

Küttner's Tumour (Chronic Sclerosing Sialadenitis). Clinical, Pathological, and Immunohistochemical Study in 8 Cases of a Little-Known Entity

Nayeli Martínez Consuegra,^a Javier Baquera Heredia,^a Rodolfo Sánchez Cisneros,^b María Luisa Márquez Rocha,^c and Carlos Ortiz-Hidalgo^{a,d}

^aDepartamento de Patología, Centro Médico ABC, México DF, México.

^bDepartamento de Patología, Centro Médico Nacional 20 de Noviembre, ISSSTE, México DF, México.

^cDepartamento de Patología, Hospital de Especialidades, Centro Médico Nacional Siglo XXI, México DF, México.

^dDepartamento de Biología Celular y Tisular, Universidad Panamericana, México DF, México.

Objective: To present the clinical-pathological characteristics of Küttner's tumour (KT) or chronic sclerosing sialadenitis.

Material and method: We studied 8 cases of KT that were graduated histologically according to the Seifert grading system. An immunohistochemistry panel including CD20, CD3, and keratin AE1-3 was performed.

Results: All cases involved the sub-maxillary gland. Microscopically the cases were in stages 2, 3, and 4. There was a chronic inflammatory infiltrate, marked fibrosis, variable degrees of parenchymal atrophy, PAS+ intraluminal material, and microliths. The infiltrate was polymorphic and polyclonal, without lymphoepithelial lesions.

Conclusions: Although it has a typical clinical and pathological presentation and was described more than a century ago, KT remains under-diagnosed and often reported as non-specific inflammatory infiltrate or as "low grade lymphoma." In this latter diagnosis lies the greatest importance for recognizing KT, as confusion with lymphoma would result in a different therapeutic approach.

Key words: Küttner's tumour. Chronic sclerosing sialadenitis. Sub-maxillary gland.

Tumor de Küttner (sialoadenitis crónica esclerosante). Estudio clinicopatológico e inmunohistoquímico de 8 casos de una entidad poco reconocida

Objetivo: Presentar las características clinicopatológicas del tumor de Küttner (TK) o sialoadenitis crónica esclerosante.

Material y método: Se estudiaron 8 casos de TK. Se graduaron los casos histológicamente de acuerdo con la clasificación de Seifert. Se realizó una batería de anticuerpos contra CD20, CD3 y queratina AE1-3.

Resultados: Todos los casos afectaron a la glándula submaxilar. Microscópicamente se encontraban en estadios 2, 3 y 4. Había inflamación crónica folicular y fibrosis acentuada, con atrofia parenquimatosa variable, material PAS+ intraluminal y microcalcificaciones. El infiltrado inflamatorio fue polimorfo, policlonal y sin lesiones linfocitales.

Conclusiones: A pesar de su descripción hace más de un siglo y su presentación clínica e histopatológica característica, el TK es poco diagnosticado y a menudo se informa como proceso inflamatorio inespecífico o como linfoma de bajo grado. En este último diagnóstico radica la mayor importancia del reconocimiento del TK, ya que resultaría en un manejo terapéutico diferente.

Palabras clave: Tumor de Küttner. Sialoadenitis crónica esclerosante. Glándula submaxilar.

Correspondence: Dr. C. Ortiz Hidalgo.
Departamento de Patología. Centro Médico ABC.
Sur 136#116 Las Américas. México DF 01120. México.
E-mail: cortiz@abchospital.com

Received August 23, 2006.

Accepted for publication October 24, 2006.

