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CLINICAL COMMUNICATION

Hodgkin's lymphoma of the thyroid in a woman with autoimmune thyroiditis

Linfoma Hodgkin de tiroides en una mujer con tiroiditis autoinmune

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Introduction

Autoimmune thyroiditis is associated with the development of thyroid lymphoma, and in particular mucosa-associated lymphoid tissue (MALT) lymphoma,[1] though this type occurs in only 0.5% of cases.[2] It has been reported that 20–30 years are needed for a lymphoma to develop as a result of autoimmune thyroiditis.[3] The association between thyroiditis and Hodgkin's lymphoma (HL) is more questionable, and is difficult to clarify due to the low number of cases of HL that arise. Nevertheless, in a previous study of 21 HL patients, 7 presented autoimmune thyroiditis.[4] The hypothesis of an association between the two conditions is based on the fact that the thyroid gland does not contain native lymphoid tissue; therefore, intrathyroid lymphoid tissue develops because of the presence of autoimmune thyroiditis. In this context, antigenic stimulation of lymphocytes in autoimmune disorders may trigger a malignant transformation. Primary extranodal HL accounts for less than 2% of extranodal lymphomas[2] and usually occurs due to the spreading of a contiguous lymphatic ganglion or hematogenous dissemination. It is questionable whether this is actually a primary disease, as it usually has an extrathyroid origin. Moreover it is considerably infrequent, with only 37 cases reported until now in the literature.[3] Its diagnosis is confirmed by the presence of Reed–Sternberg cells. We report the case of a patient with autoimmune thyroiditis with a fast-growing thyroid nodule. No evidence was detected of another tumor foci or adjacent lymphadenopathy, which led us to consider a diagnosis of primary thyroid gland HL. The peculiarity of this case lies in that, despite suffering autoimmune thyroiditis, the patient developed HL rather than MALT lymphoma, which is the usual clinical course in such cases.

Patient

A 54-year-old woman was monitored for subclinical autoimmune hypothyroidism with anti-peroxidase antibodies 2933.70 U per mililiter. At the time, she was receiving treatment with 75 μg per day of levothyroxine. Her thyroid function was controlled with TSH 1.90 μIU per mililiter and T4 free 1.3 ng per deciliter. The patient had no family history of thyroid pathology and no personal history of toxic substance abuse. During her initial visit, her cervical

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palpation was found to be normal, and a thyroid ultrasound scan revealed a solid left thyroid nodule with a maximum diameter of 9 mm that was hypoechoic, clearly defined, avascular and without calcification. According to current guidelines of clinical practice,[5] fine needle-aspiration biopsy (FNAB) was not indicated. Ultrasound was scheduled one year later and revealed no significant changes. Three years later, the thyroid lesion began growing rapidly, demonstrating a palpable thyroid nodule with a maximum diameter of 2 cm. Ultrasound revealed an increase in the size of the nodule to 17.8 mm × 22.6 mm, and showed it to be solid, occupying practically all the left thyroid lobe, hypoechoic, unstructured and heterogeneous, with mixed vascularization and without microcalcifications (Fig. 1).

In response to these developments, FNAB was carried out and revealed atypically large and multinucleate lymphocytes with features of Reed–Sternberg cells, which raised suspicions of lymphoma (Fig. 2). Given the difficulty in distinguishing between inflammatory and lymphoproliferative processes (especially MALT-type LNH) in a patient with autoimmune thyroiditis, it was decided to repeat FNAB with flow cytometry. Atypical lymphocytes were observed once again, but there was no sign of infiltration due to lymphoma ($CD3^+$ T lymphocytes were observed in 48%, of which 73% were $CD4^+$ and 22% were $CD8^+$; 44% were polyclonal $CD19^+$ B lymphocytes without evidence of immature cells). In light of these results, a biopsy was carried out (left hemithyroidectomy) to confirm a suspected thyroid HL. The intraoperative biopsy suggested autoimmune thyroiditis without any evidence of lymphoma. The definitive pathological anatomy study revealed classic HL of a nodular sclerosis type in the presence of autoimmune thyroiditis, with no apparent affect on the cervical lymph nodes. Immunohistochemistry of Reed–Sternberg cells produced the following results: $CD15^+$ $CD30^+$ $CD20^+$ (weak expression), $CD79a^-$, $MUM1^+$ $PAX5^+$ and $EBER^+$. A gene rearrangement study of T cell receptor (TCR) genes and immunoglobulin heavy chain (IgH) antibodies was carried out by means of quantitative polymerase chain reaction (PCR), whose result was negative. A fluorescence hybridization in situ (FISH) study for MALT-1 produced negative results. A positron emission tomography–computed tomography (PET–CT) scan of the cervicothoracic area, abdomen and pelvis was performed and revealed no hypermetabolic foci suggestive of active tumor disease. Thus, a diagnosis of primary thyroid gland LH (Ann Arbor Stage Ie) secondary to autoimmune thyroiditis was confirmed. As a consequence, ABVD (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) chemotherapy was initiated. It is now 8 months since surgery and the patient has completed four ABVD cycles. A recent PET–CT scan revealed no hypermetabolic foci suggestive of active tumor disease, therefore pointing to complete remission.

