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A case of kuttner tumour misdiagnosed as malignant neoplasia with a review of the literature

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A case of kuttner tumour misdiagnosed as malignant neoplasia with a review of the literature

AIM: *The aim of this study is to demonstrate how surgery is fundamental in case of Kuttner Tumour (KT). In literature, there are few reported cases of KT and for this reason, diagnostic errors could occur with subsequent underestimation of the disease.*
MATERIALS OF THE STUDY: *We review cases of KT published from 1976 to today in order not to run into diagnostic errors. It was carried out a systematic review of the literature on chronic sclerosing sialadenitis, also known as KT.*
RESULTS: *KT is an immune-mediated localized fibro inflammatory condition that often mimics other pathological processes, such as neoplasms.*
DISCUSSION: *The variables analysed in each article included in this review were the age and gender of the patients, the location of the disease, the type of study; clinical presentation, instrumental tests performed, presence of IgG4, surgery performed and the evolution of patients after treatment were also assessed. Diagnosis should be based on clinical, serological and pathological findings, but in a small percentage of cases (just as in the case presented) the cytological data provided by FNAB and serum IgG4 levels do not allow a diagnosis.*
CONCLUSIONS: *Our experience shows that only surgery with subsequent histological examination makes it possible to correctly diagnose the disease.*

KEY WORDS: Kuttner Tumour, Salivary glands, Immunoglobulin G4-related disease, Maxillofacial surgery

Introduction

Kuttner tumour (KT), also known as chronic sclerosing sialadenitis, is a chronic inflammatory disease of salivary glands. It was first described by Küttner in 1896 [1] and has since been referred to in literature as "Kuttner tumour". Clinically, it manifests as a firm swelling of the gland that may be difficult to distinguish from neoplasia; for this reason, it is classified as a tumour-like lesion of the salivary glands by the World Health Organization [2]. Recent studies have also shown that KT is an Immunoglobulin G4-related disease (IgG4-RD) [3]. IgG4-RD is a recently designated fibroinflammatory condition characterized by swelling lesions, dense IgG4-positive plasma cell-rich lymphoplasmacytic infiltrate, storiform fibrosis, and, frequently, elevated serum IgG4 levels [4]. It was also observed that IgG4 serum concentration correlates with reduction of saliva production and glandular fibrosis, suggesting that IgG4 concentration in serum can represent a useful marker to follow the evolution of the disease and efficacy of treatment [5]. According to the new classifications, KT along with Mikulicz's disease (MD) are the main manifestations of IgG4-RD in the salivary glands [6]. In this report we describe a 61-year-old male with KT of the left submandibular gland initially diagnosed as malignant neoplasm with a systematic review of the literature.

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Case Report

A 61-year-old male presented to Maxillofacial Unit of University "Magna Graecia" of Catanzaro in January 2020 with enlargement of a left submandibular gland mass that had been present for 6 months with no pain. There was no history of dry eyes or dry mouth. His past medical history was significant for artery hypertension, gastroesophageal reflux, diverticulosis of the colon and presence of thyroid nodules. The anamnesis was negative for autoimmune diseases. Physical examination of the neck revealed a 2.5 cm x 3 cm swelling, oval, with a smooth surface and taut-elastic consistency, mobile on the underlying planes, painless in the left submandibular region. Neither lymphadenopathy nor any other salivary gland enlargement were present. Ultrasound examination revealed enlargement of the right submandibular gland measuring 2,5 cm. The echotexture revealed an uneven and hypoechoic formation. MRI detected a 3 cm x 3 cm x 2,7 cm, well-defined
formation with clear margins in the left submandibular salivary gland. This mass had low to medium signal intensity in T1-weighted sequences and fairly high in T2-weighted and IR ones; moreover, it had marked contrast enhancement after intravenous contrast injection (Fig. 1). No pathologic nodes were identified. An ultrasound-guided fine-needle biopsy was performed. Cytology revealed basaloid neoplastic cells suspected of malignancy (C4). Surgery was performed under general anaesthesia. After incision of the skin and subcutaneous tissue, a hard mass with a rough surface without clear borders was revealed. There was no pus in the submandibular space. Clinically, the lesion appeared to be a malignant neoplasm (Fig. 2). The specimen collected measured about 3 cm at its longest diameter, and it was darker in colour than the surrounding gland; its cut surface demonstrated a firm consistency. The whole tissue sample was submitted for histopathological examination which revealed chronic sclerosing sialadenitis (Fig. 3). No evidence of malignancy was observed, and the final diagnosis was KT. Clinical follow-up was performed at 7 days and at 1, 6 and 12 months; all were silent, without symptoms and/or post-operative complications. Ultrasound follow-up was performed 3 months after surgery and showed no recurrence or swelling. In addition, after histological outcome, the patient underwent research on serum IgG4 immunoglobulins, which were negative.

