

Primary thyroid lymphomas

N. AVENIA

Primary thyroid lymphomas (PTLs), although rare, must always be considered in the study of thyroid masses, due to the specific diagnostic and therapeutic approach. The incidence of such lymphomas is increasing, from 0,5% of the sixties (1) to 1-5% of all thyroid neoplasms today (2, 3). A Danish epidemiologic study reported an annual incidence of 2,1 cases per million (4). The increase in incidence of such disease paralleled the increase of Hashimoto's thyroiditis; such tight correlation can be explained with the fact that thyroid lymphomas are more frequent in women, (M/F ratio 2:1-14:1) (4, 5), the gender that presents the greater incidence of the Hashimoto's thyroiditis. In 83% of patients with PTL coexists Hashimoto's thyroiditis (6). In patients affected by chronic autoimmune thyroiditis the probability of developing PTL is 20 times greater as compared to general population (7); the longer duration of such autoimmune sickness correlates with the increased risk of developing a PTL.

PLTs represent 2-7% of all extranodal primitive lymphomas (3, 8). Non-Hodgkin lymphoma is the most common PLT (93%) (8), and is divided in two subtypes (4, 9): cellular B lymphoma and cellular T lymphoma (6-27%) (10). The cellular B lymphoma group includes large type-high grade lymphoma (very aggressive) and MALT lymphoma (low grade); large cell lymphomas derive from transformation of MALT lymphomas (4, 9).

Various classifications have been proposed for such diseases, inducing much confusion in the literature (11). According to the National Cancer Institute Working Formulation, about 70% of PTLs are of intermediate grade (12-15). If Kiel's classification is used, 65% are low grade, 30% are high grade, and in 5% of cases grade is impossible to be defined (6).

Large B cell thyroid lymphomas present as an asymptomatic fast-growing mass; MALT lymphomas instead grow slowly. PTLs generally infiltrate the surrounding structures, inducing roughly in 25% of cases dysphagia, hoarseness or dyspnea (17). In 10-40% of cases hypothyroidism occurs (12, 17), while hyperthyroidism is extremely rare (8,19). General symptoms associated with lymphomas, such as fever, excessive perspiration and weight-loss, are present in only 10-20% of patients. Physical examination reveals a diffusely hypertrophic thyroid gland, fixed to surrounding structures. In 40-50% of cases cervical lymphadenopathy coexists (11, 17).

Specific lab tests are lacking; in the majority of cases thyroid function values are altered (TSH increase) due to hypothyroidism, together with autoimmune disease indicators (increase of antithyroglobulin and antiperoxidase antibodies) (11).

Radiologic studies and scintiscan are of fundamental importance in defining the extension of disease, in planning therapy and in the differential diagnosis of the lymphoma from other thyroid neoplasms or thyroiditis (21, 22). CT scan for lymphomas presents some peculiarities; it is impossible anyway to reach the definitive diagnosis only with imaging (23) (Tab. 1). A characteristic finding at TC in thyroid lymphoma is the "donut sign", caused by the tendency of the neoplasm to encircle completely the trachea (22). Radioiodine scintiscan is not useful, as lymphocytes do not have the capability of concentrating iodine. Gallium-67 instead highlights an uptake defect in 90% of patients (24, 26). PET scan shows an aspecific uptake in Hashimoto's thyroiditis and large cell

TABLE 1 - CT FINDINGS IN THYROID NEOPLASMS.

	Calcification	Necrosis	Local Invasion
Papillary carcinoma	+/-	+++/-	--/+
Follicular carcinoma	---/+	----/+	--/+
Medullary carcinoma	+/-	---/+	--/+
Anaplastic carcinoma	+++/-	+++/-	+++/-
Lymphoma	----/+	----/+	+/-

B lymphoma (27, 28); such examination therefore is not useful in the diagnosis of PTL (29). On the other hand, MALT lymphomas generally induce false negative results at PET (11).

Preoperative diagnosis of PTL may be reached during the workup of patients presenting with a solitary thyroid nodule, a nodule in multinodular goiter, or a nodule in Hashimoto's thyroiditis. Preoperative diagnosis is often formulated at cytology on FNAB (Tab. 2): it is very easy in the case of large cell lymphomas (30-32). More complex is the definition of MALT lymphomas in patients affected by chronic autoimmune thyroiditis; in such cases immunohistochemical studies are often necessary (33). Needle-biopsy is utilized only in rare cases, when FNAB is not diagnostic.

Once diagnosis is made, total body CT scan completes staging, according to Ann Arbor's classification (Tab. 3). In about 50% of patients the disease is confined to the gland (stage IE), in another 45% the gland and regional lymph nodes are involved (stage IIE); only 5% of cases show lymph node involvement above and below the diaphragm (stage IIIE) or extranodal disease (stage IV) (4, 11, 34-36).

PTLs are easily curable if diagnosed early and correctly treated. At present no significant advantage in survival has been demonstrated in patients at IE-IIE stage submitted to radical surgery (37-39); some surgeons never take the surgical option in consideration in presence of PTL (40). Others propose treating only stage IE with total thyroidectomy followed by radiotherapy, but preoperatively it is very difficult to individuate the cases presenting thyroid capsule invasion (41, 42). The best results after thyroidectomy have been obtained in the treatment of MALT lymphomas (43).

Thyroidectomy performed in patients affected by lymphoma presents a higher incidence of complications if compared to procedures carried out for goiter or differentiated neoplasms; the reason is the important pericapsular edema that hampers the correct individuation of anatomical structures. In such cases the most frequent complications are bleeding, parathyroid ablation and recurrent laryngeal nerve injury (44). If the procedure is performed by a dedicated surgeon the complication rate does not change significantly in the different clinical settings (45).

According to the National Comprehensive Cancer Network (NCCN) Guidelines surgery embodies only one of the therapeutic options for stage IE, and does not afford a better prognosis if

TABLE 2 - CYTOLOGIC DIAGNOSIS OF PTLs BY FNAB.

	Diagnosis by FNAB
Cha, 2002 (30)	7/8 (88%)
Sangalli, 2001 (32)	10/17 (59%)
	<i>40% in MALT (4/10) vs 86% (6/7) in large B cells lymphomas</i>

TABLE 3 - ANN ARBOR CLASSIFICATION OF PTL.

Stage	Disease localization
IE	Only thyroid
IIE	Thyroid and cervical lymph nodes
IIIE	Thyroid and lymph nodes above and below diaphragm
IV	Thyroid and extension to extranodal sites

compared to radio- and/or chemotherapy (46). Radiotherapy is frequently the treatment of choice for stages IE-IIE; a systematic review of the literature found only three randomized controlled studies demonstrating that chemo-radiotherapy is the best treatment (47-49). For more advanced stages (IIIE or IV) therapy of choice is chemotherapy (CHOP – cyclophosphamide, doxorubicin, vincristin, prednisone).

Prognosis is related to lymphoma extension: 5-year survival rates are 55-80% for tumors confined to the gland (IE), 20-50% for lesions with extracapsular invasion (IIE); for stages IIIE and IV the rates are 15-35% (4, 13, 14, 34, 39, 42, 50). Surgery for palliation is rarely indicated: in such case treatment consists of debulking and tracheostomy carried out for tracheal invasion.

On the basis of the scant and controverse clinical evidence present in the literature we can affirm that PTLs require accurate multidisciplinary approach (51), in order to choose the most appropriate therapy case by case.

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