study by Takano and colleagues found a slight preponderance in females.[5] The disease commonly affects the submandibular glands, but involvement of the parotid and minor salivary glands has been described.[6–9]

Patients with IgG4-related chronic sclerosing sialadenitis can present to the ENT surgeon with: dry eyes and mouth (sicca syndrome); diffuse enlargement of the submandibular, parotid or lacrimal glands (Mikulicz's disease); or a solitary submandibular gland mass (Küttner's tumour).[8,9] In the absence of clinical suspicion and awareness of the condition, IgG4-related chronic sclerosing sialadenitis is under-diagnosed and mistaken for other diseases.[10]

Immunoglobulin G4 related chronic sclerosing sialadenitis can be detected incidentally after patients present to a different specialty with other organ involvement. Systemic involvement is more common in patients presenting with diffuse enlargement of submandibular glands and/or lacrimal glands, and/or sicca symptoms, compared to those who have solitary submandibular gland enlargement alone. In Japan, the salivary gland is the third most common location for extra-pancreatic lesions associated with autoimmune pancreatitis, with the incidence of IgG4-related sclerosing cholangitis and lymphadenopathy being higher than that of salivary gland enlargement.[11]

## Disease investigation

In a patient presenting to the ENT surgeon with enlargement of the submandibular gland or diffuse enlargement of glands, or sicca syndrome, non-invasive serological evaluation for total immunoglobulin G (IgG) and IgG4 subclass can readily be performed. An elevated serum IgG4 level (greater than 1.4 g/l) alone is not sufficient for the diagnosis of IgG4-related chronic sclerosing sialadenitis, but it can be supportive in the correct clinical context and aid the decision for referral. The sensitivity of elevated serum IgG4 for IgG4-related chronic sclerosing sialadenitis is estimated at 70–80 per cent, which is similar to that described for other organ manifestations.[12] However, serum IgG4 may be elevated (usually 2–3 times the upper limit of normal levels) in a range of inflammatory and malignant diseases, including lymphoma, and so is not disease-specific.[12] The serum IgG4 level is reportedly higher in those with multi-organ rather than single-organ disease. The literature suggests that serum IgG4 levels can be normal in 20 per cent of patients with autoimmune pancreatitis, but there are limited data regarding normal IgG4 values in those with IgG4-related chronic sclerosing sialadenitis.

Ultrasound of the head and neck usually reveals enlargement of the gland(s) and the presence of local lymphadenopathy. It is useful in guiding a site for biopsy (discussed below), but is otherwise non-specific in diagnosis. A magnetic resonance imaging scan of the salivary glands can be useful to look for distribution and involvement of the disease, which may not be clinically apparent, and to differentiate it from mimics such as Sjögren's syndrome. In IgG4-related disease, the parotid, submandibular and labial glands can all be diffusely enlarged, with ill-delineated infiltration, T1 and T2 hypointensity, homogeneous marked contrast-enhancement and restricted diffusion.[13] Local lymph nodes may also be enlarged, with restricted diffusion, but this is a non-specific finding. The absence of necrosis and lack of extracapsular spread point to a benign diagnosis. However, sarcoidosis and other granulomatous diseases (e.g. Wegener's granulomatosis) may also present with the combination of generalised salivary involvement and reactive lymph node enlargement, with the former appearing on imaging as a diffuse non-nodular enlargement with homogeneous enhancement of the glands.

The primary role of fine needle aspiration (FNA) is to exclude a neoplastic process. In the presence of significant fibrosis, FNA is non-diagnostic. Furthermore, when cellular material is obtained, it comprises a mixed population of chronic inflammatory cells. This is a non-specific feature on its own. Fine needle aspiration is not suited to demonstrating an increased proportion of IgG4 plasma cells, which is one of the features in the pathological diagnosis of IgG4-related disease.