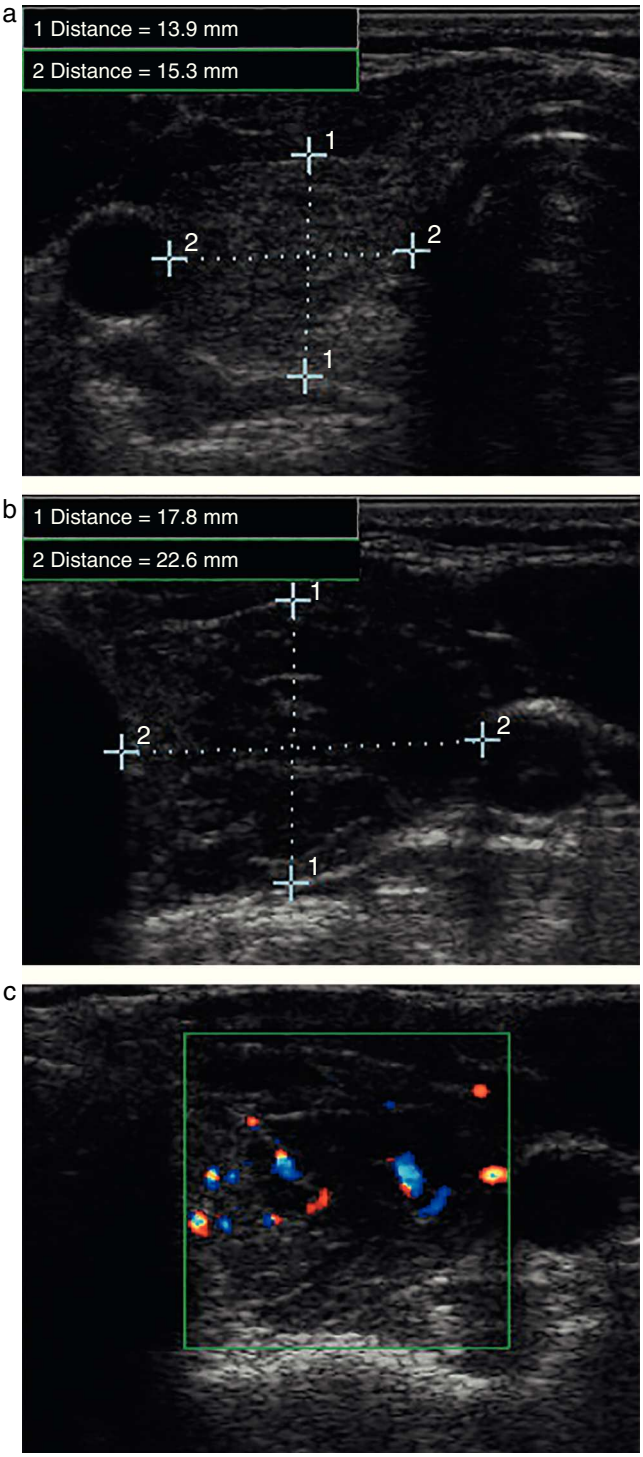

Figure 1 Thyroid ultrasound scan. (a) Right thyroid lobe with typical echogenicity of autoimmune thyroiditis and no nodular formations. (b) Left thyroid lobe occupied by thyroid nodule. (c) Ecodoppler of the left thyroid nodule showing mixed vascularization.