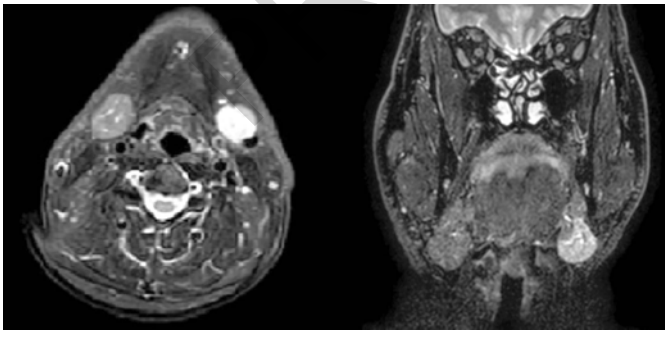

Fig. 1: Magnetic Resonance Imaging: Axial and coronal T2-weighted images, respectively, showing a heterogeneous hyperintense mass with clear margins in the sub-mandibular gland.

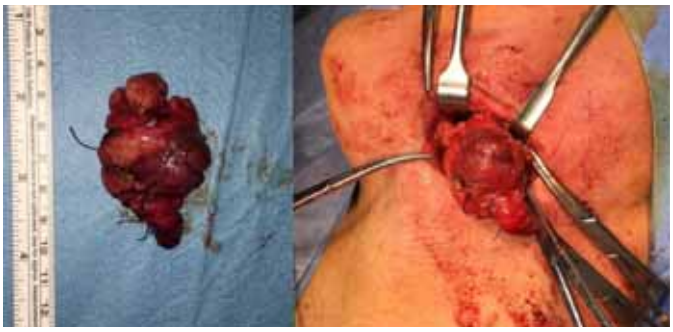

Fig. 2: Intraoperative macroscopic views: the specimen collected was darker in color than the surrounding gland and its cut surface demonstrated a firm consistency.

A) B) C)

Fig. 3: Chronic sclerosing sialadenitis (Kuttner Tumor). (A). Immunohistochemical analysis for p63 showed positivity of myoepithelial cells in the glandular component (Magnification 40x). (B) Salivary gland tissue characterized by acinar atrophy associated with a dense inflammatory infiltrate around the ducts and within the lobules (Magnification 40x). (C) Dense inflammatory cells infiltrate throughout the parenchyma, with germinal center formation and associated perilobular fibrosis (Magnification 100x).

Material and Methods

It was designed and implemented by a systematic review of the literature on chronic sclerosing sialadenitis, also known as KT. The study population included all publications, English-language or other languages, that addressed KT, without restriction as to the period researched. Descriptive literature reviews, clinical reports, series of clinical reports, and expert opinions were excluded. The variables analysed in each article included in this systematic review were the age and gender of the patients, the location of the disease, the type of study. The clinical presentation, the instrumental tests performed, the presence of IgG4, the surgery performed and the evolution of patients after treatment were also assessed.

Search Strategy

The authors performed an extensive bibliographic search using PubMed, Cochrane and Scopus databases to identify relevant articles which were published from 1976. We focused on clinical manifestations in the head and neck area and the following key words were employed: Küttner, Kuttner's tumour, Chronic sclerosing sialadenitis, salivary glands, salivary gland tumour, IgG4-related diseases, sialadenitis, xerostomia, swelling. To broaden the search, the "related articles" function was used, and all citations were considered relevant.

Study Research

All the articles found were analysed by two authors (F.F. and B.I.): titles and abstracts were read and where a study was considered potentially relevant, the full text of the publication was revised. Subsequently they were subjected to the inclusion and exclusion criteria.
The inclusion criteria were: (1) patients with swelling in head and neck area; (2) surgically treated; (3) with definitive histological diagnosis of KT.
The exclusion criteria were: (1) Descriptive reviews in literature, reports of clinical cases, series of clinical cases, and expert opinions; (2) Studies involving cases of malignant transformation or recurrence over time.
After the analyses were compared, disagreements between authors were settled through further discussion with senior evaluator (C.M.G.).

