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ASSOCIATION OF PRIMARY THYROID LYMPHOMA WITH COMPRESSIVE GOITER

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ABSTRACT

Primary thyroid non-Hodgkin's lymphoma is a rare entity. It is defined as a lymphoma occurring in the thyroid gland with or without the involvement of regional lymph nodes. Diffuse large B-cell lymphoma is the predominant subtype, followed by the extranodal marginal zone B-cell lymphoma of MALT, mantle cell lymphoma, SLL, and follicular lymphoma. Hashimoto's thyroiditis is considering as a causal factor. Diffuse large B-cell lymphoma and mantle cell lymphoma are known by an aggressive course while MALT lymphoma and small lymphocytic lymphoma (SLL) are characterized by an indolent clinical course. The most common clinical presentation is an enlarging painless neck mass, growing rapidly and causing an obstruction of the upper airway. Differential diagnosis is an anaplastic carcinoma, squamous cell carcinoma, metastasis of unknown primary and thyroiditis. The sensitivity and the specificity of the FNAC can be increased if consolidated by the use of the flow cytometry, the immunohistochemistry (IHC) and PCR. Three modalities of treatment could be proposed: surgery, radiotherapy, and chemotherapy-dependent on the histologic subtype.

KEYWORDS: Thyroid, lymphoma, immunohistochemistry.

INTRODUCTION

Malignant lymphoma, with its types Hodgkin's and non-Hodgkin's (NHL) lymphoma, constitute the third most common neoplasm in the head and neck region.[1,2,3] The extranodal disease is more common among NHL.[2,3]

Primary thyroid non-Hodgkin's lymphoma (PT-NHL), which defined as a lymphoma occurring in the thyroid gland with or without the involvement of regional lymph nodes, is a quite rare pathologic entity, accounting for 1,3-1,5 % of thyroid neoplasm, and 0,5% of lymphoma.[4] We describe different subtypes of NHL which are classified according to histological and immunological features, having different natural histories, and therapeutic responses.[3,5] Diffuse large B-cell lymphoma is the predominant subtype accounting 50% to 68% of PTL, followed by the extranodal marginal zone B-cell lymphoma of MALT which occurring in 23% of PTL, and less common mantle cell lymphoma, SLL, and follicular lymphoma.[1,2,4,6,7]

The present paper aimed to evaluate the clinicopathological features and treatment outcomes of patients with primary thyroid lymphoma.

CASE REPORTS

Case one

A 58-year-old man, without pathological history, complaining from acute progressive dyspnea and dysphagia, associated with an enlarging anterior neck mass that increased rapidly through the last few weeks. On the clinical examination, we found a painless, hard huge goiter which depends mainly on the left lobe, fixed to the musculature, associated with bilateral lymph nodes (Figure1).

Fig. 1: anterior cervical swelling related to a goiter and causing a cervical shielding.

The laryngeal fibroscopy showed severe edema of the larynx, without modification of cordal mobility showed diffuse swelling of the thyroid compressing the airway tract. We proceed for diagnosing by a biopsy guided by the ultrasound imaging which confirms the mantle lymphoma of the thyroid; we complete the general evaluation by realizing a full body computed tomography in which we note the absence of other lymph node and a gastroscopy that eliminated the stomach localization. The disease was staging according to the classification proposed by Ann Arbor and modified by Myssof: stage IV. After 5 courses of chemotherapy R-CHOP, A complete remission was achieved. After a follow-up of 3 years, no relapse has occurred.

Case two
81-year-old women with no pathologic history consulted us with a rapid enlarging anterior neck mass, associated with compressive symptoms of the upper airway, i.e., a severe dyspnea. The clinical examination objective a huge painless compressive goiter with numerous bilateral lymph nodes, without alteration of cordal mobility. The dyspnea required an urgent release of the obstruction by tracheotomy. The histological subtype was a DLBCL. Unfortunately, the patient was dead in two weeks after intervention.

