Mucosa Associated Lymphoid Tissue lymphoma of the thyroid gland: a case report and literature review

MALT linfoma della tiroide: caso clinico e revisione della letteratura

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Summary

Mucosa associated lymphoid tissue (MALT) lymphomas are low-grade, non-Hodgkin's B cell lymphomas, mainly occurring in the gastrointestinal tract, but also in other tissues. We describe the management of a patient with hypothyroidism, tracheoesophageal compressive symptoms and chest tightness affected by a thyroid MALT lymphoma. The patient underwent debulking thyroidectomy and temporary tracheostomy in order to reduce dysphonia and dysphagia, followed by adjuvant chemotherapy and subsequently radiation therapy. A CT scan performed at the end of radiotherapy 6 months after surgery revealed remnants of residual tissue from the thyroidectomy without any pathological findings. Eur. J. Oncol., 17 (2), 93-98, 2012

Key words: **thyroid, lymphoma, MALT**

Riassunto

I linfomi MALT sono dei linfomi non-Hodgkin a cellule B a basso grado che in genere insorgono a livello del tratto gastrointestinale, ma anche in altri tessuti. Descriviamo in questo articolo il management clinico-chirurgico di un paziente con ipotiroidismo, sintomi da compressione tracheo-esofagea e senso di oppressione toracica, affetto da linfoma MALT della tiroide. Il paziente è stato sottoposto a parziale asportazione della massa tiroidea e tracheostomia allo scopo di ridurre i sintomi compressivi ed in seguito a trattamento chemioterapico e radioterapico. L'esame TC effettuato una volta conclusa la radioterapia, circa 6 mesi dopo l'intervento, ha evidenziato gli esiti della tiroidectomia parziale in assenza di altri reperti patologici. Eur. J. Oncol., 17 (2), 93-98, 2012

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Introduction

Isaacson and Wright described the existence of mucosa associated lymphoid tissue (MALT lymphoma) for the first time in 1983 from a small subgroup of patients with gastrointestinal B-cell lymphoma (1). It was classified as "extranodal marginal zone B cell lymphoma" in the REAL (1994) classification and recently in the 4th edition (2008) of WHO classification of lymphomas (2, 3). MALT lymphomas are low-grade, non-Hodgkin's B cell lymphomas, mainly occurring in the gastrointestinal tract, but also in other tissues such as salivary glands, skin, liver, thyroid, prostate and ocular conjunctiva and adnexa (4). They generally follow an indolent course; however in one third of the cases malignancies have already spread to other mucosal locations, bone marrow or lymph nodes at the time of diagnosis (5). We report in the present article a case of thyroid MALT lymphoma in a patient with hypofunctioning thyroid goiter and describe the clinical and surgical management adopted.

Case Report

A 60-year-old male was admitted to our institution in November 2010 with a 3-month history of worsening tracheoesophageal compressive symptoms (dysphonia and dysphagia for solid foods) and chest tightness. The patient was diagnosed with chronic hypothyroidism in 1998 and he was under levothyroxine therapy. Physical examination revealed halitosis, thick neck with increased thyroid size with a uniformly hard consistency and fixed during swallowing but without pain at palpation. Cornage and tirage were present. Furthermore, laterocervical lymph nodes were palpable and swollen bilaterally. Laboratory tests which included the thyroid functional status due to levothyroxine treatment were within the normal range.

Neck ultrasound demonstrated an enlarged left lobe of the thyroid measured as 99 x 44 x 66 mm, characterized by the presence of heterogeneous tissue surrounding a nodular lesion without microcalcifications or a pattern compatible with a malignant nature. No pathological findings were detected in the right lobe.

Cervical and mediastinum computed tomography (CT) scans showed a large goiter that extended from the left lobe to the mediastinum, displacing vascular structures to the left. The trachea and the esophagus were surrounded by thyroid tissue and displaced to the right (fig. 1). The tracheal lumen was reduced and multiple swollen lymph nodes of as much as 1 cm in diameter were found bilaterally in the laterocervical, supraclavicular, mediastinal and axillary areas. The patient underwent a bronchoscopy that confirmed a transverse reduction of the tracheal lumen in the upper third of the organ due to external compression. Transbronchial needle aspiration (TBNA) cytology was inconclusive.

Because of the worsening of compressive symptoms the patient was referred for total thyroidectomy and a temporary tracheostomy. During the operation the thyroid appeared to be grayish-white in color and presented a bulky, hard consistency, which made it impossible to perform a total thyroidectomy with respect to the neighboring tracheal, esophageal, vascular, and nervous structures.