Ultrasound-guided biopsy of the enlarged salivary gland for histological diagnosis of IgG4-related chronic sclerosing sialadenitis is the preferred method for diagnosis. When representative material is obtained on a biopsy, histopathological features in conjunction with IgG4 immunohistochemistry are sufficient for a collaborative diagnosis of IgG4 disease. In our experience, sublabial biopsy has not been helpful, as the presence of salivary gland tissue is variable. Sometimes, the enlarged submandibular gland is excised to exclude malignancy and diagnosis made retrospectively. Open excision biopsy is associated with potentially significant morbidity, such as facial weakness occurs due to injury of the mandibular branch of the facial nerve, or hypoglossal or lingual nerve (a risk of approximately 1–2 per cent). Open excision biopsy would be contemplated only in

https://doi.org/10.1017/S0022215115000195 Published online by Cambridge University Press

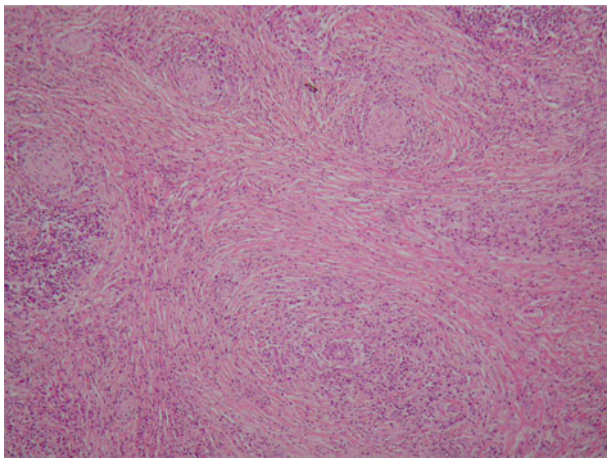

FIG. 1
Photomicrograph of the submandibular gland showing loss of parenchyma, storiform fibrosis and chronic inflammation. (H&E; ×40)

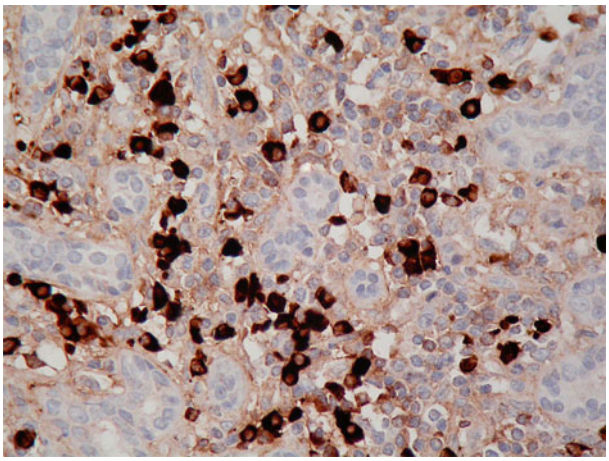

FIG. 2
Immunostaining for immunoglobulin G4 (IgG4) plasma cells, showing dark brown IgG4+ plasma cells. (IgG4; ×400)

the differential diagnosis of malignancy when the ultrasound-guided biopsy was suggestive of malignancy, or if it was inconclusive and there were worrying clinical signs or symptoms.

There are characteristic morphological changes in the tissue that distinguish IgG4-related chronic sclerosing sialadenitis from other forms of sialadenitis or sialectasis-related inflammation.[14] The three key morphological findings in organs affected by IgG4-related disease are: marked lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis (Figure 1).[15] In the salivary gland, there is preservation of lobular architecture, large irregular germinal centres, acinar atrophy, an absence of lymphoepithelial lesions, and, characteristically, the presence of prominent interlobular fibrosis, composed of activated fibroblasts, lymphocytes and plasma cells (both T and B cells). The plasma cells are predominantly IgG4-positive (counts of more than 10 per mean of three high power fields in biopsy sections and more than 50 per mean of three high power fields in resection specimens), with an IgG4-positive to IgG-positive plasma cell ratio of over 40 per cent (Figure 2). The use of these cut-offs has been recommended in the Boston consensus criteria to support a histopathological diagnosis of IgG4-related disease, and discriminate it from other disease mimics.[16] Both the morphological changes and the presence of IgG4-positive cells are needed for a definite or probable histological diagnosis. It must be remembered that IgG4-positive plasma cells can be seen around an area infiltrated with malignancy, so morphological examination is crucial.[17]

Histological assessment is important in IgG4-related disease investigation in order to exclude malignancy and to carry out supportive immunohistochemical analysis. The submandibular and parotid glands are often the most accessible sites to obtain tissue, whilst the pancreas, renal and lung tissue, for example, are less accessible.