Case three
A patient aged 56 years, without any antecedents, presented a progressive, growing goiter, without compressive symptoms or B-symptoms. On clinical examination, we notice a moderate homogenous goiter; there were no lymph nodes or involvement of the other organs of the ENT sphere. Biological data objective a hypothyroidism. The patient underwent a thyroid surgery removing all the gland. The definitive histopathologic examination concluded for a MALT lymphoma. There was no relapse after 4 years.

Case four
A woman aged 62 years, complaining from a rapidly enlarging neck mass and dysphonia. No B symptoms were reported. The physical examination found a goiter associated with a vocal cord paralysis. The biological data founded a hypothyroidism. A core biopsy was practiced and objective a diffuse large Bcell lymphoma. An invasion of the medullary bone was confirmed by biopsy. We indicated chemotherapy (CHOP) for 6 cycles, but the patient could not stand it, then she dead after one year.

Case five
70-year-old women who consulted for a progressive, growing goiter, without compressive symptoms or B symptoms. This goiter was moderate on the clinical examination, and we do not have objective lymph nodes or immobility of vocal cord. We objective a biological hypothyroidism. The therapeutic decision was to remove the thyroid gland. The definitive histological examination confirms the DLBCL. There were no

extension of the disease. Then, the decision in an RCP was to associate 6 cycles of chemotherapy, and the patient does not show any relapse along one year.

DISCUSSION
PTNHL of the thyroid gland often affects elderly women.[1,5,8,9] aged between 50-80 years and less often younger people aged 40 years,[2,3,10] with typically a history of lymphocytic thyroiditis.[4,9,11] In our study, the median age was 65 years (58-81 years),the Sex ratio was (2:5).

The underlying pathogenesis of PTL remains obscure.[12] Usually, the thyroid gland is devoid from lymphocytic tissue.[11,13] In the case of lymphoma, this lymphoid tissue appears in the condition of chronic inflammation which is a response to infection conditions or autoimmune process.[11] Links among auto-immune disease, chronic antigenic stimulation, and PTL have been demonstrated, and Hashimoto's thyroiditis represents the major risk factor.[1,12,14] especially in a delay of 20-30 years after initial diagnosis.[5,7,10,12]

Commonly, Hashimoto's thyroiditis is considering as a causal factor of primary thyroid MALT lymphoma, which itself may evolve into aggressive lymphoma,[6,12,14,15] by activating B-cells to secrete antibodies, conducting to hyperplasia or malignant transformation of lymphoid tissue,[4] Concerning our patients, we didn't notice any antecedent of Hashimot's thyroiditis, but we suggest a pre-existing chronic thyroiditis within 3 patients having a biologic hypothyroidism.

The most common clinical presentation is an enlarging painless neck mass, growing rapidly between 1 and 3 months at about 70% of cases[5,7,15] and causing an obstruction of the upper airway tract in an approximately 30% of cases.[12] most often we notice a dysphagia, dyspnea, rarely it's about stridor, hoarseness, dysphonia, or vena cava obstruction.[11,12,13,14,16] In our cases, the prevalent clinical presentation was a rapid enlarging goiter causing an obstruction of the upper airway revealing by dysphonia (paralysis of vocal cord) in one case of DLBCL, and dyspnea in another two cases ; first one was about a women aged 81 years consulting with dyspnea requiring an urgent intervention of desobstruction by tracheotomy, it was a DLBCL; and for the second case we practice a CT that objective a huge goiter associated to a bilateral lymph nodes, there were a resolution of dyspnea after treatment by corticoids and chemotherapie, it was a rare case of MCL (mantle cell lymphoma).

