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BRIEF COMMUNICATION

Primary Non-Hodgkin Lymphoma of the parotid gland: Revision of 8 cases

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KEYWORDS
Non-Hodgkin lymphoma;
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Abstract
The manifestation of non-Hodgkin lymphoma as a primary parotid tumour account for 5%of all tumours at this location.
We present 8 patients diagnosed and treated for parotid non-Hodgkin lymphoma in our hospital between 1996 and 2003. Of the cases, 62%were women who had an indurated mass for almost 4 months. A fine needle aspiration and computed tomography were performed on all patients. The immunohistochemical study provided us with the definitive diagnosis. Biopsy was done in all cases. The treatment was chemotherapy in 75%cases and surgery in 25%
The objective was to analyse the clinical and pathological patterns, plus the different treatment modalities and prognoses, which characterise this type of pathology based on the analysis of our patients and compared with those reported in the literature.

PALABRAS CLAVE
Linfoma no Hodgkin;
Glándula parótida;
Quimioterapia

Linfoma no Hodgkin primario de la glándula parótida: revisión de 8 casos

Resumen
La manifestación de un linfoma no Hodgkin como tumor primario de la parótida representa el 5% de los tumores en esta localización.
Se presentan 8 pacientes diagnosticados y tratados de linfoma no Hodgkin parotídeo en nuestro hospital entre 1996-2003. El 62% eran mujeres que presentaban una masa indurada de 4 meses de evolución. En todos los casos se realizó una punción aspiración con aguja fina y una tomografía computerizada siendo el estudio inmunohistoquímico esencial en el diagnóstico definitivo. Para ello, se realizó en todos los casos una biopsia. El tratamiento fue con quimioterapia en el 75%de los casos y en el 25%quirúrgico.

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El objetivo es analizar los patrones clínicos y patológicos, así como las distintas modalidades terapéuticas y pronósticas, que caracterizan a este tipo de patología basándonos en el análisis de nuestros pacientes y comparándolos con los reflejados en la literatura.

Introduction

Parotid lymphomas represent 0.3% of all malignant tumours of the organism. Of these, 85% are non-Hodgkin lymphomas (NHL).[1]

Regarding their pathogenesis, a relationship was found with a state of chronic glandular infection known as chronic immune sialadenitis. In addition, bilateral glandular hypertrophy, called Mikulicz syndrome, which is characteristic of Sjögren syndrome, presents an incidence of parotid gland lymphoma up to 40 times higher than in the rest of the population.[1] It has also been described in the evolution of benign lymphoepithelial lesions.

The most common histological type is low grade, mucosa-associated lymphoid tissue (MALT) type NHL, but this may evolve in a highly variable interval (from months to 29 years) into a high grade B cell NHL.[2]

Diagnosis is carried out after biopsy of the lesion, which includes complete tumour removal in all cases. The anatomopathological and immunohistochemical studies are essential in characterising the lesion. Standard treatment is chemotherapy and radiotherapy, with a better prognosis than other lymphomas of the head and neck.[3]

The aim of this study is to analyse the clinical and pathological patterns, as well as the different therapeutic and prognostic modalities, that characterise this type of pathology based on analysing our patients and comparing them with those reported in the literature.

Material and method

We reviewed parotid NHL cases diagnosed and treated at our hospital during the period between 1996 and 2003 with a minimal follow-up time of 21 months.

Clinical-pathological data were collected for the identification process. These included age, gender, associated diseases, mode of presentation, diagnostic methods, CT, MRI, FNA, biopsy (enucleation after locating the facial nerve), immunohistochemical study (CD3,5,20,43,79 and Bcl2), prognostic and tumoral markers (b-2 microglobulin, IPI[4]), classification (Working Formulation and Ann Arbor),[5] treatment and outcome.

Data processing was performed using the Microsoft Excel 2007 program.

Results

In the study period we diagnosed 8 cases of primary NHL of the parotid gland.

There was a predominance of females, 5/8 (62.5%). The mean age was 74 years (range 52-85 years).

The most common reason for consultation was the appearance of a painless hard mass, of a mean size of 2.8cm, with progressive growth in the parotid region. The mean period of growth of the lesion was 3.93 months (range 1-8 months); in 87.5% of cases it was found in the left parotid. Exploration of the 8th cranial nerve was normal in all cases. Up to 50% (4/8) of patients presented associated underlying diseases (Table 1).

Contrast-enhanced CT was performed on all patients. Findings included moderately enhanced attenuation masses, with poorly defined edges, and lymphadenopathy in 37.5% (3/8), 2 at a systemic level, and 1 in the parotid region.

MRI was performed in only one case. That lesion suggested malignancy in the scan image.