Immunoglobulin G4-related chronic sclerosing sialadenitis can mimic many other diseases. For example, a patient with Sjögren's syndrome may present to the ENT surgeon with sicca symptoms and diffuse enlargement of the salivary glands, which often includes the parotid gland. Typically, there is immune-mediated destruction of the exocrine glands, with prominent lymphoepithelial lesions and cystic dilatation of peripheral ducts.[18] Whilst plasma cells and lymphoid follicles can be observed, fibrosis is unusual. Sialolithiasis may present with intermittent swelling and pain affecting the submandibular gland, and may show periductal fibrosis and inflammation, and patchy, lobular atrophy and inflammation. Granulomatous diseases can present with generalised salivary involvement and reactive lymph node enlargement, with other systemic features. Sarcoidosis can be suggested by non-caseating epithelioid cell granulomas; these resolve or convert into hyaline connective tissue, and lack necrosis or an intact reticular pattern. In Wegner's granulomatosis, the hallmarks are necrotising granulomatous inflammation, and a pauci-immune vasculitis in small- and medium-sized vessels.

Importantly, IgG4-related chronic sclerosing sialadenitis should be differentiated from lymphoproliferative disease. The association of lymphoma with longstanding Sjögren's syndrome or hepatitis C infection is well known.[19] An increased risk of malignancy has been reported in patients with IgG4-related disease, but a specific association with IgG4-related chronic sclerosing sialadenitis has not been shown.[20] Malignant transformation has been reported in patients with IgG4-related orbital disease.[21,22] Lymphomas of the salivary glands such as non-Hodgkin's lymphoma and mucosa-associated lymphoid tissue should be excluded.

A pathway for investigation of IgG4-related chronic sclerosing sialadenitis by the ENT surgeon is proposed in Figure 3.

https://doi.org/10.1017/S0022215115000195 Published online by Cambridge University Press

