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ORIGINAL ARTICLE

Clinical relevance of Küttner tumour and IgG4-related dacryoadenitis and sialoadenitis

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OBJECTIVES: Küttner tumour (KT), so-called chronic sclerosing sialoadenitis, is characterised by concomitant swelling of the submandibular glands secondary to strong lymphocytic infiltration and fibrosis independent of sialolith formation. However, recent studies have indicated that some patients with KT develop high serum levels of IgG4 and infiltration of IgG4-positive plasma cells, namely IgG4-related dacryoadenitis and sialoadenitis (IgG4-DS), so-called Mikulicz's disease. The aim of this study was to clarify the clinical and pathological associations between KT and IgG4-DS.

MATERIALS AND METHODS: Fifty-four patients pathologically diagnosed with KT or chronic sialoadenitis were divided into two groups according to the presence or absence of sialolith (KT-S (+) or KT-S (−), respectively).

RESULTS: There were no significant differences in the clinical findings, including the mean age, sex and disease duration, between the two groups. All patients in the KT-S (+) group showed unilateral swelling without infiltration of IgG4-positive plasma cells or a history of other IgG4-related diseases (IgG4-RD), while those in the KT-S (−) group showed bilateral swelling (37.5%), strong infiltration of IgG4-positive plasma cells (87.5%) and a history of other IgG4-RD (12.5%).

CONCLUSIONS: These results suggest an association between the pathogeneses of KT-S (−) and IgG4-DS, but not KT-S (+).

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Introduction

Küttner tumour (KT) is a non-neoplastic disease also termed chronic sclerosing sialoadenitis (CSS). It was first described by Küttner in 1896 (Küttner, 1896). This disease is characterised by acinar atrophy and lymphocytic infiltration within the unilateral submandibular gland (SMG; Yamamoto *et al*, 2006; Takano *et al*, 2010). The World Health Organization has categorised it as a tumourlike disease of the salivary glands (Seifert, 1992). Some reports have indicated that the distribution pattern of lymphocytic infiltration is induced by an immunological abnormality (Rasanen *et al*, 1972; Ikeda *et al*, 1994), while other reports have indicated that sialoliths and mucous plugs are found in 29% to 83% of lesions (Isacsson and Lundquist, 1982; Ahuja *et al*, 2003). Seifert and Donath, (1977) classified many cases of chronic sialoadenitis (CS) into four stages regardless of unilateral or bilateral swelling: (i) focal sialoadenitis, (ii) diffuse lymphocytic sialoadenitis with salivary gland fibrosis, (iii) chronic sclerosing sialoadenitis with salivary gland sclerosis and (iv) chronic progressive sialoadenitis with salivary gland cirrhosis. They also found that 41% of patients diagnosed with KT had concomitant sialolithiasis. The histopathological diagnoses in these cases were achieved by the presence of marked lymphocytic infiltration and fibrosis in the SMGs with or without sialolith. The differences between KT/CS with and without sialolith remained unclear based on these findings. In contrast, Mikulicz's disease (MD) is a unique condition characterised by bilateral enlargement of the lacrimal glands (LGs) and salivary glands secondary to lymphocytic infiltration. KT was conventionally considered to

be an aspect of MD because of the clinical similarities between these two diseases. However, Yamamoto *et al* (Yamamoto *et al*, 2005) reported that patients with MD had high levels of serum IgG4 and infiltration of IgG4-positive plasma cells in the glandular tissues. Such findings have been also identified in patients with other diseases, including autoimmune pancreatitis (AIP; Hamano *et al*, 2001), sclerosing cholangitis (Zen *et al*, 2004), retroperitoneal fibrosis (RPF; Hamano *et al*, 2002), tubulointerstitial nephritis (Hamed *et al*, 2007), Riedel's thyroiditis (Hamed *et al*, 2007) and KT (Kitagawa *et al*, 2005). These diseases are now termed IgG4-related diseases (IgG4-RD). We previously described the concept of IgG4-RD and provided up-to-date information regarding this emerging disease entity (Umehara *et al*, 2012a). MD and KT are also associated with IgG4-related dacryoadenitis and sialoadenitis (IgG4-DS; Maehara *et al*, 2012; Stone *et al*, 2012). However, the clinical relevance of KT and IgG4-DS remains to be elucidated. Therefore, the aim of this study was to determine the clinical and histopathological characteristics of KT and clarify the clinical relevance of these two diseases.