This clinical presentation can also occur with other pathologies realizing a differential diagnosis with primary lymphoma, which are an anaplastic carcinoma, squamous cell carcinoma, metastasis of unknown primary and thyroiditis.[3]

The diagnosis of lymphoma is often delayed because systemic symptoms, such as fever, night sweat, and weight loss are often missing.[13,15] and reported for only 20% of cases,[12] and if present, a secondary thyroid infiltration by lymphoma of another organ seems to be most likely.[13] None of our population study reported B-symptoms.

On clinical examination, we can objective a diffuse or nodular thyroid enlargement,[7] regional lymph node is often achieved and has a particular presentation compared to those related to other thyroid malignancies, so they appear larger and numerous.[12] Often patients are in clinical and biological euthyroid, contrary to what we conclude with our study population, in whom 3 cases wherein hypothyroid situation.

Microscopically, large cell lymphoma is observed as atypical large lymphocytes with frequent mitosis and reveal positive cell markers CD20 and CD 79 on immunohistochemical staining.[5] While MALT lymphoma is composed of small to intermediate sized lymphocytes with slight nuclear irregularity and pale cytoplasm imparting a monocytoid or plasmacytoid appearance.[9] These cells originated within the marginal zone lymphoid follicles and extended into the interfollicular space, the thyroid follicular epithelium and the germinal center.[9,13] Mantle cell lymphoma is derived from naive, pregerminal center B cells of the primary lymphoid follicles or the mantle zone of secondary lymphoid follicles[17] MCL and small lymphocytic lymphoma have similar morphologies,[17] it is the IHC who could differentiate. Mostly, extranodal NHL of head and neck are presented in the early stage compared with nodal nonHodgkin's lymphoma. Nevertheless, subtypes of NHL have different natural history. In fact, Diffuse Large B-Cell Lymphoma (DLBCL) and Mantle Cell Lymphoma (MCL) are considered as a high-grade lymphoma.
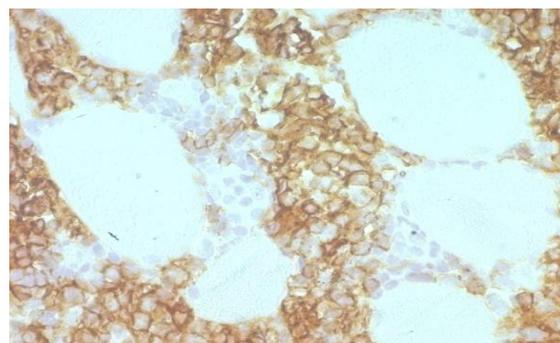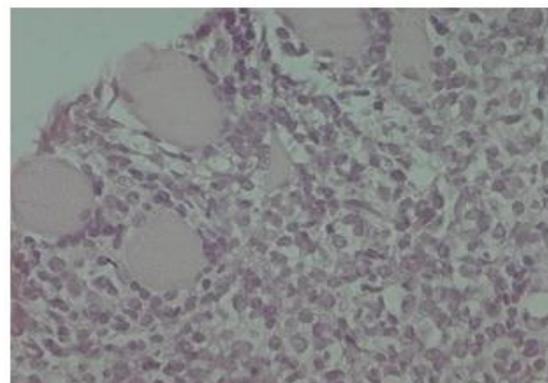

Figure-2.

Figure-3.

Fig. 2 & 3: Expression by tumoral cells of CD20 and CD5.

