An unusual case of parotid gland B-cell lymphoma complicating Sjögren Syndrome

Un caso inusual de linfoma de células B de la glándula parótida a complicar el Síndrome de Sjögren

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ABSTRACT

Sjögren Syndrome is a multisystemic autoimmune disease that is heterogeneous in its presentation, course and outcome. There is no single clinical, laboratorial or radiological feature that serves as gold standard for the diagnosis and/or classification of this syndrome. The occurrence of lymphoma is known to be one of the most severe complications. We report a case of a 66-year-old female diagnosed with Sjögren Syndrome secondary to systemic lupus erythematous that presented with an enlargement of the left parotid gland consistent with the diagnosis of lymphoma confirmed with biopsy. She received chemotherapy with favorable response and today is asymptomatic with hydroxychloroquine 400mg id. This case report highlights the importance of optimal interventions and active surveillance of Sjogren Syndrome, in order to achieve an early identification of its complications and to prevent worse outcomes of this disease.

Keywords: Sjögren Syndrome, B-cell lymphoma, parotid gland, biopsy

INTRODUCTION

Sjögren syndrome (SS) is a multisystemic autoimmune disease characterized by lymphocytic infiltrates of the exocrine glands leading to loss of secretory function with dryness of the main mucosal surfaces[1]. It's associated with the production and secretion of autoantibodies, related to a consistent immunoregulatory abnormality of B-cell activation[2,3]. The association of SS with Systemic Lupus Erythematous (SLE) was mentioned for the first time in 1959 and it has been reported with a rate of 9-31%, what seems to be related to the difficulties in achieving the diagnosis of both diseases and the different criteria used for that purpose[4].

A multidisciplinary approach is usually required for the diagnosis of SS. Although the disease is usually benign, the majority of individuals have only sicca symptoms, systemic manifestations can occur, with accountable mortality and morbidity, mainly related to extraglandular involvement and haematological cancer[1,2,5,6].

The prompt diagnosis of SS and the acknowledgement of its severe complications allow an early therapeutic intervention in order to slow down the progression of a benign to malignant lymphoproliferation.

CASE PRESENTATION

We describe the case of a 66-year-old female who was referred to our hospital owing to enlargement of the left parotid gland. She had complaints of xeropthalmia and xerostomia for the last 3 years, associated with inflammatory polyarthralgias without arthritis. Photosensitivity was also present as well as malar rash with sun exposure. She denied any other constitutional symptoms or relevant medical, family, and psychosocial history. The physical exam was unremarkable except for a diffuse enlargement of left parotid gland that had developed in the past year. There were no associated preauricular, submandibular or cervical enlarged lymph nodes or masses.

Laboratory analysis were done revealing significant alterations, namely leucopenia (3.53 x 10^3/UL), anti-nuclear antibody (ANA) positive (1:1280; fine speckled pattern), anti-Ro/SSA (614 U/mL) and anti-La/SSB (137 U/mL) positive and low complement levels, C3 0.896 g/L (N 0.90 – 1.80g/L) and C4 0.060 g/L (N 0.1-0.4g/L). Anti-double stranded DNA was negative (9.7 UI/mL; negative < 10 UI/mL) (Table 1). The parotid gland scintigraphy identified a marked functional compromise of both parotid and submandibular salivary glands that had decreased response to the secretory stimulus. In the light of these findings, the diagnosis of SS secondary to SLE was confirmed and the patient started treatment with hydroxychloroquine 400mg and prednisolone 7.5mg once daily. After 6 months there was resolution of the sicca symptoms and of the parotid gland enlargement.

Two years after the diagnosis, in a regular visit, she complained of odynophagia and trismus and had a new enlargement of the left parotid gland with preauricular and infra-auricular

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Table 1. Laboratory routines during follow up. Legend: ANA – anti-nuclear antibody, dsDNA - double-stranded DNA, Hb – hemoglobin, LDH - lactate dehydrogenase, Leuk – leukocytes, Neut – neutrophils, Lymph – lymphocytes, Plat – platelets, R – CVP - Rituximab – Cyclophosphamida-Vincristine-Prednisone, RF – rheumatoid factor.