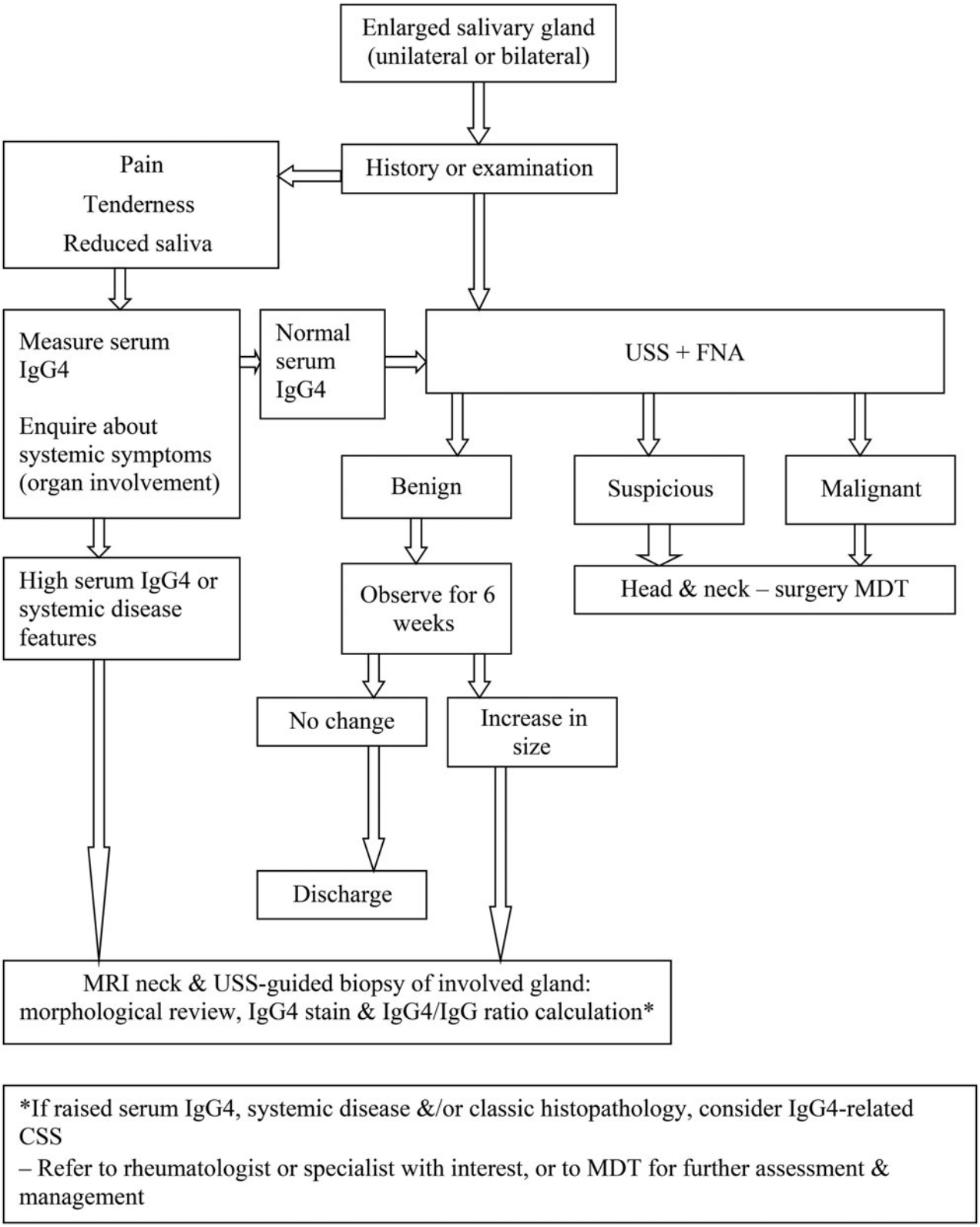


FIG. 3

Pathway in the investigation of immunoglobulin G4 related chronic sclerosing sialadenitis. IgG4 = immunoglobulin G4; USS = ultrasound; FNA = fine needle aspiration; MDT = multidisciplinary team; MRI = magnetic resonance imaging; IgG = immunoglobulin G; CSS = chronic sclerosing sialadenitis

https://doi.org/10.1017/S0022215115000195 Published online by Cambridge University Press

## Disease management

The roles of the ENT surgeon are to exclude malignancy and to aid in the diagnosis of IgG4-related disease in cases where the glandular tissue is the most accessible to biopsy. Patients with submandibular gland enlargement and a history of sicca symptoms, in whom malignancy has been excluded, should be referred to a rheumatologist (or alternative clinician with an interest in the disease) for consideration of a systemic disease process. Evaluation of serum IgG4 levels and histopathological assessment of biopsies with IgG4 immunohistochemistry form a part of the systemic disease investigation (Figure 3).

Diagnostic criteria for IgG4-related disease have been established. The original criteria were developed to diagnose autoimmune pancreatitis in Asia and the USA,[23,24] but have since been adapted to reflect the multi-systemic nature of the disease.[25] These incorporate the classical histological characteristics, imaging findings, serological elevations of IgG4, organ manifestations and responses to corticosteroids (Table I). More recently, the Boston histological consensus criteria have been agreed.[16] These reflect changes in our understanding of the importance of characteristic morphology, thresholds of IgG4 cells, and the IgG4 to IgG ratio used to distinguish between disease mimics. The presence of sialomegaly and elevated serum IgG4 in isolation do not meet the diagnostic criteria for IgG4-related chronic sclerosing sialadenitis as part of IgG4-related disease.

Ultimately, patients with IgG4-related chronic sclerosing sialadenitis will benefit from multidisciplinary discussion and management involving a rheumatologist, gastroenterologist, histopathologist and radiologist with an interest in the disease. Further biochemical and serological tests, imaging and the need for biopsies will be guided by clinical presentation and organ involvement.

The necessity and urgency of treatment depends on the involvement of vital organs, and risk of organ dysfunction or failure. Urgent treatment is needed for presentations with potentially irreversible consequences. In the case of the salivary gland, this is chronic salivary and lachrymal gland dysfunction. In the case of other organs, this can include visual impairment from compression of the optic nerve, aortic dissection from an inflammatory aortic lesion, and irreversible fibrosis within the mesentery and retroperitoneum. The first-line treatment is corticosteroids. Most patients respond rapidly to an initial high dose of prednisolone (a starting dose of 30–40 mg daily) that is tapered over three to six months.[26] However, relapse is common, occurring in over 50 per cent of patients in whom steroids have been discontinued.[27] In those with recurrent or refractory disease, second-line immunosuppressant agents have included azathioprine and mycophenolate.[27] More recently, B-cell depletion with rituximab, the monoclonal antibody against cluster of differentiation 20, has been used with success in those who are intolerant of steroids or those with refractory disease.[28] Such cases should also be managed in a multidisciplinary setting with appropriate assessment of response to therapy using objective measures.