Materials and methods

Patients

This study included 54 patients (22 men and 32 women; mean age, 51.3 ± 28.3 years) pathologically diagnosed with KT or CS based on specimens obtained from extirpating SMGs. All patients were referred to the Department of Oral and Maxillofacial Surgery, Kyushu University Hospital, Fukuoka, Japan, from 2003 to 2013. As shown in Figure 1, these patients were divided into two groups according to the presence or absence of sialolith: with sialolith [KT-S (+)] ($n = 46$; 20 men and 26 women; mean age, 49.8 ± 20.4 years) and without sialolith [KT-S (−)] ($n = 8$; two men and six women; mean age, 61.3 ± 4.6 years). The study design was approved by the Ethics Committee of Kyushu University, Japan, and all participants provided written informed consent (IRB serial number: 25-287).

Laboratory data

We retrospectively analysed the serum levels of IgG, IgG4, anti-SSA antibody and anti-SSB antibody. The serum level of IgG4 was not determined in any patients with KT-S (+).

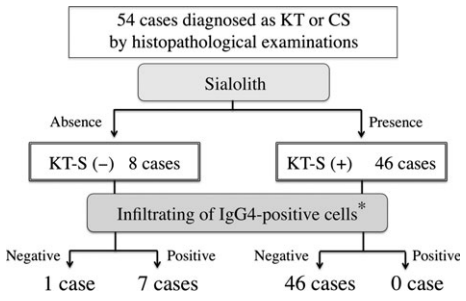

Figure 1 Classification tree performance of patients with chronic sialoadenitis (CS). KT-S (+), Küttner tumour (KT) with sialolith; KT-S (−), KT without sialolith; *IgG4-positive plasma cells/IgG-positive plasma cells >0.4

Histological and immunohistochemical analyses

For histological analysis, 4-μm formalin-fixed, paraffin-embedded sections were prepared and stained with haematoxylin and eosin. For immunohistochemical analysis, 4-μm formalin-fixed, paraffin-embedded sections were prepared and stained with a conventional avidin–biotin complex technique as previously described (Tanaka *et al*, 2012). An anti-IgG rabbit polyclonal antibody was used to analyse the molecule of IgG (A0423; Dako, Glostrup, Denmark). An anti-IgG4 mouse monoclonal antibody was used to analyse the molecule of IgG4 (MC011; Binding Site, Birmingham, UK). The sections were sequentially incubated with primary antibodies for 2.5 h and subsequently with biotinylated anti-rabbit IgG and anti-mouse IgG secondary antibodies (Vector Laboratories, California, USA), avidin–biotin–horseradish peroxidase complex (Vector Laboratories) and 3,3′-diaminobenzidine (Vector Laboratories). Mayer's haematoxylin was used for counterstaining. Photomicrographs were obtained using a light microscope equipped with a digital camera (BZ-9000; KEYENCE, Tokyo, Japan). Stained IgG-positive and IgG4-positive cells were counted in 1-mm^2 sections from five different areas, and the number of IgG4-positive cells and ratio of IgG4-positive to IgG-positive cells were calculated. Evaluations of immunostaining were conducted by two pathologists (T K and H S) who were blinded to information on the samples. Positive cells were counted randomly, and the data of T K and H S were averaged.

Histological staining for evaluation of fibrosis

To evaluate the degree of fibrosis, Masson's trichrome staining (MT; Polysciences, Warrington, PA, USA) was performed. In short, 4-μm formalin-fixed, paraffin-embedded sections were prepared and stained. As a result, connective tissue and fibrosis tissue can be selectively visualised as blue, whereas nuclei stained by Weigert's iron haematoxylin marked as dark brown to black, and cytoplasm marked as red.

Statistical analysis

Values are given as mean ± standard deviation. The means of two groups were compared with Student's *t*-test, Fisher's test or the Mann–Whitney *U*-test, as appropriate. Values of $P < 0.05$ were regarded as statistically significant.

Results

Clinical findings

Table 1 shows the clinical characteristics of the eight patients in the KT-S (−) group. All patients were negative for anti-SS-A and anti-SS-B antibodies. Two of the eight patients showed bilateral swelling of the LGs. As shown in Table 2, there were no differences in the mean age, sex or disease duration between the KT-S (+) and KT-S (−) patients. All patients in the KT-S (+) group showed unilateral swelling of the SMG, while three of the eight KT-S (−) patients showed bilateral swelling of the SMGs. Four