Data Collection & Extraction

Once the articles were fully read, the following information of interest was obtained: study characteristics (author, year of publication, country of origin, study design, patient number), patient demographics (age, gender), clinical outcomes, surgery and complications. All data were collected and tabulated using a Microsoft Excel spreadsheet. The methodological quality and reporting standard of the results were independently assessed by two researchers (F.F. and B.I.). Furthermore, the methodological quality was assessed by analysing the risk of bias.

Discussion and literature review

KT is a chronic inflammatory disease of salivary glands characterized by firm swelling. Clinically, it may be difficult to distinguish from neoplasia, but a histological diagnosis should not be difficult if the pathologist is aware of the tumour's existence. In the literature, there are not many reported cases; for this reason, diagnostic errors could occur with subsequent underestimation of the disease. Precisely, we review the cases of KT published from 1976 to today; in these forty-five years 47 studies have been published for a total of 279 cases of KT, summarized in Table I.
According to Seifert, KT may evolve through four different histologic stages [7-8] as follows:
1. Focal chronic inflammation with nests of lymphocytes around salivary ducts, which are moderately dilated and contain inspissated secretion;
2. More marked diffuse lymphocytic infiltration, and more severe periductal fibrosis. The ductal system shows inspissated secretion and focal metaplasia with proliferation of ductal epithelium. Periductal lymphoid follicles are well developed. There is fibrosis in the centres of the lobules, accompanied by atrophy of acini;
3. Even more prominent lymphocytic infiltration, with lymphoid follicle formation, parenchymal atrophy, periductal hyalinization, and sclerosis. Squamous and goblet cell metaplasia in the ductal system;
4. Cirrhosis-like, with marked parenchymal loss and sclerosis (the "burnt out" phase).

The aetiology of KT is poorly understood, many etiological agents are involved: the main one is the presence of sialoliths, found in 29-83% of cases [8-11]; although it is still unclear whether the stone is the cause or result of the inflammatory process. In our case, no stones were found. Other possible etiologist of KT is ascending bacterial infections of the oral cavity and duct obstruction by foreign bodies [12]. Any event that causes salivary flow obstruction or secretion stasis can cause swelling of the acinar cells resulting in necrosis, ductal dilation, and secretion retention. All this is associated with oedema and inflammatory cell infiltration [13]. Seifert and Donath put forth a theory of obstructive electrolyte sialadenitis, in which a secretion disorder produces inspissated secretion that obstructs the small ducts, leading to inflammation, fibrosis, parenchymal atrophy, and immune reaction of the duct system [7].
KT can affect any salivary gland, although it occurs most commonly in the submandibular gland (95,34%); it rarely affects the parotid gland (3,22%) and very rarely the minor salivary glands (0,36%) or the lacrimal glands (1,08%). It usually occurs in the middle-aged and elderly adults (mean age 53,86-years-old) with a slight male predominance (Male = 59,65%; Female = 40,35%).
Most patients note recurrent pain, discharge, and swelling that is often associated with eating, but others only have an asymptomatic hard swelling of the submandibular gland.
The duration of symptoms before the patient is seeking treatment varies from a few weeks to about a few years. Often, gradual hardening and enlargement of the lesion leads doctors to diagnose swelling as a salivary gland neoplasm. But KT is a totally benign inflammatory lesion and until now there have been no reports of malignancy. In fact, KT have often been removed

Table I - *Review of the published cases of Kuttner Tumors of the salivary glands*

