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Commentary on IgG4-related sialadenitis: Mikulicz's disease, Küttner's tumour, and eponymy

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Mikulicz's disease; salivary gland disease

Abstract: The paper by Laco et al. (HISTOP-04-10-0251.R2) is the first description of IgG4-related sialadenitis from Central Europe, and it seems likely that the disease will be found worldwide. Although the use of the terms Küttner's tumour and Mikulicz's disease as eponyms for IgG4-related sialadenitis is widespread, it is confusing and better avoided. It appears prudent to immunostain in order to estimate the number and fraction of plasma cells with IgG4 in cases of sialadenitis that show severe fibrosis and atrophy and a heavy lymphoid infiltrate in order that cases of IgG4-related sialadenitis may be confidently diagnosed. Laco et al. found that a lower limit of 50 IgG4-positive plasma cells per 1 high-power field produces a sensitivity and specificity of 100%, and that the ratio of IgG4-positive plasma cells to IgG-positive plasma cells is at least 0.40 in cases of IgG4-related sialadenitis and no more than 0.26 in control cases.

IgG4-related sialadenitis has only been established as an entity this century, and the reports include 30 patients in Japan,¹⁻⁶ 2 Chinese patients in New Zealand,^{7,8} 13 patients in the United States of America,⁹ and 1 South Asian patient in England.¹⁰ The article by Laco et al.¹¹ is the first description of IgG4-related sialadenitis from Central Europe. It adds 6 cases to make a total of 52 cases, and it seems likely that the disease will be found worldwide.

The term Küttner's tumour has been used as an eponym for IgG4-related sialadenitis that involves one or more salivary glands and Mikulicz's disease as an eponym when the lacrimal glands are also involved.^{1,2,4-6,9} However, this has introduced confusion and is unjustified, as is clearly shown by an appraisal of the work of Küttner and Mikulicz.

Küttner¹² in 1896 described 2 cases of chronic submandibular sialadenitis that were unilateral and presented as firm swellings, and in one of the cases there was an associated sialolith, which he considered to be secondary to the inflammation. He did not publish

illustrations of the histology, and it was Seifert and Donath¹³ in 1977 and Harrison et al.¹⁴ in 1997 who described and illustrated the histology in detail and included a range of cases from those with minimal change to those with extensive fibrosis, inflammation and atrophy. Seifert and Donath¹³ coined the term 'chronic sclerosing sialadenitis', which had not been used by Küttner, but which from his histological description would be applicable to his cases. The terms 'Küttner tumour' and 'chronic sclerosing sialadenitis' were only introduced to the English-speaking medical profession in 1991 in the second edition of the WHO 'Histological typing of salivary gland tumours',¹⁵ of which the principal editor was Seifert. This was followed by a spate of case reports of a purportedly rare disease, namely 'Küttner's tumour', without the realization that it was no more than mundane chronic submandibular sialadenitis.¹⁶

The extent of the current classificatory confusion is evident in the article by Laco et al.¹¹ when they quote from a major textbook on tumours of salivary glands¹⁷ that describes chronic sclerosing sialadenitis or Küttner's tumour as the most common disease of the submandibular gland, yet the disease to which Laco et al. refer is IgG4-related sialadenitis. Although the incidence of IgG4-related sialadenitis among cases of chronic sialadenitis is unknown because no large series have been examined, it appears likely to be low if comparable to IgG4-related pancreatitis.¹⁰ The textbook refers to all cases of chronic submandibular sialadenitis, many of which are associated with sialolithiasis,¹⁷ and does not mention IgG4-related sialadenitis. However, the presence of sialolithiasis does not exclude the possibility of IgG4-related sialadenitis, as a lith was present in one of the cases of Laco et al.¹¹

Mikulicz¹⁸ published a detailed coloured illustration of the histological features of one of the swollen submandibular glands of his patient, who suffered from bilateral swollen major and minor salivary and lacrimal glands. The original illustration of what Mikulicz described

as a uniform infiltrate of small round cells was recently examined and found to show the features of a MALT lymphoma.¹⁹

Deheragoda et al.¹⁰ found that IgG4 immunostaining added to the diagnostic accuracy that was possible by morphological examination alone, and this is confirmed by the following example of two cases of chronic submandibular sialadenitis.

