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CASE REPORT

Hodgkin lymphoma as a complication of primary Sjögren's syndrome

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Abstract Sjögren's syndrome (SS) is a chronic autoimmune disease that is characterized by lymphocytic infiltration of the exocrine glands, mainly the salivary and lachrymal glands, usually manifesting with xerostomia and xerophthalmia. Around 50% of patients with primary SS develop systemic complications, lymphoma being the most feared of these. The majority of these neoplasias originate from B cells and are of the non-Hodgkin type. We describe here a rare case of SS in which the patient developed a Hodgkin lymphoma. We also review the literature on this subject.

Keywords Hodgkin lymphoma · Sjögren's syndrome

Introduction

Sjögren's syndrome (SS) is a chronic, inflammatory autoimmune disease that is characterized by focal and progressive lymphocytic infiltration of the exocrine glands and other extraglandular structures. It preferentially affects the salivary and lacrimal glands, inflicting structural harm to these organs that results in secretory dysfunction [1]. Dryness of the eyes (xerophthalmia leading to keratoconjunctivitis sicca) and mouth (xerostomia) constitute the typical clinical condition of the syndrome.

A particular concern in SS is the possibility of developing lymphoproliferative disease, in this context, the risk of developing lymphoma is 40–44 times greater than it is in the general population [2–4]. It is estimated that 4–10% of cases of SS will present this complication [2, 3, 5–7].

The onset of lymphoma is signaled by a persistent increase in the parotid gland, regional or generalized lymphadenopathy, hepatosplenomegalia, pulmonary infiltrate, vasculitis, hypogammaglobulinemia and negativation of the rheumatoid factor [8]. Malignant lymphoproliferative disease may appear at the onset of lymphoma or later during the course of the syndrome, with non-Hodgkin lymphomas (NHL) being the commonest form of presentation [3, 4, 7].

The association of Hodgkin lymphoma (HL) with SS has been described only rarely [9–12]. This neoplasia is characterized by the presence of giant cells, denoted Reed–Sternberg cells (RS), which originate from B lymphocytes from the germinative centers [13]. The aim of our study was to describe a rare case of SS in a patient that developed a Hodgkin lymphoma and to review the literature on this subject.

Case report

The patient, a 47-year-old woman, had been diagnosed with primary SS since the age of 32, based on the presence of xerostomia, xerophtalmia, vaginal dryness and recurrent episodes of parotid gland enlargement. This diagnosis was supported reinforced by the presence of antinuclear antibodies (ANA) on HEp2 slides, as evidenced by a 1/320 fine speckled pattern, positivity for anti-SSA and anti-SSB antibodies, as detected by enzyme-linked immunosorbent

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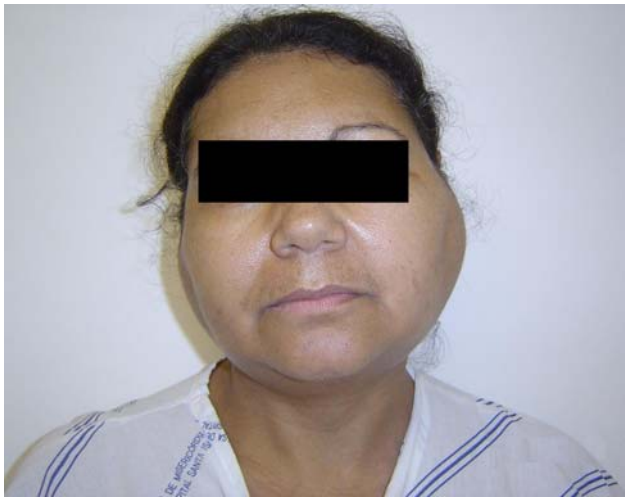

Fig. 1 Significant increase in the size of the parotid glands in a patient with primary Sjögrens syndrome who developed Hodgkin lymphoma

assay (ELISA), rheumatoid factor (latex) 1/16 and polyclonal hypergammaglobulinemia. The sialography was compatible with bilateral chronic sialodenitis, non-obstructive chronic sialectasia and a cavitary pattern, together with a loss of parotid gland architecture: globules coalescence became irregular with dilatation of the ducts [14].

During the past 2 years the patient started to complain of fever, an extreme increase in both parotids with local inflammatory signs (Fig. 1), peripheral neuropathy in the lower limbs, which was confirmed by electroneuromyography, and a painful enlargement of the cervical and axillary lymph nodes. Computerized tomography (CT) of the cervical region revealed submandibular lymph nodes to the right with anterior jugular and spinal accessory chain, the CT of the thorax showed infracarinal lymph nodes, and the CT of the abdomen revealed periaortic lymph nodes. An initial axillary lymph node biopsy showed an unspecific inflammatory process. The serology for several infectious diseases, including toxoplasmosis, cytomegalovirus and mononucleosis, was negative, with the exception of the presence of immunoglobulin G (IgG) for Epstein–Barr virus (EBV), as determined by ELISA.

The administration of low-dose prednisone and hydroxichloroquine resulted in partial improvement of the symptoms. Six months later, there was recurrence of the symptoms, and a new lymph node biopsy revealed lymphoid neoplasia with histiocytic mononuclear cells that were positive for CD30, as shown by immunohistochemistal tests, suggesting Hodgkin lymphoma (mixed cellularity). The majority of the cells were also positive for CD20 but negative for CD3, CD15, LCA, CD10, CD45RO and EBV (Fig. 2).