No.	Year	Author	Case number	Mean Age	Sex	Location
1	1976	Y Nomura	1	unavailable		Submandibular
2	1997	Harrison JD	154	42	unavailable	Submandibular
3	2000	H K Williams	1	83	M	Parotid
4	2002	C Huang	1	45	M	Submandibular
5	2003	Mario Blanco	1	64	F	Submandibular
6	2003	A T Ahuja	13	unavailable	7 M / 6 F	Submandibular
7	2004	Yi-Hong Chou	1	13	M	Parotid
8	2004	Mitsuo Adachi	1	72	M	Submandibular
9	2004	Antoni Osmólski	3	unavailable		Submandibular
10	2005	Satoshi Kitagawa	12	64,58	8 M / 4 F	Submandibular
11	2005	Jong-Lyel Roh	1	30	F	Submandibular and lacrimal glands
12	2005	VV Afanas'ev NV Nosenko	1	unavailable		Submandibular
13	2006	M Unal	1	41	M	Submandibular
14	2006	Sadayuki Kaba	5	61,8	2 M / 3 F	Submandibular
15	2007	K Markou	4	48,75	2 M / 2 F	2 Submandibular 1 Submandibular 1 Parotid
16	2008	TL Chow	9	61	6 M 3 F	8 Submandibular 1 Parotid
17	2008	E Kiverniti	1	47	M	Submandibular
18	2008	A Abu	3	77,3	unavailable	Submandibular
19	2008	Masaru Kojima	3	67	M	Submandibular
20	2009	R Paul	1	57	F	Minor salivary gland
21	2009	Justyna Soltys	2	44,5	2 M	Submandibular
22	2010	Güçlü Kaan Beriat	1	28	M	Parotid
23	2010	J Turbiner Geyer	13	61	6 M 7 F	12 submandibular 1 parotid
24	2010	Kazuki Nagal	3	71,3	2 M 1 F	Submandibular
25	2011	J Carneiro Melo	1	11	M	Submandibular
26	2011	Jaroslaw Markowski	1	62	M	Submandibular
27	2011	Jan Laco	6	57	2 M / 4 F	Submandibular
28	2011	Henrietta W M	1	40	F	Lacrimal Glands
29	2012	Yong Un Shin	1	56	M	Submandibular and lacrimal glands
30	2013	Cyril Pandarakalam	1	68	M	Submandibular
31	2013	Uhliarova B	7	55	4 M 3 F	6 Submandibular 1 Parotid
32	2013	A Weitz Tuoretmaa	1	45	M	Submandibular
33	2014	Britta Kaltoft	1	53	M	Submandibular
34	2015	E L Culver	1	unavailable		unavailable
35	2015	Kae Tanaka	1	64	F	Submandibular
36	2015	Tzu-Wei Wei	1	61	M	Submandibular
37	2015	Hwan jun Choi	1	57	M	Submandibular
38	2016	B Tagnon	1	56	F	Submandibular
39	2016	Juan Putra	1	61	F	Submandibular
40	2016	Marino E	4	66,2	2 M 2 F	3 Submandibular 1 Parotid
42	2016	Wah Cheuk	7	61,6	6 M / 1 F	Submandibular
42	2016	David Low	1	55	M	Parotid
43	2019	A Poghosyan	1	67	F	Submandibular
44	2019	Somu Lakshmanan	1	33	F	Submandibular
45	2019	J Godbehere	1	22	M	Parotid
46	2019	A Poghosyan	1	67	F	Submandibular
47	2020	Sushama Govindrao Gurwale	1	65	M	Submandibular