INTRODUCTION

Chronic sclerosing sialadenitis or Küttner's tumour (KT) is a benign pseudotumoural lesion first described in 1896 and mainly affecting the submandibular salivary glands (Figure 1). Clinically, it presents as a slow-growing painless mass occasionally accompanied by pain on swallowing¹. More than a century after its original description, KT continues to be little recognized as an entity and it is often

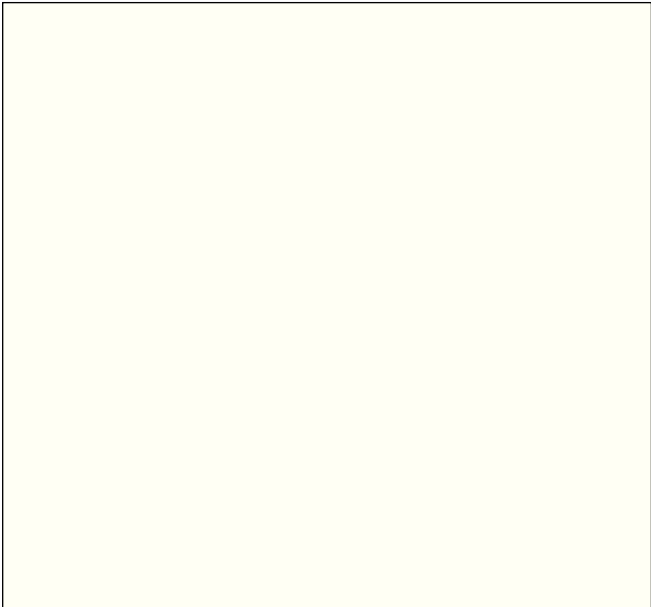


Figure 1. Cover of the original article published by Hermann Küttner in 1896¹.

Table I. Antibodies Used

Antibody	Commercial Clone	Company	Dilution	Antigen Recovery
CD20	Ks20,8	Cell Marque	1:50	Trilogy
CD3	Polyclonal	Cell Marque	1:500	Trilogy
Kappa	L1C1	Cell Marque	1:100	Declere
Lambda	Lamb 14	Cell Marque	1:100	Declere
CKAE1-3	AE1 + AE3	Cell Marque	1:100	Declere

diagnosed as “benign lymphoepithelial lesion”, “Sjögren syndrome” or “low grade lymphoma”. Although some authors have considered it a rare condition^{2,3}, the Hamburg Salivary Gland Register in Germany, which has recorded a total of 1,004 cases over 25 years, acknowledges KT as the most common lesion of the submandibular gland^{3,4}. KT gradually goes through a series of progressive histological stages that may culminate in total fibrosis of the submandibular gland. Histologically, there is a polymorphous polyclonal inflammatory infiltrate, with numerous active lymphoid follicles, fibrosis starting at the periductal area and subsequently becoming diffuse, dilations and occasional squamous metaplasia of ducts, with the presence of PAS-positive dense secretion inside them, and there may be calculi or microcalcifications inside the ducts². In the initial stages, the inflammatory infiltrate may become so intense that KT may be mistaken for a lymphoma, especially marginal zone lymphoma (MALT lymphoma)⁵. Although transformation into a malign form is a rare phenomenon, there are isolated reports of marginal zone lymphoma originating from KT⁶, probably due to a mechanism similar to that of these lymphomas in other locations, preceded by chronic inflammatory lesions⁷⁻⁹. In

this study, we present 8 cases of chronic sclerosing sialadenitis or KT diagnosed at the ABC Medical Centre in Mexico City. In this review we indicate the histopathological characteristics of this entity through the various stages of its progress.

MATERIAL AND METHOD

Eight cases were obtained from the files of the Pathology Department of the American British Cowdray (ABC) Medical Centre between January 1997 and March 2006. The preparations stained with hematoxylin and eosin were studied and a battery of histochemical and immunohistochemical tests were applied to assess the degree of sclerosis, the inflammatory infiltrate and the characteristics of the salivary gland ducts in order to discard limphoepithelial lesions. This nattery of tests included reaction to periodic acid Schiff (PAS), Masson’s trichrome and anti-CD20, anti-CD3, anti-kappa and -lambda light chains and antikeratin (CK AE1-3) antibodies (Table 1). The histological stage was assessed using the classification of Seifer et al⁴ that divides KT into: stage 1 (focal sialadenitis), stage 2 (diffuse lymphocytic sialadenitis with glandular fibrosis), stage 3 (chronic sclerosing sialadenitis with glandular sclerosis) and stage 4 (chronic progressive sialadenitis with cirrhosis of salivary gland).