Table 1 Clinical characteristics of eight KT-S (−) patients

No.	*Age*	*Sex*	*Disease duration*	*Swollen glands*					*Serological test*			*Immunohistological test*				
				LG	*PG*	*SMG*	*SLG*	*LSG*	*IgG*	*IgG4 (mg dl^{-1})*	*Anti-SS-A*	*Anti-SS-B*	*Number of IgG4 + cells (/HPF)*	*Frequency of IgG4 + cells (%)*	*Other IgG4-RD*	*Treatment*	*Lesions of Recurrence*
1	67	M	1 M	–	–	U	–	–	1244	220	–	–	133	633	–	None	SMGs, LGs
2	59	F	3 Y	B	–	B	–	–	2236	452	–	–	85	82.5	AIP, RPF	PSL	–
3	64	F	6 M	–	–	B	–	–	2016	19.5	–	–	102	72.8	–	PSL	–
4	67	F	4 M	B	–	B	–	–	1223	232	–	–	112	76.3	–	None	–
5	56	F	3 M	–	–	U	–	–	961	24.9	–	–	137	65.2	–	None	–
6	59	M	5 M	–	–	U	–	–	ND	ND	–	–	121	61.7	–	None	–
7	57	F	4 M	–	–	U	–	–	1188	151	–	–	52	71.2	–	None	–
8	62	M	4 M	–	–	U	–	–	1682	ND	–	–	4	4.9	–	None	–

KT-S (−), Küttner tumour (KT) without sialolith; lacrimal gland; PG, parotid gland; SMG, submandibular gland; SLG, sublingual gland; LSG, labial salivary gland; B, bilateral; U, unilateral; IgG4-RD, IgG4-related disease; AIP, autoimmune pancreatitis; RPF, retroperitoneal fibrosis; PSL, prednisolone; –, negative; ND, not done; bold and italicised numbers indicate abnormal values.

Table 2 Comparison of clinical and laboratory findings between KT-S (+) and KT-S (−) patients

	KT-S (+) n = *46*	*KT-S (−)* n = *8*	*P value*
Mean age (years)	49.8 ± 20.4	61.3 ± 4.6	0.30649
Sex (Male:female)	20:26	2:6	0.44913
Lesion part of SMG (unilateral: bilateral)	46:0	5:3	0.00226*
Duration disease (months)	50.7 ± 70.0	7.8 ± 11.5	0.10007
Serum IgG4 (mg ml^{-1})	ND	183.2 ± 162.1	
IgG4-positive cells/IgG-positive cells (%)	3.0 ± 2.0	62.5 ± 24.3	0.00071†
IgG4 + cells (/HPF)	1.5 ± 1.3	93.2 ± 95.4	0.00022†
Complicated of other IgG4-RD	0% (46/46)	12.5% (1/8)	0.14815
Recurrence (%)	0% (0/46)	12.5% (1/8)	0.14815

KT-S (+), KT with sialolith; KT-S (−), KT without sialolith; HPF, high-power field; IgG4-RD, IgG4-related disease.
*Student's *t*-test.
†Fisher's test.

of the six KT-S (−) patients had high serum IgG4 levels (the IgG4 level was not determined in two KT-S (−) patients and all KT-S (+) patients). The average serum IgG4 level among the six KT-S (−) patients was 183.2 ± 162.1 mg ml^{-1}. No patients in the KT-S (+) group had a history of other IgG4-RD, while one of the eight KT-S (−) patients had other IgG4-RD (AIP and RPF). During follow-up, no KT-S (+) patients demonstrated recurrence, while one of the eight KT-S (−) patients demonstrated relapse of the bilateral swelling of the SMGs and expansion of the LGs. Two of the eight KT-S (−) patients were treated with prednisolone, and then, the swelling of the SMGs was immediately disappeared.

Histological findings in the SMGs

Representative sialographic findings in the SMGs of both KT-S (+) and KT-S (−) patients are shown in Figure 2. KT-S (+) showed strong non-IgG4 lymphocytic infiltration and severe widespread fibrosis. Seven of the eight KT-S (−) patients showed selective infiltration of IgG4-positive cells [IgG4-positive cells/IgG-positive cells >0.4 based on 'Diagnostic criteria for IgG4-related Mikulicz's disease' (Umehara *et al*, 2012b)] and severe cordlike fibrosis with formation of ectopic germinal centres (eGCs). In contrast, one of the eight KT-S (−) patients showed moderate widespread fibrosis and diffuse lymphocytic infiltration without eGCs and a very small number of IgG-positive and IgG4-positive cells. The frequency and number of IgG4-positive cells in the SMGs of KT-S (−) patients were significantly higher than those of KT-S (+) patients (Figure 3).

