An Unwonted Clinicopathological Subtype of Thyroid Primary Lymphoma

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Abstract
Primary thyroid lymphomas account for less than 5% of all thyroid malignancies and the majority of cases concern non-Hodgkin’s lymphoma of B and T-cell origin as well as Hodgkin’s lymphoma. Mucosa-associated lymphoid tissue (MALT) lymphomas are a relatively recently described subset of low grade B-cell non-Hodgkin’s lymphoma representing between 6 and 27% of the patients with thyroid lymphomas. These cases occur usually in patients with Hashimoto’s thyroiditis having a long indolent course and delayed diagnosis, actually benefit from several therapeutic opportunities among them even surgery and a favorable prognostic. Herein we present a 42-year-old female admitted in our unit for a right firm sensitive thyroid swelling, nonhomogeneous on ultrasound images. FNAB showed cellular smears of mixed follicular cells on a background of mature lymphocytes displaying some nuclear atypia and scanty cytoplasm but no definite malignant elements. Intraoperatively, in addition to the “banal” goiter that was found, some subcentimeter cervical lymph nodes were evidenced. Frozen section showed no evidence of malignant or even suspected cellular elements. However a total right lobectomy and lymph node excision was performed. Microscopy revealed a diffuse lymphoproliferative infiltrate in a background of lymphocytic...
thyroiditis suggesting a diagnosis of B-cell lymphoma of MALT type and the patient was referred to chemotherapy. She was currently under follow-up without recurrences or metastases after two years from surgery.

**Key words:** thyroid lymphoma, mucosa-associated lymphoid tissue lymphoma

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**Introduction**

Thyroid carcinoma is the most common endocrine malignancy however primary thyroid lymphoma (PTL) accounts from only 1-5% of all thyroid malignancies. B-cell type non-Hodgkin lymphoma (NHL) is a frequently described type of PTL, while Hodgkin's and T-cell lymphoma are rare. (1) Mucosa-associated lymphoid tissue also known as MALT lymphoma is a subtype of B-cell NHL described in 1983 by Isaacson. (2) The lesion having an eventual history of Hashimoto’s thyroiditis (HT) appears as a more or less rapidly enlarging anterior cervical mass associated or not with lymphadenopathy which in time add symptoms related to compression such as hoarseness, dyspnea and dysphagia. Preoperative diagnosis can be established using modern imaging methods (mainly ultrasonography) and FNAB with immunochemistry and flow cytometry (3). Despite controversies regarding the optimal management of these lesions, this is similar to that of PTL, the mainstay being the combined chemotherapy with loco-regional radiotherapy. The role of surgery is limited to EI stage intrathyroidal MALT lymphoma which has a benign biological behavior (4). The authors focused on distinct clinicopathological features of this entity together with value of early diagnosis and initial adequate therapy for its complete and definitive remission.

**Case report**

SM, a 42-year-old overweight female originating from an endemic goiter area that was monitored 15 years for “banal” goiter presenting a few months ago an increase in her neck swelling. She was admitted in our unit accusing appearance of pain, hoarseness and progressive shortness of breath in the recent weeks. The patient did not show fever, weight loss or sweating. She had a firm, mobile, sensitive thyroid mass of 4-5 cm in size, situated in the right glandular lobe, difficult to perceive in her thick neck where are no palpable lymph nodes. Besides essential hypertension we have no found other general or endocrine sufferings.

Laboratory current tests and thyroid function tests together with thyroglobulin were normal. Thyroid autoantibodies were also within normal ranges.

Ultrasoundography revealed in the center of the enlarged right thyroid lobe a 30 mm irregular bordered, heterogeneous area characterized by segmental pattern through multiple hypoechoic segments and increased vascularity on but no defined hemorrhage or necrotic portions (Fig. 1).

However left thyroid lobe was normal in structure and dimensions. There was no evidence of pathologic lymph nodes. A chest x-ray and abdominal ultrasonography were normal. FNAB showed cellular smears of mixed follicular and Hurthle cells on a background of mature lymphocytes displaying some nuclear atypia and scanty cytoplasm, but no definite malignant elements. Based on clinical appearance and suspect FNAB surgical exploration was decided.

Intraoperative appearance of the thyroid gland was asymmetric, the right lobe slightly adherent to surrounding structures having a noticeably large volume of 5x4x3 cm with a heterogeneous pseudo-nodular lobulated pattern and soft rubbery consistence. The smooth, pale cut surface disclose a proper central irregular distinctive mass of about 3 cm in diameter, with a fish flesh appearance characteristic of lymphoid proliferation which is poorly delimited irregular infiltrating the glandular parenchyma but without necrosis or hemorrhages. The left thyroid lobe have an astonishing normal morphology and sizes. In addition with the known lesion, some apparent innocent cervical, central and delphian adjacent subcentimeter lymph nodes were discovered.

However frozen section showed no evidence of malignant or even suspected cellular elements in the gland and adjacent lymph nodes such as a total right lobectomy with isthmusectomy together with satellite lymph nodes excision was only performed.

Histopathology of the specimen identified atypical lymphoid cells originating within the marginal zone of lymphoid follicles and lymphocytic thyroiditis in the background suggestive for diagnosis of MALT-oma. (Fig 2). Immunohistochemistry support this finding showing CD45 positivity in atypical lymphocytes and centrocyte-like cells. Excised lymph nodes assessed only reactive hyperplasia.