RESULTS

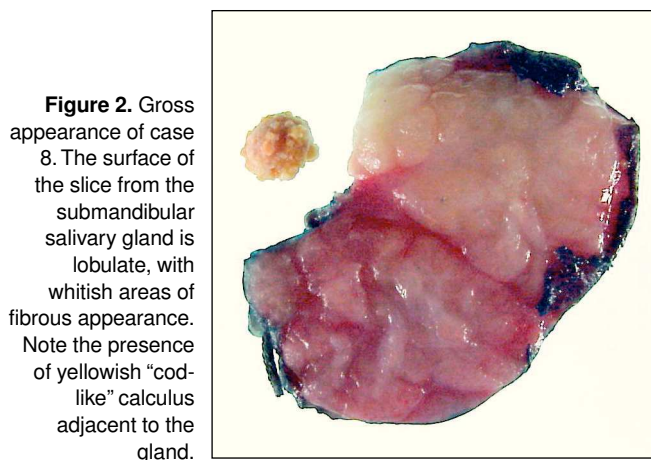
The age of the patients varied between 38 and 76 years and there were 6 males and 2 females. Three cases corresponded to the left submandibular gland, 2 to the right and the side was not specified in 3 cases. One of the cases had evolved over a period of 5 years and in the remainder the evolution time was unknown. The diagnoses reported included: 5 as “neck tumour” without further specification, 1 as “benign lymphoepithelial lesion”, 1 as “tumour of the submandibular gland” and 1 as “low grade lymphoma”. In our 8 cases, we received a surgical sample from only 5; in the other 3 cases we were sent only the histological slices for a diagnostic opinion. On gross examination, the lesions of the submandibular gland measured between 1.6 cm and 3.9 cm (Table 2). The samples were firm, lobulate and whitish yellow. Case 8 presented a calculus on gross examination (figure 2). Histologically, the cases were assessed using the classification criteria of Seifer et al^{4,10,11} by means of a hematoxylin and eosin stain, Masson’s trichrome to assess the degree of fibrosis and PAS staining to evaluate the presence of intraluminal secretion.

Three cases (37.5%) were at stage 3, with diffuse lymphoid inflammatory infiltrate and marked formation of lymphoid follicles with mostly periductal germinal centres. In these cases there was moderate-marked atrophy of the acinar parenchyme with fibrosis and periductal hyalinization, most evident with Masson’s trichrome stain (Figure 3). One case presented focal epidermoid metaplasia in interlobular ducts and main ducts. Three cases (37.5%) corresponded to stage

Table 2. List of Cases and Their Clinical and Histological Characteristics

Case	Age/Sex	Submandibular Gland, Side Affected	Size	Histo-Logical Stage	PAS+ Secretion	Epidermoid Metaplasia	Calculi
1	65 years / M	NS	NS	3	Absent	Absent	Absent
2	76 years / M	NS	NS	3	Present	Absent	Present
3	73 years / F	Left	2.5 cm	4	Present	Absent	Absent
4	43 years / M	Right	NS	4	Present	Absent	Absent
5	58 years / M	NS	2.5 cm	4	Present	Absent	Absent
6	46 years / M	Left	3.9 cm	3	Present	Focal	Present
7	65 years / M	Right	3.7 cm	2	Present	Absent	Absent
8	38 years / F	Left	1.6 cm	2	Present	Focal	Present (visible on gross examination)

F, indicates female; M, male; NS, not specified.



4, and the submandibular salivary gland showed almost total replacement of the glandular parenchyme by inflammatory infiltrate, diffusely forming lymphoid follicles, with formation of fibrous walls, sclerosis and parenchymatous hyalinization with few ducts remaining isolated. Two cases were found at stage 2, with intense diffuse inflammatory infiltrate, with some periductal lymphoid aggregates and periductal sclerosis evidenced by Masson's trichrome.

In 7 of the 8 cases, thick PAS-positive intraluminal material was identified in the intercalary and interlobular ducts, and in 2 more cases microscopic calculi were identified (Figure 4 and Table 2). Two cases presented microabscesses (cases 6 and 8), and in one of these the acute inflammation extended into the neighbouring tissue of the salivary gland (case 8).