and no additional treatment has been required [14].
Ultrasound is certainly a first level examination that highlights, in most cases, a widespread involvement of the gland with hypoechoic lesions, single or multiple, on a heterogeneous background associated with dilation of the excretory ducts.
The ultrasound aspect is very reminiscent of that of a "cirrhotic liver" [15-16]. In many cases, the use of FNAB (fine needle aspiration biopsy), a low-cost method with low risk for the patient, is decisive. However, some cytopathological features of KT may result in misinterpretation, as they share some cytological features with inflammatory processes involving numerous lymphoid cells [17-18]. In our case, as Leon et al. Also reports, it is possible to find a discrepancy between the cytological diagnosis and the final histopathological diagnosis. On MRI, these lesions typically demonstrate homogeneous high signal intensity on T2-weighted images and low-to-intermediate signal intensity on T1-weighted images, with homogeneous enhancement. All cases described in the literature note that the diagnosis of KT is mainly based on histopathological examination.
The histological features show various characteristics, according to stage in the progressive process and the severity of inflammation. These features include interlobular cellular fibrosis, periductal inflammation, lobular chronic inflammation with numerous plasma cells, obliterative phlebitis, and florid follicular hyperplasia [1,7-9,17-26]. Recently KT has been regarded as an IgG4-related idiopathic sclerosing lesion, which is frequently associated with regional lymph nodal adenopathy [27-34]. Affected parts of the body may include even the head and neck, commonly involving the salivary glands, lacrimal glands, lymph nodes, sinus cavities, as well as (though less commonly) the larynx, tongue, and palate [35-37].
Lesions tend to develop in multiple organs simultaneously or metachronously but are sometimes confined to a single organ.
The sites of such lesions vary, but the histopathological features are similar across organs and all lesions generally respond well to steroids. Although serum IgG4 levels will be raised in most patients (Serum IgG4 concentration > 135 mg/dl^{-1} have been defined as a threshold value for diagnosis) [38]. 20% of individuals may have normal serum levels yet, especially in localised diseases [6,39-41] just like in the case we presented. In addition, IgE and eosinophil counts are usually increased and hypocomplementemia is frequent [42]. Hence, laboratory tests on blood could confirm the diagnosis.
Possible differential diagnoses of KT include other benign inflammatory lesions of salivary glands, such as simple chronic sialadenitis, granulomatous sialadenitis, vasculitis, necrotising sialo-metaplasia, sialolithiasis, radiation effects, an inflammatory pseudotumor, benign lymphoepithelial lesions (with or without Sjögren syndrome), Kimura's disease, extra-nodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [8,12,14,40,43-46].
One of the most common causes of chronic inflammation of the salivary glands is related to rheumatoid arthritis, which is consistent with immune pathogenesis [47].
Surgery is the standard therapy of KT: in this way the sample is sent for histopathological examination.
Sialoadenectomy offers the best treatment option: perioperative mortality and morbidity are minimal; in addition, after surgery the mass disappears immediately. In the literature, there are few publications focusing on the medical treatment of KT, although many authors point to systemic steroid therapy as a first-line treatment [42,48-50]. Long-term prednisone is generally the most widely used drug; it is weighted by disease activity and body mass and is gradually reduced. However, steroids can cause serious side effects; according to some authors, steroids should be reserved for patients with extra-salivary involvement (pancreas/biliary tract) or for those who refuse surgery [24].
Long-term glucocorticoid treatment appears to significantly improve symptoms. Contrariwise, the role of immunosuppressants (azathioprine or methotrexate) is still controversial and poorly studied. For patients with painless, non-progressive KT in whom the preoperative diagnosis is unambiguous, observation should also suffice. There are no standard guidelines for follow-up; as a rule, clinical follow-up is carried out at one, six and twelve months after surgery. Furthermore, the prognosis is good: no reported cases showed disease recurrence or neoplastic evolution.

Conclusions

Kuttner's tumour (or chronic sclerosing sialadenitis) is a rare disease that is often clinically misdiagnosed as a malignant lesion, just as in the case reported. KT has recently been defined as a disease related to immunoglobulin G4 (IgG4-RD) and precisely as a localized expression of this group of pathologies. It therefore represents an immune-mediated localized fibroinflammatory condition that often mimics other pathological processes, such as malignancies. In most cases, the FNAB is decisive and allows a differential diagnosis to be made; but in a small percentage of cases, just as in the case presented, some cytopathological characteristics of KT can cause misinterpretations.
Even the IgG4 dosage did not allow to diagnose the disease as they were not positive. The diagnosis surely should be based on clinical findings, serological and pathological findings.
Even if, our experience shows that only total sialoadenectomy with subsequent histological examination allows to correctly diagnose the disease. Surgery also represents the definitive treatment of the disease, which does not require any other drug therapy, other than the supportive one.

Riassunto

In letteratura i casi segnalati di tumore di Kuttner (KT) sono pochi e per questo motivo potrebbero verificarsi errori diagnostici con conseguente sottostima della malattia. In questo lavoro esaminiamo i casi di KT pubblicati dal 1976 ad oggi per cercare di non incorrere in errori diagnostici. È stata effettuata una revisione sistematica della letteratura sulla scialoadenite sclerosante cronica, nota anche come KT. Le variabili analizzate in ogni articolo incluso in questa recensione sono state l'età e il sesso dei pazienti, l'ubicazione della malattia, il tipo di studio; Sono state inoltre valutate la presentazione clinica, gli esami strumentali eseguiti, la presenza di IgG4, la chirurgia eseguita e l'evoluzione dei pazienti dopo il trattamento. KT è una condizione fibro-infiammatoria immuno-mediata che spesso imita altri processi patologici, come le neoplasie. La diagnosi dovrebbe essere basata su reperti clinici, sierologici e patologici, ma in una piccola percentuale di casi (proprio come nel caso presentato) i dati citologici forniti dalla FNAB e i livelli sierici di IgG4 non consentono una diagnosi. La nostra esperienza dimostra che solo un intervento chirurgico con successivo esame istologico consente di diagnosticare correttamente la malattia.

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