The postoperative course was uneventful and the patient began chemotherapy treatment consisting in four cycles of combined cyclophosphamide, doxorubicin, prednisone and vincristine. Finally, surgery and chemotherapy realized the stable cure of the disease and the patient is alive after two years without recurrence or metastases.
In the large group of PTL thyroid MALT lymphomas occupies a particular place so that frequency, pathogenic and clinical characteristics, as well as therapeutic resources, prognostic and results in time. Thyroid MALT-oma is a quite rare neoplasm accounting for 2-8% of all thyroid malignancies and 1-2% of all extranodal lymphomas. They have a peak incidence during the seven decade of life and a manifestly female predilection (m/f ratio 1:2-4). (5,6)

Etiopathogenesis

Patients with a background history of chronic thyroiditis have a 67- to 80-fold greater risk factor to developing PTL than those without this inflammatory process. Autoimmune thyroid diseases are also thought to be risk factors for the development of MALT lymphoma since these patients have been reported to have an raised mischance for the development of thyroidal MALT-oma with an overall rate of 13-80%. (7,8) These lesions are considered to arise from intrathyroid lymphoid tissue acquired during the course of chronic inflammation or an autoimmune process. Also in HT lymphomatous change susceptible to neoplastic transformation may be due to chronic antigenic stimulation and proliferation of lymphoid tissue. (9)

MALT thyroid lymphoma developed during the long evolution of an endemic goiter or chronic thyroiditis up to 2-3 decades associating sometimes subclinical or overt hypothyroidism, which changes more or less rapidly its volume and consistence. In a time of their evolution it becomes sensitive or develop local obstructive symptoms like hoarseness, dysphagia and breathing difficulties sometimes together with regional lymphadenopathy. The clinical course may be delayed or quieter, diagnosis being established by chance during a puncture, biopsy or surgical exploration.

Thyroid MALT lymphoma must be differentiated from HT but also from other neoplastic lesions i.e. papillary, medullary and anaplastic thyroid carcinomas. (3,4)

The diagnosis of MALT thyroid lymphoma is often postponed by its prolonged indolent evolution which do not always appear clear. Although FNAB has become the procedure of choice for the diagnosis of any thyroid tumor it has yielded mixed results asserting the presence of MALT so that core or open biopsy and even surgical excision (as in our case) is decisive for diagnosis. (10)

Combined pathology and immunohistochemistry may specify microscopy of these lesions orienting therapeutic planning and predicting prognosis of the patients. (11) Ultrasound showed irregular, pseudocystic, hypechoic mass with variable edge characteristics, where echogenicity is less than that of the adjacent neck musculature. Computed tomography and position emission tomography can be useful in determining the stage or extent of PTL and even in MALT thyroid lymphoma and whether any residual tissue after treatment. However cross-sectional imaging (CT/MRI) or PET have not typical features. (12)

Determining the extent of disease is decisive for estimating prognosis and select therapeutic plan-ning such as PTL and MALT thyroid lymphoma cases must be staged on the basis of the Internatio-nal Prognosis Index of these lesions i.e. MALT-oma located within the thyroid (1E), MALT-oma located within the thyroid and regional lymph-nodes (2E), MALT-oma located at both sides of diaphragm (3E) and disseminated MALT-oma. (13)

The management of MALT thyroid lymphoma although it is still controversial depends on the histological subtype of the neoplasm, its stage and the tumor bulk as well as the other associated comorbid factors. The current treatment of this rare disease involves surgery, chemotheraphy with standard and new drugs and radiotherapy. However the optimal therapeutic strategy remains controversial comparing the efficacy of singly versus multimodal modality treatment. (14,15)

Surgery that was once the mainstay of treatment for these lesions, now plays a reduced role being only recommended under ideal condition such as MALT subtype stage IE and complete resectability with minimal morbidity. For many authors surgery is confined mainly to some extent incisional core or open biopsy for a confirmatory diagnosis or a critical airway compression with resection of the thyroid mass in some cases. (16,17)

Like surgery radiotherapy alone should be considered only for localized stage IE tumors achieving remarkable local control in 70% and 100% of cases. The method is frequently used as either primary therapy, consolidation after systemic therapy, salvage treatment or palliation.

Recent radiotherapy guidelines for all types of thyroid lymphoma have involved site radiotherapy, involved node radiotherapy and irradiation of residual therapy after full-course therapy. (18,19)

While radiation therapy can achieve local control of these lesions, chemotherapy can solve distant dissemination of the disease. The conventional chemotherapeutic regimen for all PTL includes cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) to which rituximab was added in more aggressive cases. Typically, patients with these lesions respond rapidly to this regimen However current literature suggest that...
the combination between radiation therapy and chemotherapy is most appropriate for patients with MALT thyroid lymphoma – a conclusion substantiated by the significant complete response rate with reduction of the relapse percentage and encouraging overall survival rates. (20,21)

Actual possibilities of treatment and clinical follow-up enables a new paradigm in prognosis of PTL including also MALT-oma, the overall 5-years survival for these pathology being 50% to 70% ranging to 90% in lesions confined to the gland (IE) and 20-50% for those with extracapsular invasion. For stages IIIIE and IVIE these rates are only 15-35%. (22,23)

In summary mucosa-associated lymphoid tissue thyroid lymphoma has excellent prognosis when it is confined to the regional neck area and treated properly according to histologic type and stage.

Conclusion

We report a case of PTL presenting as a thyroid mass with longstanding history and proved diagnosis of MALT subtype of non-Hodgkin thyroid lymphoma which was successfully treated with surgery and intensive chemotherapy. The awareness of this entity will help the practitioners to achieve timely diagnosis and management substantial improving the prognosis.

Evidence-based recommendations must be applied to any individual patient with PTL with the involvement of a competent treatment modalities.

Contribution of the authors

MRD conceived and drafted the paper, IC member of operative team, MG corresponding author, SD analyzed the clinical data and revised critically the paper.

References