	1st Appointment	2nd Appointment (hydroxychloroquine 400mg id and Prednisolone 7.5mg id)	After 2nd cycle R-CVP	After last cycle R-CVP
Hb (12-16 g/dL)	14.6	15.0	12.8	12.9
Leuk (4-10 x 103 /UL)	3.53	4.8	4.84	6.82
Neut (2-7 x 103 /UL)	1.79	2.38	2.6	4.91
Lymph (1-63 x 103 /UL)	1.16	1.69	1.37	1.19
Plat (150-400 x 103 /UL)	222	216	195	204
C3 (0.90 – 1.80 g/dL)	0.896	0.958	-	-
C4 (0.1-0.4 g/dL)	0.06	0.082	-	-
ANA's (N<1:160)	1:1280	-	-	-
dsDNA (N<15.0))	9.7	-	-	-
Anti – Ro/SSA (N<10)	614	-	-	-
Anti – La/SSB (N<10)	137	-	-	-
LDH (313-618 U/L)	637	491	486	571
B2 microglobulin (1.09-2.35 mg/L)	-	2.22	-	-
RF (N<15 UI/mL)	32.4	-	-	-
Monoclonal gammopathy	Negative	Negative	-	-

distribution, with roughly 6x7cm, non-mobile and of hard consistency (Figure 1). Two cervical ipsilateral enlarged lymph nodes were observed. A computed tomography (CT) of the neck was performed, revealing a bulky mass in the left parotid gland suggesting malignancy. The biopsy of the parotid gland confirmed the suspected diagnosis of B-cell non-Hodgkin Lymphoma (NHL) – MALT type (Figure 2). Chemotherapy with Rituximab–Cyclophosphamide-Vincristine-Prednisone (R-CVP) was initiated, for a total of 8 cycles. After 10 months, a control neck CT showed normal morphology and dimensions of the left parotid gland. The patient remained asymptomatic for 6 years, medicated with hydroxychloroquine 400mg once daily. There was no evidence of malignancy relapse after stopping chemotherapy.

DISCUSSION

SS is one of the 3 most common systemic autoimmune diseases, along with rheumatoid arthritis and SLE[2]. It is unclear whether SS associated with another autoimmune rheumatic disease represents a distinct overlapping entity or a manifestation in the clinical spectrum of the concomitant rheumatic disorder[7]. Therefore, the expression of SS that coexists with SLE needs to be further addressed.

SS is a good example of a crossroad between autoimmunity and malignant transformation, given the high risk of developing lymphoma. Occurrence of lymphoma is known to be one of the most severe complications of SS, being equivalent for both primary and secondary SS and is estimated to be 10 to 44 times greater than that observed in a comparable normal population[5,6]. B-cell NHL occurs in approximately 5% of the patients[8]. Lymphomagenesis in the setting of SS is considered as a multifactorial process which is not fully understood but there are some clinical features which have been identified has adverse predictors for its development[2,6] (Table 2). In this case, the enlargement of parotid gland was unilateral, fixed and of hard consistency (Figure 1). Even though B symptoms were absent, the presence of cervical lymph nodes occurred later in the course of the disease. Skin involvement was not observed, but when present, is usually linked with cryoglobulinemia. In terms of laboratory findings, the patient had low C3 and C4. Although rare, bone marrow involvement can be present and was excluded.

The therapeutic approach must be adapted to each case. In localized low-grade lymphomas affecting only the exocrine glands, a watchful policy can be an option. However, in order to prevent transformation into a more aggressive type of lymphoma, chemotherapy may be justified[2]. In this case, taking into account the large dimensions of the parotid gland

Table 2. Main classical clinical and paraclinical predictive factors of lymphoma development. Legend: GC – germinal center, RF - rheumatoid factor. The predictive factors present in our patient are in bold.