We performed a partial debulking of the thyroid located anteriorly to the trachea, and the frozen section examination of the specimen demonstrated the presence of a small-cell lymphomatous lesion. Final histological diagnosis was MALT lymphoma of the thyroid gland. Immunohistochemistry was positive for CD20, CD45, CD79a, CD43, BLC2, BLC6, and BLC10 and was negative for CD5, CD10, CD45R0, Cyclin-1, LMP1, TDT, CAM5.2, TTF1, TGB, and calcitonin. Immunoreaction was strongly positive for CD20 (fig. 2), focally positive for BCL6 (fig. 3), and exclusively cytoplasmatic for BCL10.

The post-operative course was uneventful, the compressive symptoms were reduced and the patient

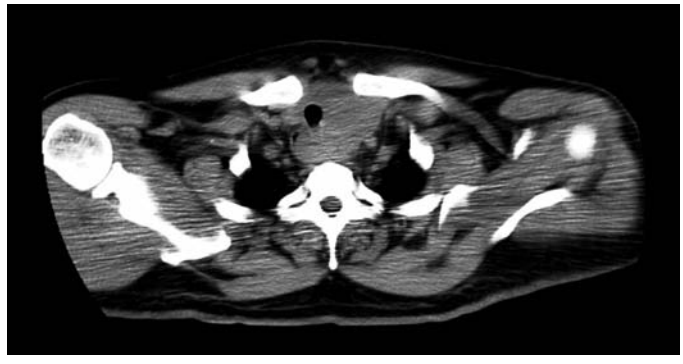

Fig. 1. CT scan: CT showing the lesion before surgery

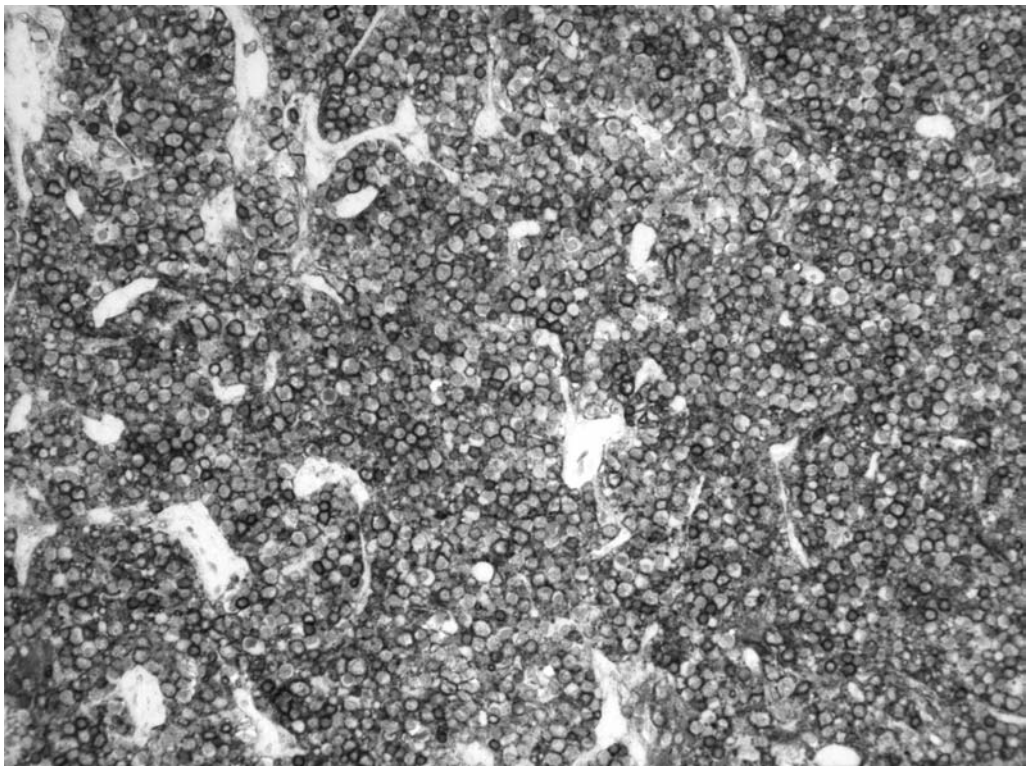

Fig. 2. Diffuse immunohistochemical positivity for CD 20

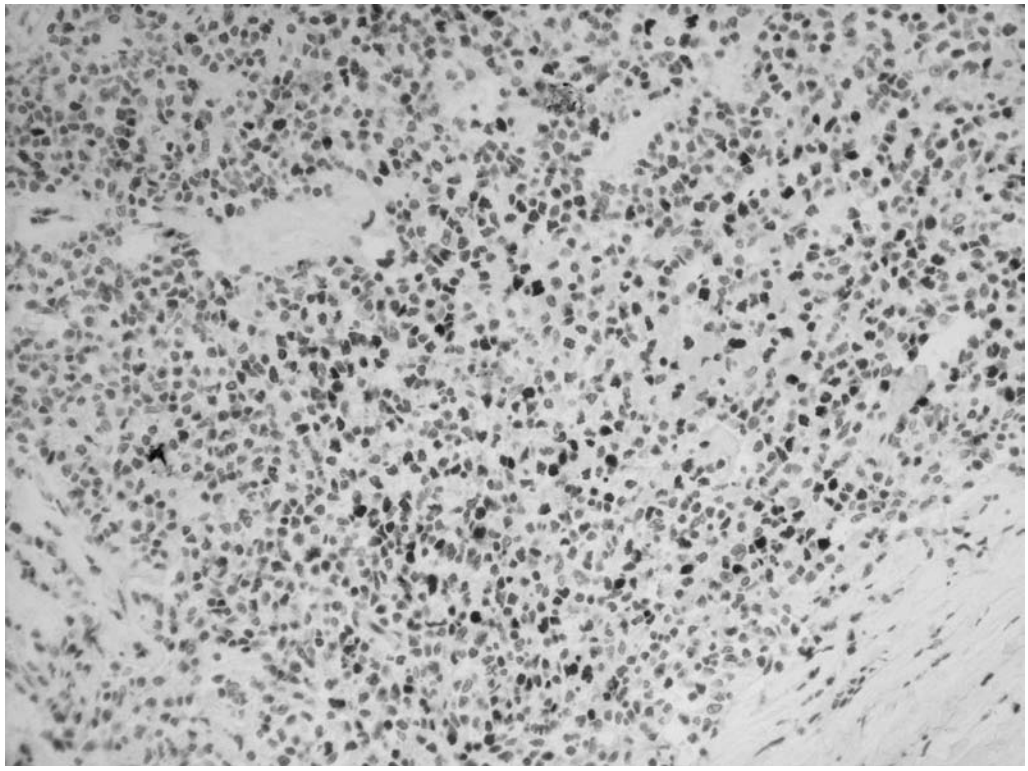

Fig. 3. Focal immunohistochemical positivity for BCL 6

was referred to the hematology department where he began chemotherapy treatment. Regimens included 4 cycles of combined rituximab, cyclophosphamide, doxorubicin, prednisone and vincrisitine. At the end of chemotherapy, approximately 3 months after surgery, a CT scan was performed and documented the reduction of the neoplastic mass. Radiotherapy treatment was subsequently employed with 18

cycles for a total amount of 36 Gray. A new CT scan after radiotherapy (6 months after surgery) revealed remnants of residual tissue from the thyroidectomy without any pathological findings.

Discussion