Discussion

Küttner tumour presents with sclerosis of the bilateral or unilateral SMGs as first described by Küttner *et al* (Küttner, 1896). In 1976, Seifert and Donath, (1977) demonstrated that KT could be histopathologically diagnosed by strong lymphocytic infiltration and fibrosis in the

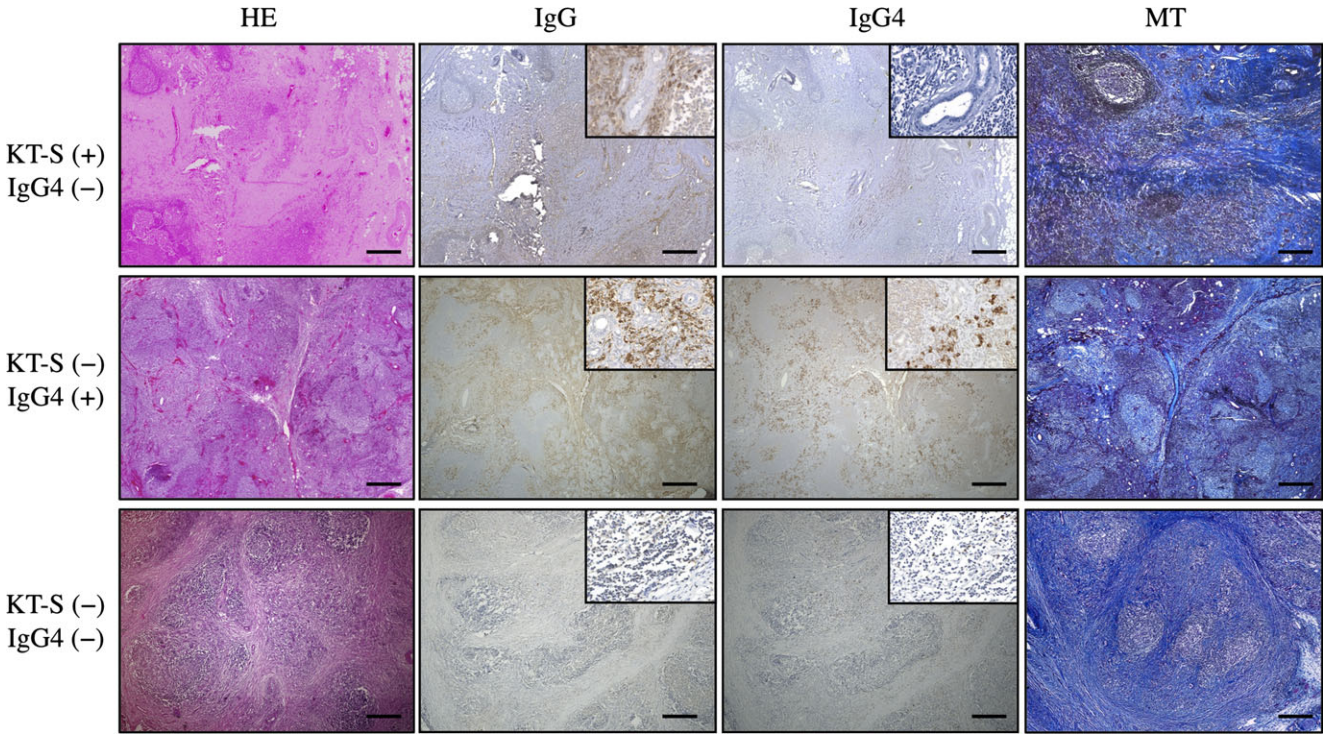

Figure 2 Histological findings in submandibular glands of patients with CS. IgG4 (+), IgG4-positive plasma cells/IgG-positive plasma cells >0.4; IgG4 (−), IgG4-positive plasma cells/IgG-positive plasma cells ≤0.4; MT, Masson's trichrome staining; Scale bars, 400 μm

