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Case report

SJOGREN SYNDROME AND PAROTID MARGINAL ZONE LYMPHOMA: REPORT OF A CASE AND REVIEW OF LITERATURE.

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ABSTRACT

Five percent of the cancers in the parotid region are non-hodgkin lymphomas. This lymphoma, involving the mucosa-associated lymphoid tissue (MALT), is called MALToma. A chronic autoimmune inflammatory process of the parotid gland, such as Sjogren's syndrome, results in an increased incidence of parotid MALToma. Biopsy of the parotid is essential for appropriate diagnosis; this can then be completed by radiotherapy, chemotherapy or therapy with monoclonal antibodies according to the stage of the disease. This study shows a clinical case of a 50-year-old patient with Sjogren's syndrome who developed a parotid MALToma.

1. Introduction

Sjogren's syndrome is an autoimmune disease which affects the salivary and lacrimal glands with higher incidence in middle-aged women. Several studies have shown that it is a risk factor for a very specific and rare form of parotid cancer, i.e. the extranodal marginal zone B-cell lymphoma (MLZ-marginal zone lymphoma) of the MALT type, also known as MALToma of the salivary glands. This is the most common form of MLZ and is responsible for about 5% of all non-hodgkin's lymphomas [1]. This condition can affect any glands but the parotid glandresults as the most affected due to its abundance in lymphatic tissue. The parotid is the salivary gland most frequently affected by neoplastic processes, both benign and malignant: it represents about 97% of the primary localizations of salivary gland tumors [2]. This study shows a clinical case of a patient suffering from Sjogren's syndrome who developed a MLZ of the right parotid gland.

2. Case report

A 50-year-old woman with Sjogren's syndrome was admitted in 2018 at the unit of otolaryngology of the university hospital "Policlinico Paolo Giaccone", Palermo, Italy.

The patient reported a right parotid swelling, occurring temporary during food ingestion since about 7 years. About two months beforethe admission to the UOC, she reported a single episode of right inflammation of a salivary gland associated with pain and fever as well as persistence of tumefaction in the right parotid region. In addition to Sjogren's syndrome, the patient reported diagnosis offibromyalgia, contact dermatitis and atopic eczema. On clinical examination, the right parotid region presented a roundish formation of about 2 cm of diameter, non-painful even after palpation, with elastic consistency, movableon the superficial and deep tissues. An ultrasound exam (US) of the neck was performed which detected the presence of cystic formation in the context of the parotid gland. The US was followed by a parotid needle aspiration which, at the histological examination, did not reveal atypical features.
Therefore, a Magnetic Resonance Imaging (MRI) was performed with Intravenous (IV) contrast agents (10 ml of Prohance), which detected, in both parotid glands, multiple oval formations. The majority of them had low intensity in T1 and high in T23 and STIR; some of them, on the right parotid, had high intensity in T1, without variations after IV contrast agent, and were up to 1 cm of diameter. The MRI did not detect the presence of hyperplastic lymph nodes. A right superficial parotidectomy has been therefore performed. Macroscopically, the exam showed a parotid measuring 5.5x4x2 cm with a compact, gray-whitish neo-formation of 2x2x1 cm, with irregular and shaded margins.

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Histologically showed a proliferation of monomorphic mature B-lymphoid elements associated with the presence of epi-myoepithelial reaction, with morphological and immunotypic(IIC: CD20+, bcl-2+, CD43+, CD3-,CD10-, CD23-,ki-67 7%) of MAL-type extranodal marginal B-lymphoma.

Then a total body Positron Emission Tomography - Computed Tomography (PET/CT) was performed, which did not show other localizations of the lymphoma. Therefore STAGE I of the disease was confirmed, according to the Ann Arbor staging review [3]. The patient was referred to the unit of hematology of the hospital where she started therapy with monoclonal antibodies. The patient is currently on follow-up and free of disease.