Case A was a female of 79 years with a painless submandibular swelling for 2 months, and case B was a male of 69 years with a painless submandibular swelling for 1 month. Both patients were white British. There was no associated sialolithiasis. Both glands were very fibrotic, for which reason immunohistochemistry for CD138, IgG and IgG4 was applied. The appearance in sections routinely stained with haematoxylin and eosin was similar. There was severe atrophy, severe fibrosis with cellular interlobular fibrous tissue, and a heavy lymphoid infiltrate with large, geographical germinal centres in most of each of the glands (Fig. 1A1 and 1B1). Phlebitis was not found in either gland. Immunostaining revealed that there were many plasma cells, which were stained for CD138 and IgG, in both glands (Fig. 1A2 and 1B2). Only a very small minority of these was stained for IgG4 in the gland from case A (Fig. 1A3), whereas most were stained for IgG4 in the gland from case B (Fig. 1B3).

Thus only one case is of IgG4-related sialadenitis, although both are of the appearance described by Küttner,¹² and both would have attracted a diagnosis of Küttner's tumour and chronic sclerosing sialadenitis by application of the definition in the second edition of the WHO 'Histological typing of salivary gland tumours'.¹⁵ As IgG4-related sialadenitis can be part of a hyper-IgG4 multiorgan disease and can be successfully treated with steroids, it is important to diagnose it, which necessitates immunostaining for CD138, IgG and IgG4.

There is clearly no justification for using the eponyms Mikulicz's disease and Küttner's tumour for cases of IgG4-related sialadenitis, and since such use is misleading and likely to lead to confusion and mismanagement, it is to be deprecated.

This misuse of eponymy could have been avoided by reading the original articles of Mikulicz¹⁸ and Küttner.¹² Several articles that refer to Küttner's article of 1896 have similarly and incorrectly stated the page numbers,^{1, 5, 9} and one of them incorrectly stated that Küttner 'reported a "hard swelling" of 1 or both submandibular glands',⁹ whereas Küttner¹² had reported two cases of unilateral submandibular swelling. These errors indicate that these authors had not read Küttner's article but had correctly copied the same incorrect reference from other articles. 'Dwell on the past and you'll lose an eye. Forget the past and you'll lose both eyes.'²⁰

In conclusion, it appears prudent to immunostain in order to estimate the number and fraction of plasma cells with IgG4 in cases of sialadenitis that show severe fibrosis and atrophy and a heavy lymphoid infiltrate in order that cases of IgG4-related sialadenitis may be confidently diagnosed. Laco et al.¹¹ found that a lower limit of 50 IgG4-positive plasma cells per 1 high-power field produces a sensitivity and specificity of 100%, and that the ratio of IgG4-positive plasma cells to IgG-positive plasma cells is at least 0.40 in cases of IgG4-related sialadenitis and no more than 0.26 in control cases.

REFERENCES

1. Kitagawa S, Zen Y, Harada K *et al.* Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Küttner's tumor). *Am. J. Surg. Pathol.* 2005; **29**; 783-791.
2. Yamamoto M, Harada S, Ohara M *et al.* Clinical and pathological differences between Mikulicz's disease and Sjögren's syndrome. *Rheumatology (Oxford)*. 2005; **44**; 227-234.
3. Kamisawa T, Nakajima H, Egawa N, Funata N, Tsurata K, Okamoto A. IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy. *Pancreatology* 2006; **6**; 132-137.
4. Aoki A, Sato K, Itabashi M *et al.* A case of Mikulicz's disease complicated with severe interstitial nephritis associated with IgG4. *Clin. Exp. Nephrol.* 2009; **13**; 367-372.
5. Abe T, Sato T, Tomaru Y *et al.* Immunoglobulin G4-related sclerosing sialadenitis: report of two cases and review of the literature. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endodont.* 2009; **108**; 544-550.
6. Sakuma H, Okumura F, Miyabe S *et al.* Analysis of VH gene rearrangement and somatic hypermutation in Sjögren's syndrome and IgG4-related sclerosing sialadenitis. *Scand. J. Immunol.* 2010; **72**; 44-49.
7. Gill J, Taylor G, Carpenter L, Lewis C, Chiu W. A case of hyperIgG4 disease or IgG4-related sclerosing disease presenting as retroperitoneal fibrosis, chronic