The inflammatory infiltrate was polymorphous, comprising both B (CD20 positive) and T (CD3 positive) cells with a B:T ratio of 2:1. The B cells ranged around the ducts, forming lymphoid follicles with germinal centres, and they were positive for both kappa and lambda light chains (polyclonal) with a 1:1 ratio. The T lymphoid component was diffuse (Figures 5a and b). Cytokeratin AE1-3 highlighted the presence of duct epithelium, without lymphoepithelial lesions (Figure 5c).

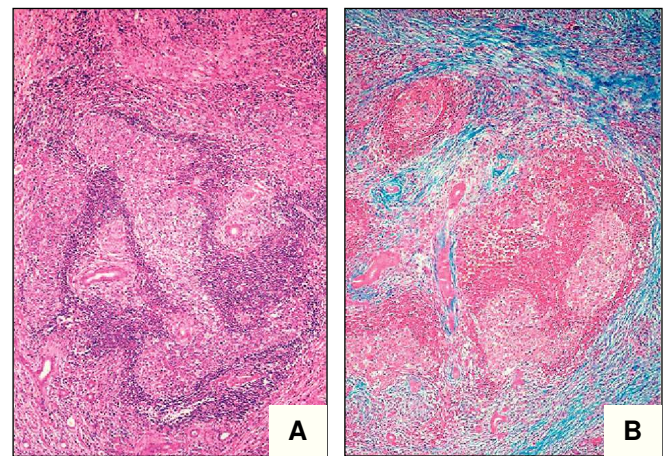


Figure 3. A: histological slice showing the lobular configuration and chronic inflammatory infiltrate (H-E, $\times 100$). B: staining with Masson's trichrome evidencing periductal fibrosis with formation of walls.

DISCUSSION

Küttner's tumour is a chronic benign pseudotumoural alteration involving inflammation that presents almost exclusively in the submandibular gland of adults¹², with a mean onset at 43 years of age^{13,14}. In clinical terms, it is manifested as an increase in volume of the submandibular gland evolving over a long time and mainly affecting male patients. In our study, the patients were between the fourth and eighth decades of life, and there was a marked preponderance of males (75%), coinciding with reports published in the literature.

Although almost always unilateral, there have been some reports of bilateral KT, and there are also reports of the involvement of minor salivary glands¹⁵. Growth is almost always painless, although some patients may present pain or inflammation associated with the intake of food¹³. The time the patient has this condition prior to visiting the doctor varies between less than one year to several decades¹⁰. The clinical diagnosis is frequently lymphoma, carcinoma or "tumour" without further specification. All our cases involved