In the 8 patients, FNA was consistent with a lymphoproliferative process and biopsy, supported by immunohistochemical studies, provided a definitive

Table 1 Summary of cases

Case	Associated diseases	Histological classification	Ann Arbor	FNA	Surgery	CHOP-R
Case 1	Sjögren SD	Low-grade B-cell NHL	IIE	LP	Biopsy	Yes+RT
Case 2	Hashimoto thyroiditis	MALT B NHL	IE	LP	Biopsy	Yes
Case 3	Waldeström's disease	High-grade B-cell NHL	IIE	LP	Biopsy	Yes
Case 4	NHL orbit, lip	High-grade B-cell NHL	IIIE	LP	Biopsy	Yes+RT
Case 5		High-grade B-cell NHL	IE	LP	Biopsy	Yes+RT
Case 6		MALT B-cell NHL	IE	LP	Superficial parotidectomy	No
Case 7		MALT B-cell NHL	IE	LP	Superficial parotidectomy	No
Case 8		Follicular NHL	IE	LP	Biopsy	Yes

Biopsy indicates enucleation after locating the facial nerve; CHOP-R, cyclophosphamide, hydroxyl daunomycin, Oncovin (vincristine), prednisone and rituximab; FNA, fine needle aspiration; LP, lymphoproliferative process; NHL, non-Hodgkin lymphomas; RT, radiotherapy.

diagnosis. All the MALT B cell NHL were positive for CD20 and CD79 markers, and one further case was also positive for CD43. The 3 cases of high-grade B cell NHL were positive for CD20 and CD79 markers, and 2 of them were positive for CD5, CD43, and Bcl2 (Figures 1-2).

The proliferation index obtained was low, with a range of 5%9% The exception was high grade B cell NHL, where the index reached a range of 25%90%

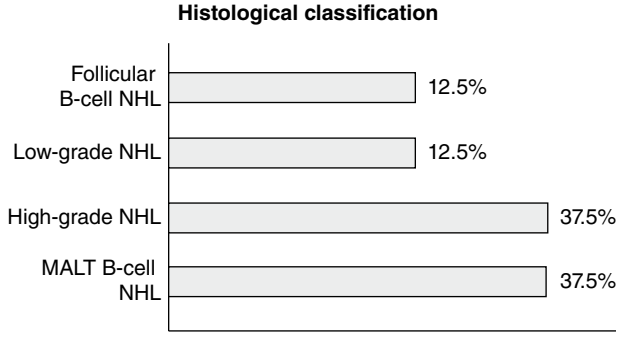

Figure 1 Incidence obtained in our series using the WHO and the Working Formulation histological classifications.

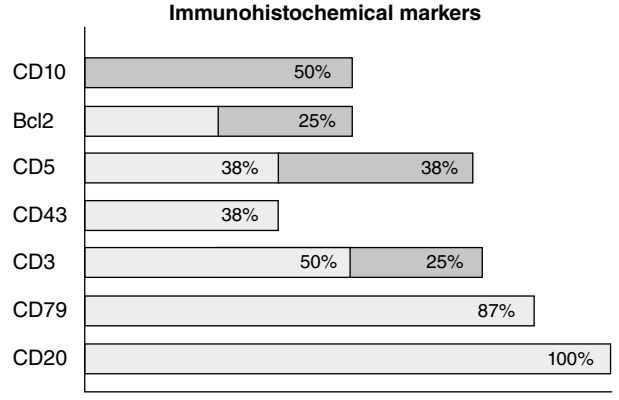

Figure 2 Immunohistochemical markers (the % of positive markers is shown in light grey and the negative in dark grey). MALT B-cell NHL: all CD20+, 79+ and 1 case 43+. High-grade B-cell NHL: all CD20+, 79+, 3+, and two CD5+, CD43+ and Bcl2+.

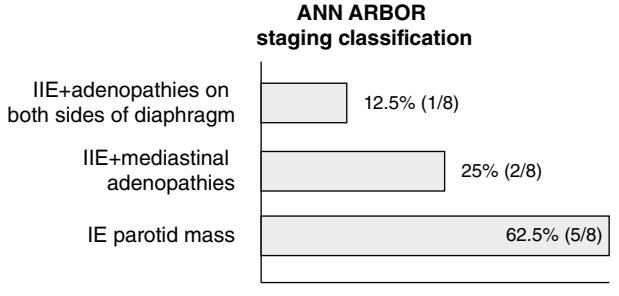

Figure 3 Ann Arbor extension classification.

Table 2 International Prognostic Index (IPI)

Prognostic factors	%
Older than 60 years	87.5
Elevated LDH values	0
Extranodal affectation	37.5
Karnofsky index higher than 70%	25
Ann Arbor stage III or IV	12.5

We used the Ann Arbor classification to assess the extension (Figure 3) and the International Prognostic Index to identify the prognostic factors (Table 2). In 25%of the patients, high levels of the beta 2 microglobulin marker were found.