- sclerosing sialadenitis and mediastinal lymphadenopathy. *Pathology (Phila)*. 2009; **41**; 297-300.
8. Gill J, Angelo N, Yeong ML, McIvor N. Salivary duct carcinoma arising in IgG4-related autoimmune disease of the parotid gland. *Hum. Pathol*. 2009; **40**; 881-886.
 9. Geyer JT, Ferry JA, Harris NL *et al*. Chronic sclerosing sialadenitis (Küttner tumor) is an IgG4-associated disease. *Am. J. Surg. Pathol*. 2010; **34**; 202-210.
 10. Deheragoda MG, Church NI, Rodriguez-Justo M *et al*. The use of immunoglobulin G4 immunostaining in diagnosing pancreatic and extrapancreatic involvement in autoimmune pancreatitis. *Clin. Gastroenterol. Hepatol*. 2007; **5**; 1229-1234.
 11. Laco J, Ryska A, Celakovsky P, Dolezalova H, Mottl R, Tucek L. Chronic sclerosing sialadenitis (Küttner tumor) as a member of IgG4-related diseases: a clinicopathological study of 6 cases from Central Europe. *Histopathology* 2010.
 12. Küttner H. Ueber entzündliche Tumoren der Submaxillar-Speicheldrüse. *Beiträge zur klinischen Chirurgie* 1896; **15**; 815-828.
 13. Seifert G, Donath K. Zur Pathogenese des Küttner-Tumors der Submandibularis. Analyse von 349 Fällen mit chronischer Sialadenitis der Submandibularis. *HNO* 1977; **25**; 81-92.
 14. Harrison JD, Epivatianos A, Bhatia SN. Role of microliths in the aetiology of chronic submandibular sialadenitis: a clinicopathological investigation of 154 cases. *Histopathology* 1997; **31**; 237-251.
 15. Seifert G. Chronic sclerosing sialadenitis of submandibular gland (Küttner tumour). In Seifert G ed. *Histological typing of salivary gland tumours*. 2nd edition. Berlin,

- Heidelberg, New York, London, Paris, Tokyo, Hong Kong, Barcelona, Budapest: Springer, 1991; 37.
16. Harrison JD. Causes, natural history, and incidence of salivary stones and obstructions. *Otolaryngol. Clin. North Am.* 2009; **42**; 927-947.
 17. Ellis GL, Auclair PL. Tumor-like conditions. In Ellis GL and Auclair PL eds. *Tumors of the salivary glands*. AFIP atlas of tumor pathology, 4th series, fascicle 9. Washington DC: Armed Forces Institute of Pathology, 2008; 481-514.
 18. Mikulicz J. Ueber eine eigenartige symmetrische Erkrankung der Thränen- und Mundspeicheldrüsen. *Beiträge zur Chirurgie. Festschrift gewidmet Theodor Billroth*. Stuttgart: Ferdinand Enke, 1892; 610-630.
 19. Ihrler S, Harrison JD. Mikulicz's disease and Mikulicz's syndrome: analysis of the original case report of 1892 in the light of current knowledge identifies a MALT lymphoma. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endodont.* 2005; **100**; 334-339.
 20. Solzhenitsyn A. *The Gulag Archipelago, 1918-1956*. Translated by Whitney TP. Waukegan Illinois, Glasgow: Fontana, Collins, 1974; x.

FIGURE LEGEND

Figure 1. A1, A2 and A3 are from the submandibular gland of case A. B1, B2 and B3 are from the submandibular gland of case B. A1 and B1 are scans of sections stained with haematoxylin and eosin in which much of each is very fibrotic, very atrophic, and with a heavy lymphoid infiltrate with large germinal centres, some of which are geographical. The left part of each of the sections is not fibrosed or atrophic, but contains focal lymphoid infiltrates with conspicuous germinal centres. A2 and B2 are medium-power photomicrographs of sections stained for IgG, which is present in similarly dense infiltrates of plasma cells. A3 and B3 are medium-power photomicrographs of sections adjacent to the above and stained for IgG4, which is present in a very small minority of the plasma cells in A3, but in B3 is present in a similar density of plasma cells to the IgG of B2.