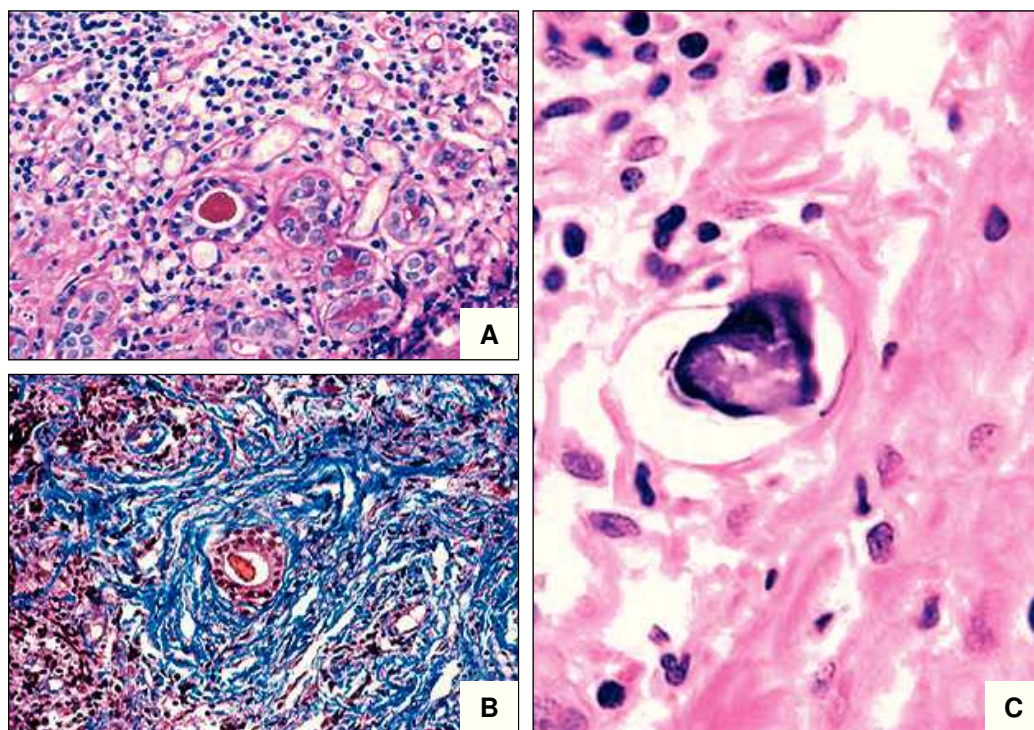


Figura 4. Staining with PAS (A) and Masson (B) showing the presence of dense intracanalicular material, as well as periductal fibrosis ($\times 200$). C: intraductal microcalcification (H-E, $\times 400$).

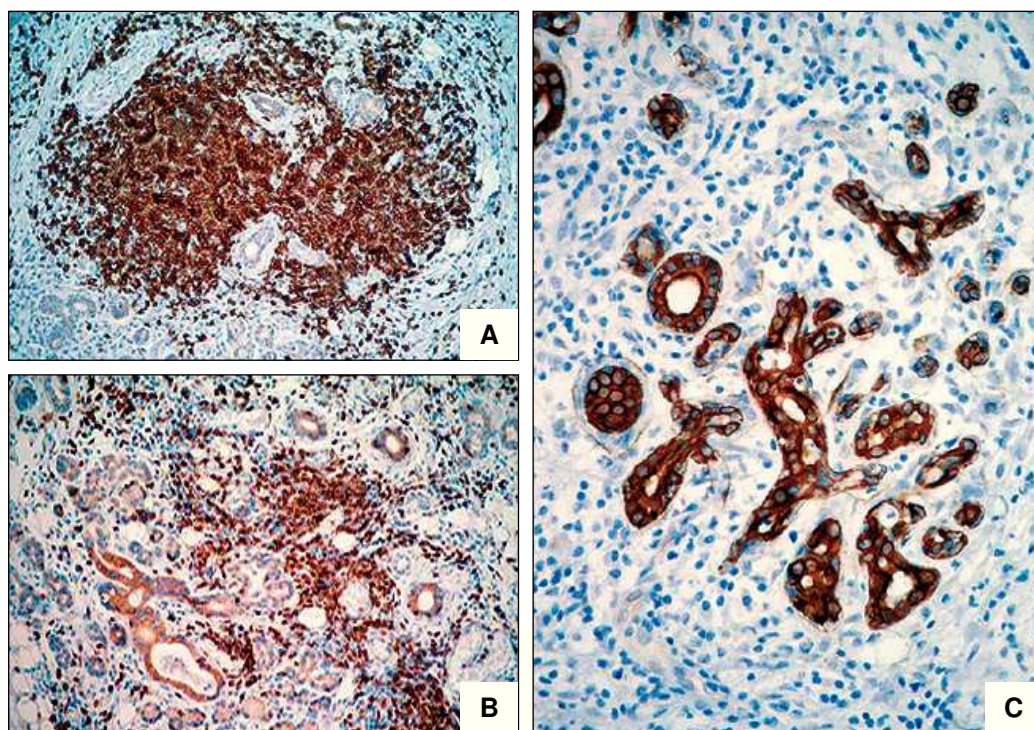


Figura 5. Immunomarking by CD20 (A); CD3 (B), where the lymphoid infiltrate is mainly periductal; and keratin AE1-3 (C) highlighting the epithelial component of ducts and showing the absence of lymphoepithelial lesion.

the submandibular salivary gland, with a long-standing increase in volume, without precise details or the total time. One patient (case 8), in addition to the increase in volume in the area under the jaw, also complained of changes in the consistency and taste of her saliva, fever and pain.