Primitive thyroid lymphomas are rare. Their annual incidence amounts to 2.1 cases out of 1 million, representing approximately 1-5% of the overall thyroid malignancies and 2-4% of the overall extranodal lymphomas (6-10). The prevalence is higher in females (male/female ratio 1:3/4), and a peak incidence occurs at around 60 years of age (11, 12). They are classically classified as either non-Hodgkin's Lymphomas (NHL), with a B-cell and a T-cell variant, or Hodgkin's Lymphomas (HL). The diffuse large B-cell lymphoma is the most common type representing about 50-70% of the overall thyroid lymphomas, while other subtypes are rarer: follicular lymphoma (12%), HL (7%) and Burkitt's lymphoma (4%) (5, 11). MALT appears as a further variant, with proper clinical and pathological features, which represents the 6-27% of thyroid lymphoma overall (13). It was originally identified as a pseudo-lymphoma because of its characteristic to remain confined to the tissue of origin, but it is now appreciated that it is a clonal B-cell neoplasm that may locally recur, metastasize or be transformed into a high-grade B-cell lymphoma. MALT lymphomas generally occur in middle to older aged individuals, particularly females (male/female ratio 1:2-4) (8).

The pathophysiological mechanisms of MALT lymphomas' genesis are not yet clear. The most accredited hypothesis is that MALT lymphomas arise in the context of persistent antigen stimulation for chronic disease or autoimmunity, which causes subsequent neoplastic transformation of antigen-dependent B-cells due to unknown mutations. The tumor is not initially able to spread beyond the chronically inflamed tissue, but with addiction of further mutations evolves into antigen-independent and capable of systemic spread neoplasia (8).