3. Discussion

Salivary gland cancers account for about 3% of head and neck cancers; they occurred usually average at the age of 45 with a peak between the fifth and sixth decade and a greater prevalence in the female sex. The most frequent localization is the parotid [4]. Five percent of the malignant tumors of the parotid region are non-Hodgkin lymphomas [5]. These lymphomas are usually of B-lymphoma and develop at the level of the marginal lymph node area. In the case of the parotid they develop at the level of the the mucosa-associated lymphoid tissue (MALT) [4]. Among the main risk factors of MALT lymphomas there are: chronic infections (i.e. *Helycobacter Pylori, Hepatitis C Virus, Campylobacter Jejuni, BorreliaBurgdoferi and Chlamydia Psitacci*) and autoimmune diseases (rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus and Wegener's granulomatosis) [6]. In the case of parotid MALToma, the main risk factor is related to the presence of a chronic inflammatory process such as Sjogren's syndrome [5]. A chronic stimulation of the immune system by autoantigens released from the primary inflammatory site, is at the basis of this mechanism [7]. According to some studies, Sjogren's syndrome can increase the risk of parotid lymphoma by about 44 times and, 80% of these, being represented by MALToma [8]. It total, a percentage between 4 and 7% of patients suffering from Sjogren's syndrome, would develop a MALToma [9].

In Sjögren's syndrome, an important sign of possible development of a parotid MALToma is the transition from an isolated glandular swelling related to a reactivation of the inflammatory process, that should be differentiated from an obstructive sialoadenitis [18] to a condition in which the swelling appears to be persistent [10].

Other signs of a possible transition to a MALToma could be the development of palpable purpura, vasculitis, renal impairment and peripheral neuropathy, especially if accompanied by other factors such as monoclonal gammopathy, reduced levels of C4 fraction, CD4 lymphocytopenia, increased IgG or crioglobulinemia[11]. Late signs, related to a more advanced stage of the disease, may include: bilateral parotid swelling, lateral-cervical lymphadenopathy, pain and paralysis of the facial nerve.

In addition to theclinical examination, the diagnosis is based on different techniques of diagnostic imaging (MRI / CT) associated or not with ultrasound guidedfine-needle ago biopsy biopsy(FNAB) of the lesion. However, the final diagnosis can be carried out exclusively by histological examination (as these techniques show specific radiological aspects of these lesions) [12].

First of all, it is needed to make a differential diagnosis with Warthintumor, pleomorphic adenoma, cystic adenoid carcinoma, mucoepidermoid carcinoma, adenocarcinoma and other initial forms of parotid tumors. Because thesetype ofcystic lesions, are also present at the level of parotid MALToma[5]. The CT and the MRI represent the two most frequently used radiological techniques, but out of the two, the MRI is preferable as it allows a better vision of the soft tissues; less frequently the PET-TC is used, while more often it is useful in staging the pathology rather than in the diagnostic phase [12]. On one hand, the radiological characteristics are often not specific; on the other hand, the FNAB may be useful since lesions non-MALTomarelated, have specific characteristics that allow excluding it. Therefore, the FNAB can exclude the presence of a MALToma but can hardly make a final diagnosis [13].

In this clinical case, the presence in the aspirate of red blood cells, leucocytes, amorphous eosinophilic deposits and epitheliomorphic cells, lacking in atypical characteristics, did not allow a final diagnosis. In fact, the diagnosis was made upon definitive histological examination accompanied by immunohistochemical evaluation of the tissue sample, obtained, in this case, after superficial parotidectomy.

The therapy of MALToma is multidisciplinary as it involves not only the surgical evaluation but also the haematological and radiological evaluation. The staging of the disease is fundamental for the correct therapeutic procedure (Table 1, Lugano review of the Ann Arbor staging) [14]. In diagnosed patients, presenting an asymptomatic clinical course, "watchful-waiting" can be adopted with close follow ups over time. In patients with suspected diagnosis, the first step is often an excisional biopsy by a superficial parotidectomy, if the mass is located at the superficial pole of the parotid; a total parotidectomy if it is located at the deep lobe of the parotid. Once the diagnosis is confirmed on histological examination, if it is limited to the parotid region, surgery can be completed by radiotherapy both in the case where the surgery was radical, but especially in cases where the margins of resection infiltrate the histological examination. In cases of disseminated disease, systemic treatments are needed, based on chemotherapy, biological therapy using rituximab, a monoclonal antibody directed against the CD20 antigen expressed at the level of the neoplastic cells, or combinations of the two[15]. In this last case, the most frequently used treatment is R-CHOP (rituximab-cyclophosphamide-doxorubicin-vincristine-prednisolone), performed every 3 weeks for 6/8 cycles during which a monitoring of drug-induced toxicity is performed by checking neutropenia, thrombocytopenia , renal and hepatic dysfunction and neurotoxicity [16]. When radiotherapy is required, doses of 24 Gray are administered for the low-grade forms and doses of 30 Gray for the high-grade forms [17]. Nevertheless, medical therapy in patients with parotid MALToma is still controversial today.