Some authors consider KT as a rare condition¹⁶⁻¹⁸, while others acknowledge it as the most frequent pathological process of the submandibular salivary gland^{10,11,13,18}. On the

Salivary Gland Register of the Pathology Department at the University of Hamburg, KT turns out to be the third most frequent cause of chronic sialadenitis, surpassed only by chronic obstructive sialadenitis and recurrent parotiditis⁴. It is likely that the real frequency of presentation of KT is greater, as this statistic took account of the entities present in the minor and major salivary glands and not only in the submandibular gland.

Histologically, KT presents the following general characteristics, which vary in percentage and intensity from one stage to another: a) progressive fibrosis starting in the periductal area and subsequently involving the rest of the gland until it is entirely replaced; b) dilation of the ducts, with the presence of thick PAS-positive intraluminal material; c) chronic inflammatory infiltrate with extensive formation of lymphoid follicles, with germinal centres starting in the periductal area and subsequently diffusing, and d) progressive squamous metaplasia of the ducts^{4,10,11}. Intraluminal calculi or microcalcifications may occasionally be identified, but this is not a constant feature. These histological characteristics were grouped together by Seifer et al^{4,11} into 4 stages: stage 1 (focal sialadenitis), chronic focal inflammation with nests of lymphocytes surrounded by the ducts of salivary gland and moderately dilated ducts with scant intraluminal secretion; stage 2 (diffuse lymphocytic sialadenitis with glandular fibrosis), diffuse inflammatory infiltrate with formation of periductal lymphoid follicles, periductal fibrosis and focal squamous metaplasia with proliferation of the ductal epithelium, centrolobular fibrosis with moderate atrophy of the acinar parenchyme (at this stage it is possible to observe invasion of the ductal epithelium by monocytoïd lymphocytes, without bringing about its destruction); stage 3 (chronic sclerosing sialadenitis with glandular sclerosis), prominent lymphoid inflammatory infiltrate with diffuse formation of lymphoid follicles, atrophy of the acinar parenchyme, periductal hyalinization and sclerosis; in addition, there is epidermoid metaplasia and cup-shaped duct cells, and stage 4 (chronic progressive sialadenitis with sclerosis, "cirrhosis", of the salivary glands) is the final stage and is known as cirrhosis type, with evident loss of the parenchyme and marked sclerosis with formation of fibrous walls⁴.

In the largest clinical study, carried out by the Register of Salivary Gland Tumours in Hamburg, 25% of patients were at stage 1, 19% at stage 2, 38% at stage 3 and 18% at stage 4¹⁰. Our cases were at stage 4 (37.5%), stage 3 (37.5%) and stage 2 (25%). None of our cases was at stage 1.

Several aetiological mechanisms have been proposed for KT, and one of these is the theory of hydroelectrolytic obstructive sialadenitis put forward by Seifer and others^{10,11,19}. This proposal considers an initial secretory imbalance that produces hyperdensity in intraluminal secretion. This leads to obstruction of the salivary ducts, with a secondary inflammatory response by the parenchyme with fibrosis and atrophy. Clinically this is seen in reduced saliva production and a greater tendency to infections. This creates a vicious circle in which the greater obstruction of the ducts leads to greater inflammation and fibrosis. Morphologically, this results in the presence of PAS-positive intraluminal secretion, a common phenomenon in KT found in 7 (87.5%) of our 8 cases (Table 2) and intraluminal inflammatory infiltrate, even with formation of microabscesses, found in 2 (25%) of our cases.