TABLE I
JAPANESE COMPREHENSIVE DIAGNOSTIC CRITERIA*

| | |
|---|---|
| 1 | Clinical examination shows characteristic diffuse or localised swelling, or masses in single or multiple organs |
| 2 | Serological examination shows elevated serum IgG4 concentrations (>135 mg/dl) |
| 3 | Histopathological examination shows marked lymphocyte & plasmacytic infiltration, fibrosis, & infiltration of IgG4+ plasma cells (i.e. ratio of IgG4+ /IgG+ cells >40% & >10 IgG4+ plasma cells per high power field) |

A definite diagnosis of IgG4-related disease is made when all criteria (1, 2 and 3) are fulfilled. A probable diagnosis is made with fulfilment of criteria 1 and 3. A possible diagnosis is made with fulfilment of criteria 1 and 2. It is important to differentiate IgG4-related disease from malignant tumours of each organ (e.g. cancer and lymphoma) and similar diseases (e.g. Sjögren's syndrome, primary sclerosing cholangitis, Castleman's disease, secondary retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis and Churg–Strauss syndrome) by additional histopathological examination. Even when patients cannot be diagnosed using the comprehensive diagnostic criteria, they may be diagnosed using organ-specific diagnostic criteria for IgG4-related disease.*For the diagnosis of IgG4-related disease, adapted from Umehara *et al.*[25] IgG4 = immunoglobulin G4; IgG = immunoglobulin G

## Conclusion

Patients with IgG4-related chronic sclerosing sialadenitis can present to the ENT surgeon with a solitary lesion, or with diffuse enlargement of the salivary glands and sicca symptoms. In those with diffuse enlargement particularly, there should be a high index of clinical suspicion for systemic disease. In those with solitary enlargement, IgG4-related chronic sclerosing sialadenitis should be considered after malignancy is excluded. It is important that the ENT community is aware of IgG4-related chronic sclerosing sialadenitis in order to facilitate early diagnosis, prevent irreversible organ dysfunction and aid detection of other systemic manifestations of disease. Diagnosis is based on identifiable criteria and is usually confirmed in the salivary gland by histological findings. If IgG4-related chronic sclerosing sialadenitis is confirmed, referral to a rheumatologist and multidisciplinary team management should be considered.

## Acknowledgement

EL Culver was supported by a Wellcome Trust Research Fellowship (095160/Z/10/Z) awarded to investigate the natural history and pathogenesis of IgG4-related disease.

### References

1 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

https://doi.org/10.1017/S0022215115000195 Published online by Cambridge University Press