The patient was given a standard regimen of chemotherapy treatment—ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). The HL and SS symptoms improved, but a new lymph node has recently appeared close to her left parotid gland. This will be biopsied.

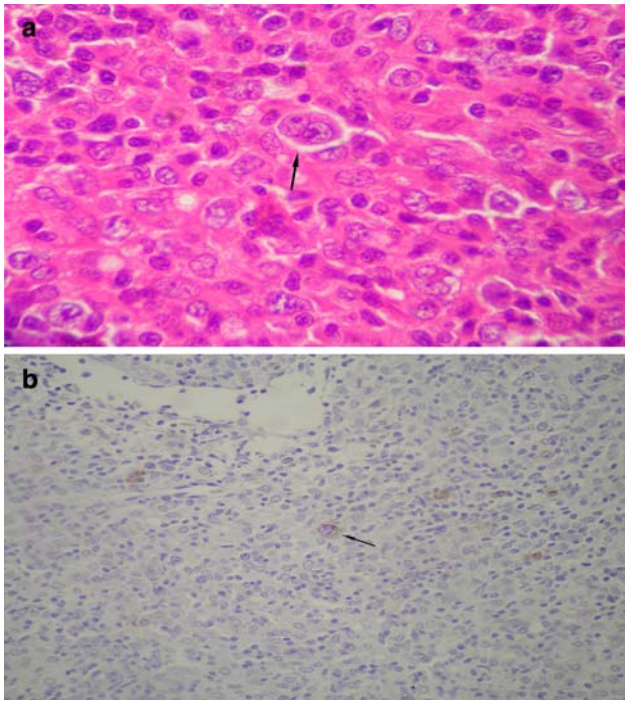

Fig. 2 **a** Histopathology of lymph node (hematoxylin–eosin) showing Reed–Sternberg cells (*arrow*) indicative of Hodgkin lymphoma. **b** Lymphoid neoplasia with histiocytic mononuclear cells (*arrow*), positive for CD30, as determined by immunohistochemical staining, suggesting Hodgkin lymphoma (mixed cellularity)

Discussion

Lymphoma was described for the first time in patients with SS in 1951 [15]. Since then, many cases have been reported that show a link between the two disorders, and lymphoproliferation is now considered to be the main complication in the progression of the syndrome [3, 16]. Ioannidis et al. [16], in a study of 723 patients with SS, reported that in approximately every five deaths of patients with SS, one was caused by lymphoma.

The high risk for these neoplasias suggests that it is a consequence of chronic lymphocytic activation related to the autoimmune disease process [17]. Lymphoepithelial lesions are considered to be the origin of malignant transformation. In these areas, activated epithelial cells express human leukocyte antigen (HLA) and co-stimulatory molecules, making them capable of presenting antigens and activating the T lymphocytes, which in turn stimulate the B lymphocytes. This interaction between epithelial cells and T and B lymphocytes allows these cell groups to survive in the lesion, thereby avoiding apoptosis [6]. The transformation into the

malignant state progresses in various stages, mainly affecting the B lymphocytes, whose initial polyclonal activation may lead to the selection of some clones that later proliferate out of control [4]. However, although the great majority of lymphoid neoplasias develop from B lymphocytes, T cells lymphomas in SS have also been described [11].

In a histochemical study, Navarro et al. [12] identified the presence of EBV markers, including LMP1, in tumor cells of patients diagnosed with primary SS that afterwards developed HL. Therefore, there is strong evidence that relates EBV with the induction of SS and lymphoproliferation, thereby demonstrating a common etiology between the two diseases. Although our patient presented serological (IgG) evidence of EBV, indicating a previous infection by this virus, this result does not necessarily establish a causal relation, since this situation is frequently found in the normal population. Moreover, during the development of HL, our patient showed not evidence of EBV re-activation, and the immunohistochemical analysis was negative for EBV antigen.

Classically, the appearance of lymphoproliferative process in patients with primary SS could be preceded by a fall in the rheumatoid factor and gamma globulin [18, 19]. Curiously, our patient maintained positivity of the rheumatoid factor even after the appearance of HL, as well as a persistent polyclonal hypergammaglobulinemia.

We were able to only identify five cases of HL secondary to SS in the literature. All of the patients reported were women, and the mean age at the time of HL diagnosis was 56.5 years. The mean time of SS evolution until the development of the neoplasia was 13 years [9–12]. In accordance with the revised version of the European Criteria for Sjögreńs Syndrome 2002, our patient presented with ocular and oral symptoms, salivary gland involvement and autoantibodies [20]. The diagnosis of HL was established in this patient at 45 years of age, after 13 years of evolution of SS. In terms of the prognosis of the patients reported in the literature, two died due to recurrence of the disease [11, 12], and one evolved with complete remission of the neoplasia [11].

Although the correlation between primary SS and HL has not been established completely, one must be alert to the fact that the risk of developing this neoplasia may be higher in patients with the former clinical condition. From the small number of cases described in the literature, it has not yet been defined whether HL in such patients predicts a different prognosis to that seen in patients without SS. Therefore, it is necessary to monitor patients with SS for the onset of HL, and prospective studies are necessary to define its prognosis.

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