Isacsson et al²⁰ have mooted that the aetiology of KT is the presence of calculi (sialolithiasis) within the ducts producing inflammation and secondary fibrosis. Harrison et al¹⁹ agreed with Seifer et al¹¹ in that the main point is

possibly infection and they indicate that the presence of microlites is linked with age, as in any normal salivary gland, and that the development of these microlites is secondary to the infection (sialoadenitis). Although microlites were shown to exist in almost 60% of the cases in this latter study, others have not reported on their presence¹⁸ (Figure 1). In our study, microlithiasis was present in 2 cases (28%) and only 1 (14%) presented a microscopic calculus (figure 4).

The studies by Tiemann et al¹⁸ have indicated that no mechanical processes of any kind are sufficient to explain one of the most prominent characteristics of KT, namely the intense lymphocytic infiltration and the final destruction of the glandular parenchyme. On this basis, they propose that the main cause of KT is a T-cell mediated autoimmune reaction, with a preponderance of CD8+ T-cells and the common presence of oligoclonal TCR γ rearrangements, although the antigen triggering this response has not yet been identified¹⁸. Considering that the immune response in KT is mainly T, this may possibly explain why these patients rarely develop MALT type B lymphomas of the marginal zone^{4,18,21}. Ochoa et al⁶ however have proposed that KT is the result of a B cell mediated reaction and might provide the lymphoma substrate similarly to what happens with similar inflammatory histories in other anatomical locations, i.e. the emergence of a monoclonal B population originating in a profuse inflammatory infiltrate in response to an antigenic, possibly infectious, stimulus⁶⁻⁸.

Even though there is a division of opinions about which system is the main cause triggering the immune response, some studies have indicated that the fibrosclerosis characteristic of KT is due to the production of IgG4 mainly mediated by plasma cells, analogously to what happens in sclerosing pancreatitis¹⁷. While the mechanism by which IgG4 induces fibrosis is not clear, it has been mooted that the IgG4-positive plasma cells stimulate proliferation of fibroblasts²². There is infiltration of the IgG4-positive plasma cells in other sclerosing conditions, indicating the possibility that KT forms part of an entity known as "IgG4-related sclerosing disease" that would include sclerosing cholangitis (for which there are reported associations with KT), inflammatory hepatic and mammary gland pseudotumour and fibrosis of the mediastinum, among others²³.

In the initial histological stages of KT, when the lymphoid immune response is very prominent, differential diagnosis is with marginal zone lymphoma or follicular lymphoma⁸. In order to distinguish these, it is essential to pay special attention to the histological characteristics mentioned above. Discrimination may be hindered where there is prominent architectural distortion with dense inflammatory response and epithelial invasion of epithelium by monocytoïd lymphocytes, constant features of stage 2. In these cases, immunohistochemistry is a crucial diagnostic factor to determine the characteristics of the lymphoid infiltrate, typically polyclonal in KT and lacking in lymphoepithelial lesion.

In short, chronic sclerosing sialadenitis or KT is a pseudotumoural alteration affecting almost exclusively the submandibular gland and is frequent in adults between the fifth and sixth decades of life. Histologically, it is

characterized by a polymorphous T and B polyclonal infiltrate. Even when there is an invasion of the ductal epithelium by monocytoid B lymphocytes, there is no lymphoepithelial lesion and it presents 4 diagnostic features: fibrosis, dilation of ducts with dense, thick PAS-positive material inside, polymorphous and polyclonal immune response with prominent formation of lymphoid follicles with germinal centres and squamous metaplasia of the ducts. There may be microlites and acute inflammation with intraluminal microabscesses, but these are not constant characteristics.