A biopsy was performed as the diagnostic method (enucleation after locating the facial nerve) in 75% (6/8) of cases. In these, the intraoperative study reported a lymphoproliferative process compatible with lymphoma. In the 2 remaining cases, the intraoperative study was inconclusive; we consequently performed a superficial parotidectomy. These 2 cases were finally diagnosed with MALT B cell NHL.

Up to 75% (6/8) of cases were treated with CHOP-R (cyclophosphamide, hydroxyl daunomycin, Oncovin [vincristine], prednisone and rituximab). Radiation therapy was added in 3 patients, according to criteria of advanced age, systemic spread and high histological grade (1/3 high histological grade; 1/3 stage IIE; 1/3 stage IIE plus high histological grade).

Discussion

Parotid NHL accounts for 5%of extranodal lymphomas and 2.5% of salivary gland tumors.[1] Low-grade cases are the most common in this location, although the MALT type can undergo a transformation into high-grade diffuse large B-cell NHL cases.[2]

They are most often diagnosed at advanced ages (60-80 years) and do not have a tendency for either gender.[6] However, as in our series, some authors indicate a female preponderance.

In general, its aetiology remains unknown. It is related to chronic sialadenitis, autoimmune diseases and other benign lymphoepithelial lesions.[2,7]

As with any tumour in this location, since the presentation mode is indistinguishable from other parotid tumours, a fine needle aspiration (FNA) should be performed. In our cases, they suggest the lymphoproliferative nature of the lesion.[8] Once this diagnosis is obtained, there must be an investigation of the presence of cervical or systemic lymphadenopathy and the coexistence of autoimmune processes, which are documented in the literature reviewed in up to 44% of cases.[7]

An additional diagnostic method that must be used is an imaging technique, since MRI increases the sensitivity and specificity of FNA with regard to NHL to 100%-88%, respectively.[9] As to whether it is better to carry out an MRI or a CT, the former is probably ideal because it can differentiate soft tissue better. At our hospital, there is better access to the use of a CT and it is therefore our first choice. In case of

doubt or if we believe the tumour to be a malignant case of another cell lineage, it is interesting to perform an MRI. In fact, as previously discussed, the final diagnosis is determined via anatomopathological examination of the lesion: imaging studies are an aid for surgery planning, helping to distinguish the location of the lesion and if it is encompassed in the deep or superficial parotid.

Some features of the CT image (such as cases of bilateral disease, multiple masses, lymphadenopathy or a tumour with poorly defined edges) suggest a lymphoma, although they cannot rule out other processes.[6,9]

Positive immunostaining with C10 and Bcl6 confirms the diagnosis of follicular lymphoma. MALT lymphoma cells express B antigens (CD20, CD79a), IgM, and positivity for Bcl2; they are negative for CD5, CD10, CD23, cyclin D1 and IgD and positive for CD21 and CD35.[10]

Knowing the histological type, as well as the extent and pattern of disease is essential in selecting the correct treatment, as there is a clear correlation with survival.[1] The Working formulation[5] and the Ann Arbor grading modified by Mushoff are used for histological classification to assess the extension.[5] In our review, we found most incipient cases in stage IE. Most of these patients with primary extranodal NHL and localized disease were treated with curative intent: good local control was obtained with radiotherapy, as well as a 5-year survival of 70%80%[11]

The use of combination therapy should be assessed in intermediate and high-grade lymphomas, depending on the prognostic factors: tumour burden, B symptoms (fever, night sweats and weight loss greater than 10%), high LDH levels and anatomical extension of the disease.[2]

A clonal similarity has been identified between lymphoepithelial lesion in the parotid and MALT lymphoma in the gastrointestinal tract, which in early stages is treated with conservative surgery followed by chemotherapy.[12]

Up to 75% of patients in this series received CHOP-R, with a complete response in all cases. The 2 patients who underwent a superficial parotidectomy to confirm the diagnosis did not receive subsequent chemotherapy because their cases were low-grade MALT NHL in stage I.[2] A total of 87.5% of patients were alive and free of disease, with a minimum follow-up time of 21 months.

These results are included within the heterogeneity found in the literature. Thus, Tiplady in 2004[7] describes a 54% survival at 5 years with an average follow up time of 90 months, and Sarris in 1997 presents a survival rate of 76% with an average follow up time of 36 months[7]

Patients with low-grade NHL of the parotid gland have an excellent prognosis, given by the slow development and the low aggressiveness of the disease as well as by its good response to current chemotherapy treatments.

Conflict of interest

The authors declare no conflict of interests.

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