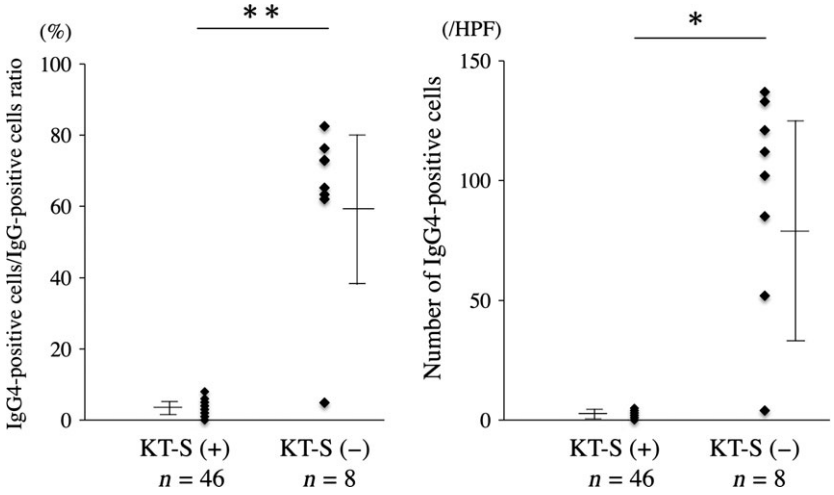

Figure 3 IgG4 production of patients with Küttner tumour (KT)-S (+) and KT-S (−). HPF, high-power field. The bar shows the mean value ± standard deviation (s.d.). *P < 0.05, **P < 0.01 (Mann–Whitney U-test)

SMGs either with or without sialolith. However, Kitagawa *et al*, (2005) reported that 12 patients diagnosed with chronic sclerosing sialoadenitis or KT showed high levels of IgG4 and strong infiltration of IgG4-positive plasma cells without sialolith. In addition, the complications in these patients frequently included other IgG4-RD. In the present study, we thus examined the involvement of IgG4 in CS regardless of the presence or absence of sialolith. We found that the histological findings in seven of the eight KT-S (−) patients in this study were consistent with the previous histological findings for KT, whereas the remaining KT-S (−) patient and all KT-S (+) patients showed strong lymphocytic infiltration without infiltration of IgG4-positive plasma cells. These results suggest that KT-S (−) is closely associated with IgG4-DS and KT-S (+) with non-IgG4-DS, so-called sialolithiasis. However, KT must be carefully diagnosed by SMG biopsy as well as the presence of sialolith, unilateral or bilateral swelling, and increased serum IgG4 levels because some KT-S (−) patients showed unilateral swelling of the SMG, normal serum IgG4 levels and slight infiltration of IgG4-positive cells. With regard to fibrosis, some of IgG4-RD including AIP and IgG4-tubulointerstitial nephritis often showed 'storiform fibrosis' in the lesions (Yoshita *et al*, 2012). However, these features were rarely seen in SMGs from IgG4-DS patients. As shown in Figure 2, there was no difference in the degree of fibrosis between KT-S(+) and KT-S(−) patients. These results suggest that evaluation of

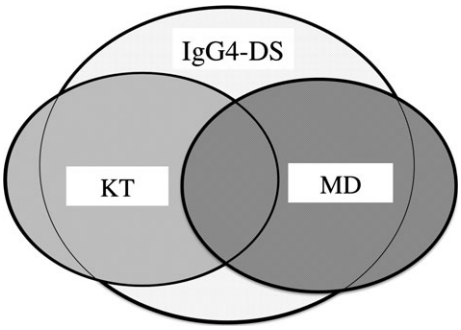

Figure 4 Clinical relevance of Küttner tumour, MD and IgG4-DS. MD, Mikulicz's disease; IgG4-DS, IgG4-related dacryoadenitis and sialoadenitis.

fibrosis pattern might be useful for diagnosis. Moreover, our previous studies demonstrated that IgG4-DS could be quickly and simply diagnosed using diagnostic criteria in conjunction with salivary gland imaging findings such as those of sonography (Shimizu *et al*, 2009; Moriyama *et al*, 2013).

In conclusion, this study suggests the clinical relevance of KT, MD and IgG4-DS (summarised in Figure 4), and as a result, KT could be considered as part of MD. However, we had selected just 54 cases diagnosed as KT or CS by SMG biopsies in this study period because many cases presenting with swelling of SMGs were diagnosed by clinical findings without biopsies. Therefore, evaluating greater numbers of patients with CS will help to elucidate the clinical and histological differences among these diseases, which might eventually lead to clarification of the pathogenesis of KT.

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Author contributions

S Furukawa and M Moriyama defined the intellectual content. S Furukawa, M Moriyama and A Tanaka carried out the literature search. S Furukawa, T Maehara, JN Hayashida and Y Goto carried out the experimental studies. S Kawano, H Shiratsuchi, Y Ohyama, M Ohta and Y Imabayashi acquired the data. S Furukawa and T Kiyoshima analysed the data. S Furukawa, M Moriyama and A Tanaka carried out the statistical analysis. M Moriyama prepared and edited the manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest.

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