Clinical predictive factors	Paraclinical predictive factors
Permanent swelling of salivary gland	Cryoglobulinemia
Adenopathy	Lymphopenia
Purpura	Low C4
Raynaud phenomenon	Anti SSA and/or SSB positivity
	RF positivity
	Monoclonal gammopathy
	GC -like structures within salivary gland

Figure 1. Diffuse enlargement of left parotid gland, with preauricular and infra-auricular distribution (6x7cm), hard consistency and immoveable.

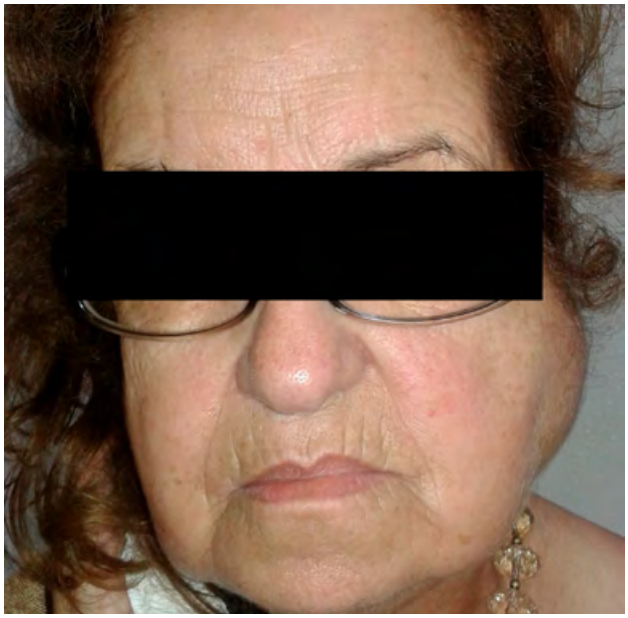
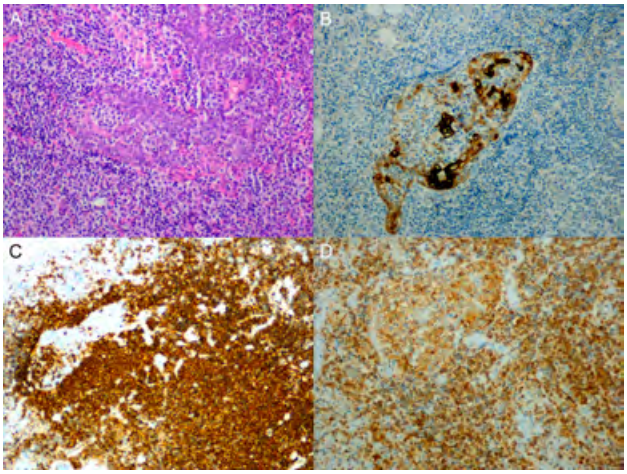


Figure 2. Biopsy of the left parotid gland. A: Hematoxylin-Eosin staining; x200 - Population of lymphoid cells with clear cytoplasm that distort and destroy the glandular/ductal epithelium, compose the lymphoepithelial lesions (B-cell non-Hodgkin Lymphoma – MALT type); B: CK CAM5.2; x200 - Epithelium penetrated by unlabeled lymphoid cells; C: x200 - Lymphoid cells have phenotype B and are CD20 +; D: x200 - Lymphocytes are bcl2 +.



and the involvement of regional lymph nodes, the patient initiated chemotherapy. The best regimen is the combination of rituximab with either alkaline agents (cyclofosfamide/chlorambucil), fludarabine or bendamustine. R-CVP was chosen for this patient with a favorable outcome.

There is no consensus on follow-up of these patients and the strategy should be adapted to the disease activity[2].

SS is a slowly progressive disease with benign course and a negligible mortality. The exception is the evolution of lymphocytic infiltrate in the exocrine gland to an overt lymphoma, comprising a worse prognosis with higher mortality. A close follow-up of the patient is indicated and the active search for risk factors should be included in the management of every case. The management of disease activity should be a primary objective in order to minimize the chronic B-cell stimulation, decreasing the risk of developing lymphoma.

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