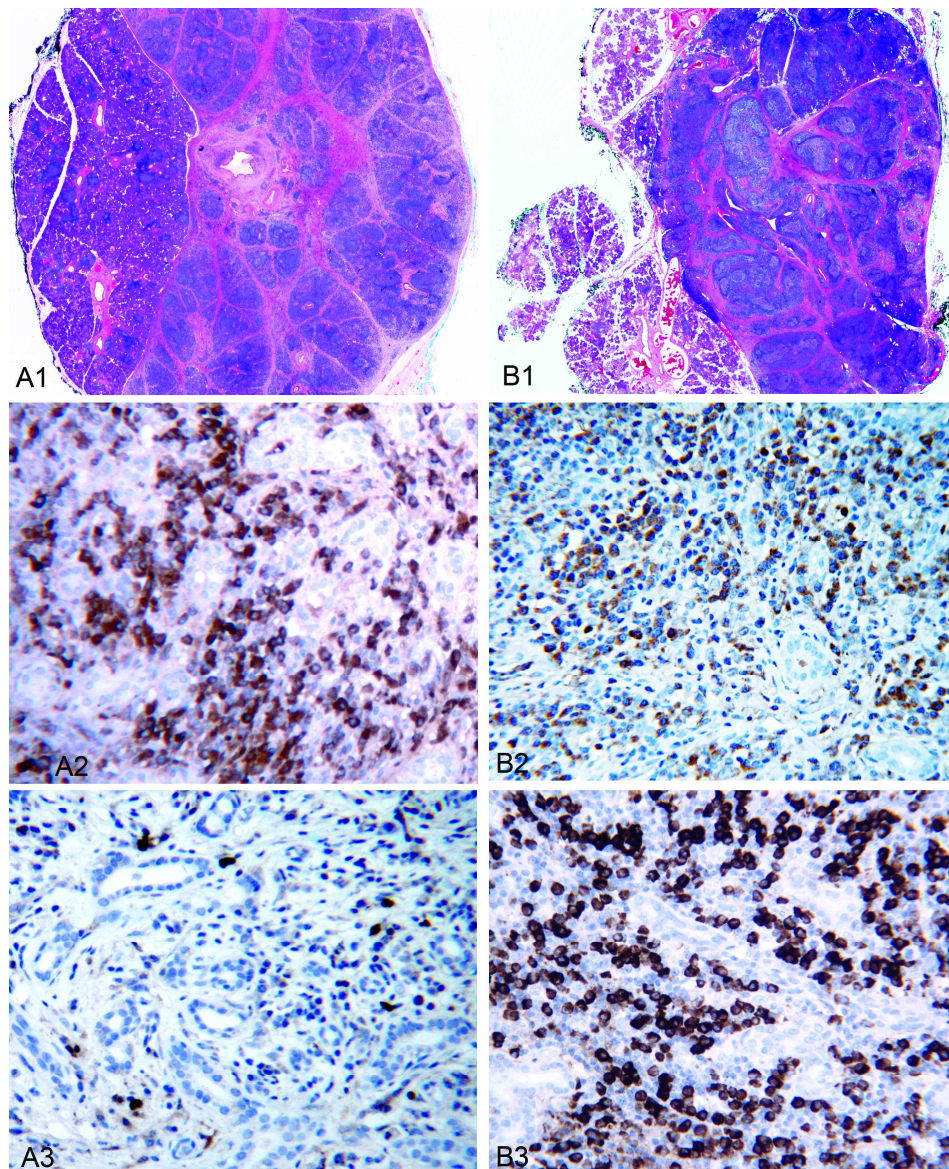


Figure 1. A1, A2 and A3 are from the submandibular gland of case A. B1, B2 and B3 are from the submandibular gland of case B. A1 and B1 are scans of sections stained with haematoxylin and eosin in which much of each is very fibrotic, very atrophic, and with a heavy lymphoid infiltrate with large germinal centres, some of which are geographical. The left part of each of the sections is not fibrosed or atrophic, but contains focal lymphoid infiltrates with conspicuous germinal centres. A2 and B2 are medium-power photomicrographs of sections stained for IgG, which is present in similarly dense infiltrates of plasma cells. A3 and B3 are medium-power photomicrographs of sections adjacent to the above and stained for IgG4, which is present in a very small minority of the plasma cells in A3, but in B3 is present in a similar density of plasma cells to the IgG of B2.
169x215mm (400 x 400 DPI)