Discussion

Approximately 75–80% of thyroid HL patients are women, in contrast to extrathyroid HL patients, among which the incident rate is similar in both sexes.[3] The average age of patients is 40 years,[4] which is lower than that of thyroid NHL patients, who tend to be in their sixth decade of life. In 80% of thyroid HL cases, there is a rapid increase of a uni- or bilateral cervical mass. Other symptoms are shortness of breath (65%) and dysphagia (53%). Most patients have concomitant lymphadenopathy at the time of diagnosis. What are known as B symptoms (fever, sweating, loss of weight) are frequent (33%) and are considered a sign

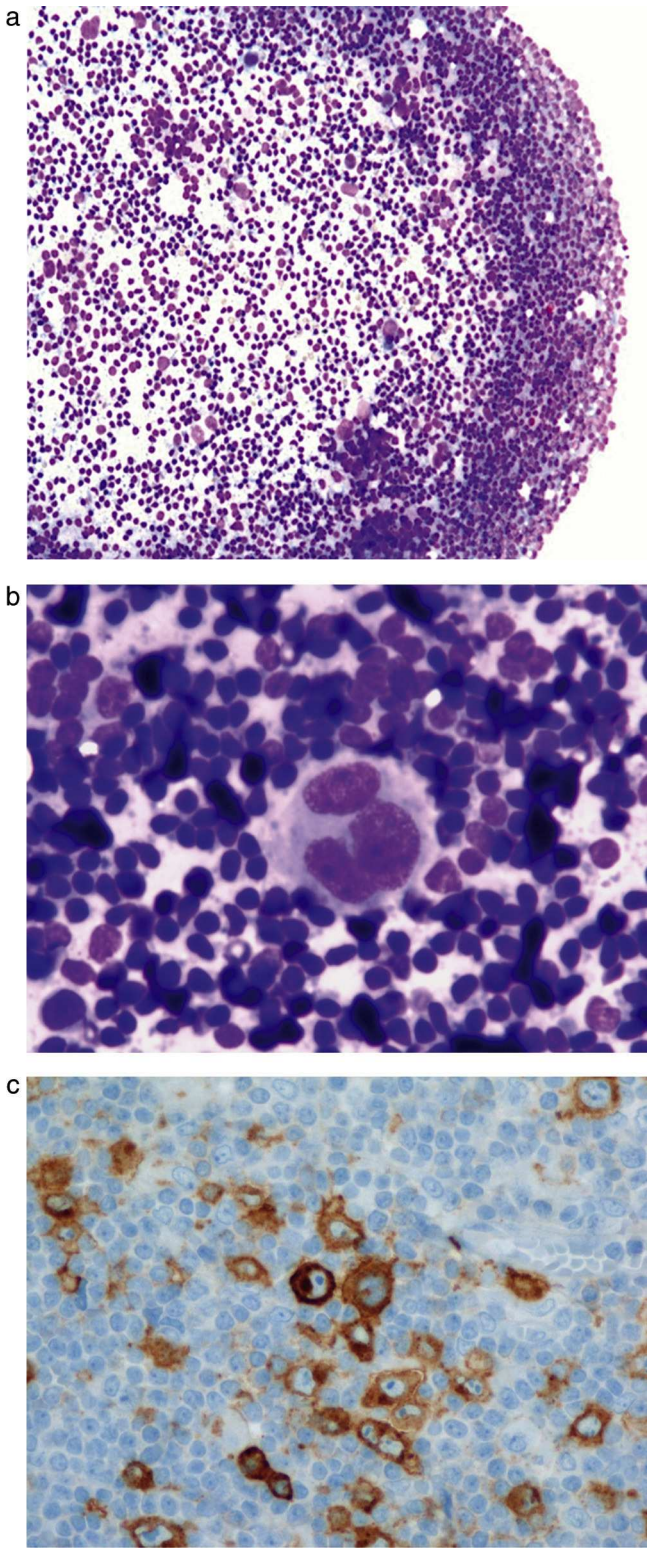

Figure 2 (a) FNAB of the left thyroid nodule. Slight increase in size with abundant lymphocytes and absence of thyroid follicles. (b) FNAB of the left thyroid nodule. Detail of the lymphoid population: predominance of small lymphocytes and presence of a large Reed–Sternberg cell with three nuclei and nucleolus. (c) Thyroid biopsy. Reed–Sternberg cells positive for CD30.