In 2014 Shum JW et el. described three cases of parotid MALToma: after the FNAB, non-specific in all three cases, the patients underwent surgical therapy and histological evaluation with the result of MALToma of the parotid. The patients were subsequently staged by PET-CT in stage I, stage II and stage III respectively according to the Lugano review of the Ann Arbor staging. The patient at stage I was treated with radiotherapy with a total dose of 30 Gray and followed up for the following 5 years with absence of recurrence. The patient at stage II was instead treated according to the R-CHOP protocol (rituximab-cyclophosphamide-doxorubicin-vincristine-prednisolone) for 3 cycles, followed by radiotherapy at a dose of 30 Gray.

At the end of this therapeutic protocol, the latero-cervical lymph-node secondarisms disappeared. The follow up at 1 year showed no recurrence. The patient at stage III was treated with the R-CHOP protocol for 6 cycles and continued treatment with rituximab for the next 2 years. In this case the follow up did not reveal a remission of the disease.

In a retrospective study published in 2014, 35 patients with Sjogren's syndrome and parotid MALToma were described, followed at the University Hospital of Groningen between 1997 and 2008: in 31% of the cases, the diagnosis of MALToma was carried out by parotid biopsy during a diagnostic investigation for suspected Sjogren's syndrome; in 51% of cases the diagnosis was performed by biopsy for suspected parotid tumor in patients with active Sjogren's syndrome and the presence of a persistent parotid swelling; finally, in 17% of cases the diagnosis was made in patients who initially presented only a parotid swelling. All 35 patients, with an age between 26 to 84 years, underwent diagnostic biopsy and staging using CT or MRI; only 11% of these had advanced pathology (stage III / IV).). According to the staging, 10 patients were monitored by watchful waiting as they presented a totally asymptomatic pathology, five were submitted to parotidectomy, two of these continued therapeutic procedures by radiotherapy, and only one patient underwent radio-therapy alone. Thirteen patients were treated with rituximab alone and six with R-CP combined therapy. The follow-up at almost 76 months, of diagnosis of Maltoma related Sjogren syndrome, showed the progression or recurrence of the disease in 10 out of 35 patients, four years after diagnosis, two of which were part of the group watchful-waiting.

Stage	*Involvement*	*Extranodal Status (E)*
Limited		
I	One node or a group of adiacent nodes	Single extranodal lesions whitout nodal involvement
II	Two or more groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky *	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additionalnoncontiguosextralymphaticinvolvement	Not applicable

Table 1. Revision of Ann Arbor Staging (Lugano Guidelines 2014).

Note: Extent of disease is determined by positron emission tomography-computed tomography for avid lymphomas and computed tomography for non-avid histologies. Tonsils, waldayer's ring and spleen are considered nodal tissue.

* *Whether stage III bulky disease is treated as limited or advanced disease may be determined by histology and number of prognostic factors*.

4. Conclusions

The primary lymphoma of the parotid may be considered a rare disease but its incidence increases in the presence of predisposing conditions, such as Sjogren's disease. Most parotid lymphomas develop from a slow-growing indolent swelling. In addition to a careful clinical-anamnestic evaluation, the diagnostic procedure includes a radiological evaluation through MRI / CT. However, FNAB is essential before the correct therapeutic procedure is started in patients presenting with parotid swelling. Although FNAB allowsidentifying the nature of most of the parotid lesions, the presence of a non-diagnostic result should lead to a diagnosis of MALT type parotid lymphoma.

The final diagnosis of MALToma, however, can only be obtained with a histological investigation performed after the removal of the gland. Once the nature of the lesion has been identified, it is possible to continue the therapy with chemo / radiotherapy or therapy with monoclonal antibodies according to the stage of the pathology.

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