REFERENCES

- Küttner H. Über entzündliche tumoren der submaxillar-speicheldrüse. Beitr Klun Chir. 1896;15:815-34.
- Kitagawa S, Zen Y, Harada K, Sasaki M, Sato Y, Minato H, et al. Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Küttner's tumor). Am J Surg Pathol. 2005;29:783-91.
- Huang C, Damrose E, Bhuta S, Abemayor E. Küttner tumor (chronic sclerosing sialadenitis). Am J Otolaryngol. 2002;23:394-7.
- Seifert G. Tumour-like lesions of the salivary glands. The new WHO classification Pathol Resp Pract. 1992;188:836-46.
- Kojima M, Nakamura S, Itoh H, Yamane Y, Shimizu K, Masawa N. Küttner's tumor of salivary glands resembling Marginal Zone B-Cell lymphoma of the MALT type: A histopathologic and Immunohistochemical study of 7 Cases. Int J Surg Pathol. 2004;12:389-93.
- Ochoa ER, Harris NL, Pilch BZ. Marginal Zone B-Cell lymphoma of the salivary gland arising in chronic sclerosing sialoadenitis (Küttner Tumor). Am J Surg Pathol. 2001;11:1546-50.
- Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. *Helicobacter pylori*-associated gastritis and primary B-cell gastric lymphoma. Lancet. 1991;338:1175-6.
- Hsi ED, Zukerberg LR, Schnitzer B, Harris NL. Developmental of extrasalivary gland lymphoma in myoepithelial sialadenitis. Mod Pathol. 1995;8: 817-24.
- Kojima M, Nakamura S, Itoh H, Yamane Y, Tanaka H, Sugihara S, et al. Sclerosing variant of follicular lymphoma arising from submandibular gland and resembling "Küttner tumor", a report of 3 patients. Int J Surg Pathol. 2003;11:303-7.
- Chan JK. Küttner tumor (chronic sclerosing sialadenitis) of the submandibular gland: An underrecognized entity. Adv Anat Pathol. 1998;5:239-51.
- Steifer G, Donath K. On the pathogenesis of the Küttner tumor of the submandibular gland. Analysis of 349 cases with chronic sialadenitis of the submandibular gland. HNO. 1977;25:81-92.
- Cheuk W, Chan KC. Küttner tumor of the submandibular gland. fine-needle aspiration cytologic findings of seven cases. Am J Clin Pathol. 2002;117: 103-8.
- Ellis GL, Auclair PL. Tumor-like conditions. En: Atlas of Tumor Pathology Tumors of the Salivary glands Third series Fascicle 17 Armed Forces Institute of Pathology 1995. p. 411-21.
- Rosai J. Major and minor salivary glands in Rosai and Ackerman's Surgical pathology. 9th ed. New York: Mosby; 2004. p. 873-5.
- Blanco M, Mesko T, Cura M, Cabello-Inchausti B. Chronic sclerosing sialadenitis (Küttner's tumor): unusual presentation with bilateral involvement of major and minor salivary glands. Ann Diagn Pathol. 2003;7:25-30.
- Huang C, Damrose E, Bhuta S, Abemayor E. Küttner tumor (chronic sclerosing sialadenitis). Am J Otolaryngol. 2002;23:394-7.
- Yanez M, Roa I, Roa JC, Villaseca M, García M. [Chronic sclerosing non-specific sialadenitis of the submandibular gland (Küttner tumor). Report of one case]. Rev Med Chil. 1999;127:600-3.
- Tiemann M, Teymoortash A, Schrader C, Werner JA, Parwaresch R, Seifert G, et al. Chronic sclerosing sialadenitis of the submandibular gland is mainly due to a T lymphocyte immune reaction. Mod Pathol. 2002;15: 845-52.
- Harrison JD, Epivatianos A, Bhatia SN. Role of microliths in the aetiology of chronic submandibular sialadenitis: a clinicopathological investigation of 154 cases. Histopathology. 1997;31:237-51.
- Isacson G, Ahlner B, Lundquist PG. Chronic sialadenitis of the submandibular gland. A retrospective study of 108 case. Arch Otorhinolaryngol. 1981; 232:91-100.
- Tiemman M, Schrader C, Teymoortash A. Clonal evolution of B-cells in Küttner's tumor. Am J Surg Pathol. 2002;26:1369-70.
- Comings DE, Skubi KB, Eyes JV, Motulsky AG. Familial multifocal fibrosclerosis. Findings suggesting that retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis, and pseudotumor of the orbit may be different manifestations of a single disease. Ann Intern Med. 1967;66: 884-92.
- Kamisawa T. IgG4-related sclerosing disease. Intern Med. 2006;45:125-6.