of bad prognosis. The majority of subjects are euthyroid at the time of diagnosis, while 30–40% are hypothyroid.[4] Thyroid lymphoma can have different appearances when visualized by ultrasounds (diffuse, nodular or mixed[2]). The diagnostic effectiveness of FNAB is variable. According to different studies, 50–80% of thyroid lymphoma cases are diagnosed by FNAB,[3] though this procedure should be backed up by other methods to confirm a diagnosis of HL. For example, a morphologic study should be carried out to confirm the presence of Reed–Sternberg cells. In HL, neoplasic Reed–Sternberg cells are in the minority (less than 1% of the cellularity), while the majority are inflammatory cells (lymphocytes, histiocytes, eosinophils and plasmatic cells[6]). Immunochemistry is also recommended.[7] Reed–Sternberg cells express CD15 and CD30 in most cases, and are normally negative for CD3 and CD45. In a small number of cases, a weak expression of different B lineage antigens can be detected, such as CD20 (as in the case of our patient) and CD79a. Moreover, PAX-5, another antigen associated with the B linage is expressed in 90% of cases. If there is absence of expression of CD30 and CD15 or an intense expression of CD20 is detected in the malignant cells, a diagnosis of classic HL should be reconsidered and nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL) and a large-cell lymphoma (LCL) of cell-type T ruled out. In the case of our patient, the presence of Reed–Sternberg cells together with the expression of CD15 and CD30 and weak expression of CD20 confirmed a diagnosis of HL. A differential diagnosis between HL and Hashimoto thyroiditis can be difficult for various reasons. Hypocellularity, a lack of Reed–Sternberg cells, the presence of strong fibrosis or sclerosis, and similarity between reactive cells (activated lymphoblasts) and Reed–Sternberg cells are all potentially confounding factors. In addition, the low incidence rate of thyroid gland HL and coexistence of thyroiditis and lymphoma can complicate matters.[4] In light of this, a biopsy is normally required to determine HL.[8] There is no consensus on whether a core biopsy or an open surgical biopsy is best, as no randomized or prospective studies have been carried out to date. Flow cytometry generally improves the accuracy of cytology in the diagnosis of NLH. It allows the immunophenotype of lymphocytes and their origin (B or T) to be determined and reveals whether they are monoclonal or polyclonal, although κ: λ ratios can increase in many cases of thyroiditis, particularly in the B $CD10^{+}$ cells of the germinal center.[9] Flow cytometry has seldom been used in cases of HL, principally due to the low incidence rate of this disease.[4] In fact, it does not help diagnosis, as benign or reactivated lymphoid cells predominate in this type of lymphoma. In our patient, flow cytometry did not reveal any monoclonal component, which ruled out LNH, but not HL, and so a biopsy was performed. A molecular study can be useful when there are doubts about the diagnosis, though its implementation is not essential.[9] It detects clonality across genetic rearrangement and provides additional information in cases in which morphology and flow cytometry results are discrepant. Lymphoid neoplasms are monoclonal and, in most of these proliferations, the rearranging of TCR and of IgH genes precedes malignant transformation. Consequently, all cells resulting from the same malignant progenitor cell share a rearranged DNA and express the same receptors (a TCR or identical IgH). For this reason, analysis of TCR and IgH by means of PCR

allows clonality of cell populations of B or T lymphoid cells to be detected. In most cases of classic HL, cloned rearrangements are not detected in TCR and IgH. Monoclonal rearrangements of IgH genes have been detected only when micromanipulation techniques are carried out and the DNA extracted from isolated neoplasic cells is studied by means of this technique. This confirms the B origin and malignant character (clonal) of Reed–Sternberg cells. In our patient, PCR did not detect gene rearrangements of TCR and IgH, therefore allowing us to rule out the presence of a clonal population of mature B or T lymphocytes and, consequently, NLH. We next performed a gene study for MALT lymphoma (the most frequent thyroid lymphoma), which proved negative. The stage of a thyroid lymphoma should be determined by means of a CT or PET–CT scan. The Ann Arbor system is used to establish a prognosis, with most cases being diagnosed in stage Ie or IIe.[10] Evidence regarding treatment of thyroid lymphoma is limited and based on retrospective research studies, none of which have been large, pilot studies.[8] The role of surgery in the treatment of lymphoma of the thyroid gland is controversial; as with all lymphomas, this type is highly sensitive to chemotherapy and radiotherapy. Indeed, surgery does not appear to influence the prognosis. Nevertheless, it can be useful in cases in which airline obstruction exists and/or the cytology is inconclusive. When planning treatment, it is necessary to bear in mind the stage and histology of the tumor. In general, all types of thyroid lymphoma are treated with a combination of chemotherapy and radiotherapy, with the exception of the MALT type, which has the best prognosis and is normally treated with only one of the afore mentioned therapies. LH generally has a good prognosis. In short, we present the case of a woman with autoimmune thyroiditis who developed primary thyroid LH and responded well to chemotherapy.

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