This hypothesis has emerged from studies on gastric lymphomas in patients with Helicobacter Pylori infection and of salivary gland lymphomas in patients affected by Sjögren syndrome. Thyroid MALT lymphomas are also frequently associated with long-term Hashimoto thyroiditis. Fortunately, despite the high frequency of chronic thyroiditis (anti-thyroid autoantibodies found in 15% of the general population), their incidence is relatively very low. The latency time after the onset of autoimmune thyroiditis is calculated to be about 20 to 30 years (8). Further investigations are necessary to comprehend the pathophysiology that causes the disease to progress from chronic inflammation to neoplasia.

The clinical presentation of thyroid MALT lymphomas is extremely variable. Patients may appear completely asymptomatic, particularly those previously affected by chronic thyroiditis. Others may present with a rapidly growing painless thyroid mass that causes compressive symptoms like hoarseness, dysphagia and dyspnea. This clinical picture was evident in our patient at the time of initial evaluation.

The use of fine needle aspiration biopsy (FNAB) in the diagnosis of thyroid MALT lymphomas is controversial (14). Our patient did not undergo FNAB, as worsening compressive symptoms led to an urgent surgical operation. Sangalli *et al.* reported 10 thyroid MALT lymphomas studied with FNAB; correct diagnoses were obtained in only four cases. Similarly, in a retrospective review of 23 primary thyroid lymphomas, Cha *et al.* demonstrated that the results of FNAB for such diagnosis were often inconsistent, even when employing immunohistochemistry. However, many studies achieved good results using a combination of FNAB and flow cytometry (14).

The most employed imaging methods for the diagnosis of lymphomas include ultrasonography (US), iodine and tecnezium scintigraphy, CT and nuclear magnetic resonance (NMR), but these techniques have a minor role in the diagnosis of MALT lymphomas (15, 16). Nonetheless, CT is crucial in staging and predicting the prognosis. In our experience we employed US and CT which revealed IIE-stage disease, according to the Ann Arbor classification revised by Mussoff. The cervical lymph nodes are most frequently involved at the time of diagnosis, while further lymph node involvement represents a negative prognostic factor (17).

The optimal treatment and appropriate follow-up program of primary thyroid lymphomas remain controversial. The selection of the best treatment strategy is based on the histologic subtype and on the extent of the disease. The principal therapeutic methods available include surgery, chemotherapy and radiotherapy.

Concerning the use of such methods as single treatments, several authors report encouraging outcomes. Thieblemont studied seven patients with stage IE thyroid MALT lymphoma treated with surgery alone and reported that 100% experienced local control of the disease, utilizing adjuvant radiotherapy in cases of incomplete surgical resection (5). In a retrospective review Tsang *et al* reported excellent local disease control in 13 patients with MALT lymphoma (stage I-IIE) treated with 30-35 Gy of radiotherapy (13). For thyroid MALT lymphomas in stage IE or IIE the regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone has been proposed as a combination chemotherapy treatment in cases of lymph nodal involvement (18). Other chemotherapy associations proposed include fludarabine and mitoxantrone or cyclophosphamide, vincristine and prednisone (19).

Several multimodal approaches have been also described. Malek *et al* have suggested that the choice of the treatment strategy depends on the size of the neoplasia. The authors propose a multimodal approach that begins with early thyroidectomy followed by chemotherapy or radiotherapy, indicating radiotherapy for thyroid MALT lymphomas larger than 7 cm (20).

Generally patients with local thyroid MALT lymphoma have an excellent prognosis after thyroidectomy, radiotherapy or chemotherapy, even with a single treatment. Many studies report a 5-year survival rate higher than 90% (21, 22). In rare cases the prognosis may be worse because of the higher aggressiveness and the early onset of compression on neighboring mediastinal structures, which occurred in our patient. In these circumstances the role of surgery seems limited to controlling the compressive symptoms and it must be followed with adjuvant treatments. The most promising adjuvant therapy seems to be a combination of cyclophosphamide, doxorubicin, vincristine and prednisone, which was the treatment offered to our patient (18).

Conclusions

MALT lymphomas of the thyroid gland are rare and generally not aggressive neoplasms. In rare cases the clinical presentation may consist in early tracheoesophageal compression symptoms. Such presentation imposes a decompressive surgical approach which furthermore allows to obtain the exact diagnosis since preoperative FNAB shows a low specificity. The surgical treatment must be followed by adjuvant chemotherapy and radiotherapy in order to guarantee the best oncologic outcomes.

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