2 Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K *et al*. A new clinicopathological entity of IgG4 related autoimmune disease. *J Gastroenterol* 2003;**38**:982–4
3 Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012;**366**:539–51
4 Geyer JT, Ferry JA, Harris NL, Stone JH, Zukerberg LR, Lauwers GY *et al*. Chronic sclerosing sialadenitis (Küttner tumor) is an IgG4-associated disease. *Am J Surg Pathol* 2010;**34**:202–10
5 Takano KL, Yamamoto M, Takahashi H, Hinomura Y, Imai K, Himi T. Clinicopathologic similarities between Mikulicz disease and Küttner tumor. *Am J Otolaryngol* 2010;**31**:429–34
6 Geyer JT, Deshpande V. IgG4-associated sialadenitis. *Curr Opin Rheumatol* 2011;**23**:95–101
7 Paul R, Shekkar K, Singh M. Kuttner tumour: an unusual cause of enlargement of a minor salivary gland in the lip. *Br J Oral Maxillofac Surg* 2010;**48**:152–3
8 Yamamoto M, Takahashi H, Ohara M, Suzuki C, Naishiro Y, Yamamoto H *et al*. A new conceptualization for Mikulicz's disease as an IgG4-related plasmacytic disease. *Mod Rheumatol* 2006;**16**:335–40
9 Blanco M, Mesko T, Cura M, Cabello-Inchausti B. Chronic sclerosing sialadenitis (Kuttner's tumor): unusual presentation with bilateral involvement of major and minor salivary glands. *Ann Diagn Pathol* 2003;**7**:25–30
10 Chan JK. Kuttner tumour (chronic sclerosing sialadenitis) of the submandibular gland: an underrecognized entity. *Adv Anat Pathol* 1998;**5**:239–51
11 Hamano H, Arakura N, Muraki T, Ozaki Y, Kiyosawa K, Kawa S. Prevalence and distribution of extrapancreatic lesions complicating autoimmune pancreatitis. *J Gastroenterol* 2006;**41**:1197–1205
12 Ghazale A, Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N *et al*. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. *Am J Gastroenterol* 2007;**102**:1646–53
13 De Cocker JL, D'Arco F, De Beule T, Tousseyn T, Blockmans D, Hermans R. IgG4-related systemic disease affecting the parotid and submandibular glands: magnetic resonance imaging features of IgG4-related chronic sclerosing sialadenitis and concomitant lymphadenitis. *Clin Imaging* 2014;**38**:195–8
14 Smyrk TC. Pathological features of IgG4-related sclerosing disease. *Curr Opin Rheumatol* 2011;**23**:74–9
15 Culver EL, Bateman AC. General principles of IgG4-related disease. *Diag Histopathol* 2013;**19**:111–18
16 Deshpande V, Zen Y, Chan J, Yi EE, Sato Y, Yoshino T *et al*. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012;**25**:1181–92
17 Strehl J, Hartmann A, Agaimy A. Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. *J Clin Pathol* 2011;**64**:237–43
18 Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE *et al*. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;**61**:554–8
19 Ambrosetti A, Zanotti R, Pattaro C, Lenzi L, Chilosi M, Caramaschi P *et al*. Most cases of primary salivary mucosa-associated lymphoid tissue lymphoma are associated either with Sjoegren syndrome or hepatitis C virus infection. *Br J Haematol* 2004;**126**:43–9
20 Ghazale A, Chari S. Is autoimmune pancreatitis a risk factor for pancreatic cancer? *Pancreas* 2007;**35**:376
21 Kim T, Grobmyer SR, Dixon LR, Allan RW, Hochwald SN. Autoimmune pancreatitis and concurrent small lymphocytic lymphoma: not just a coincidence? *J Gastrointest Surg* 2008;**12**:1566–70
22 Cheuk W, Yuen HK, Chan AC, Shih LY, Kuo TT, Ma MW *et al*. Ocular adnexal lymphoma associated with IgG4+ chronic sclerosing dacryoadenitis: a previously undescribed complication of IgG4-related sclerosing disease. *Am J Surg Pathol* 2008;**32**:1159–67
23 Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L *et al*. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. *Clin Gastroenterol Hepatol* 2006;**4**:1010–16
24 Otsuki M, Chung JB, Okazaki K, Kim MH, Kamisawa T, Kawa S *et al*. Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. *J Gastroenterol* 2008;**43**:403–8
25 Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T *et al*. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012;**22**:21–30
26 Kamisawa T, Shimosegawa T, Okazaki K, Nishino T, Watanabe H, Kanno A *et al*. Standard steroid treatment for autoimmune pancreatitis. *Gut* 2009;**58**:1504–7
27 Hart PA, Kamisawa T, Brugge WR, Chung JB, Culver EL, Czajo L *et al*. Treatment and long-term sequelae of autoimmune pancreatitis: a multicenter, international analysis. *Gut* 2013;**62**:1771–6
28 Khosroshahi A, Carruthers MN, Deshpande V, Unizony S, Bloch DB, Stone JH. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. *Medicine (Baltimore)* 2012;**91**:57–66

Address for correspondence:
Mr Pablo Martinez-Devesa,
Department of Otorhinolaryngology – Head and Neck Surgery,
John Radcliffe Hospital,
Headington,
Oxford OX3 9DU, UK

Fax: 01865 231 091,
E-mail: Pablo.Martinez-Devesa@ouh.nhs.uk

Mr P Martinez-Devesa takes responsibility for the integrity of the content of the paper
Competing interests: None declared