Hence they have an aggressive clinical course and often patients are in advanced stage of disease (III/IV). In this situation, some authors reported that about 65% of these patients have concomitant involvement of bone marrow and other extranodal sites especially the gastrointestinal system,[1] these data are in agreement with the case we report about a man having an MCL stage IV associated with the second site of lymphoma localized in the stomach, and the case of DLBCL disseminated to the bone marrow.
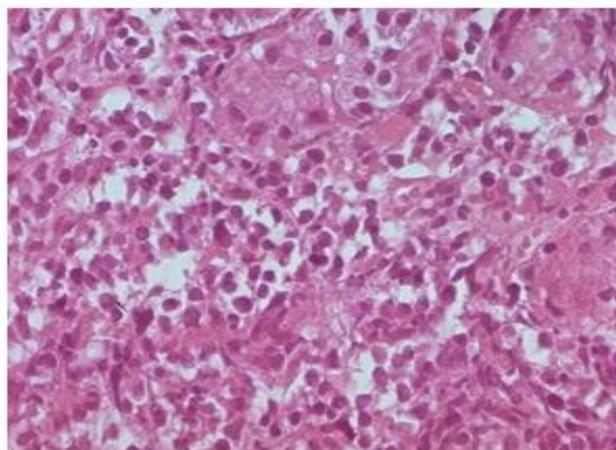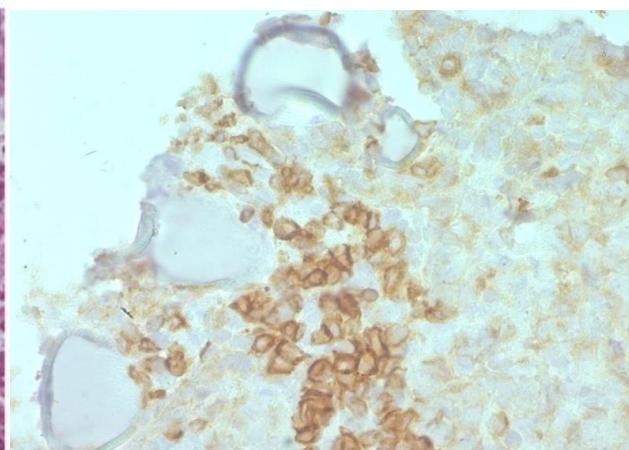

Figure-4.

Figure-5.

Fig. 4&5: Infiltration of both thyroid parenchyma and gastric mucosae by sheets of monotonous small lymphocytes with scant cytoplasm, cleaved, slightly irregular or round nuclei with condensed chromatin.

Conversely, MALT lymphoma and small lymphocytic lymphoma (SLL) are characterized by an indolent clinical course,[2,5,6,9,15,17] with early stage disease confined to the thyroid. However, transformation to higher grade lymphoma is possible.[12] Patients in our study having MALT lymphoma showed a long period of evolution and localized disease. Concerning imagery, ultrasonography (US) seems to be the modality of choice and, it has the advantage to characterize the thyroid lesions. In fact, some authors found that hypoechogenicity and asymmetrical enlargement of the thyroid were predictive of PTL. Orital et al. described 2 US patterns evocating MALT which are the interspersed linear echogenic stands pattern and the segmental pattern.[9] In addition to that, the US is helpful to eliminate other causes of the rapidly enlarging lesion[12] and to guide the biopsy. Cross-sectional imagery is not useful for diagnosis but will be for assessing the involvement of surrounding organs in case of compressive symptoms, to assist surgery when indicated, and finally for cartography of the cervical and mediastinal nodal disease.[12]

The FDG-PET seems to be the superior modality compared to MRI and CT in the diagnosis of lymphoma.[12]

The diagnosis of lymphoma needs a histologic proof.[12,14] The cytologic study through the FNAC is known by the most of the authors to be difficult.[15,18]

In fact, distinguishing PTL from Hashimoto's thyroiditis by FNA is challenging.[10,18] especially as lymphomas occur in a context of thyroiditis and there is a Continuum between the 2 entities.[18] even to diagnose the coexisting of transformation into the high-grade lymphoma won't be possible because of the absence of a monomorphic lymphoid population and the absence of marked nuclear atypical.[9]

Fig. 6: CT of the cervical region highlighting the important volume of the goiter that invades the surrounding organs, associated to lymph nodes on both sides.

Thus, the FNA cytology is judged not a reliable method,[10] but we notice through recent decades and through a multiple small retrospective studies that the sensitivity and the specificity of the FNAC can be increased if consolidated by the use of the flow cytometry, the immunohistochemistry (IHC) and polymerase chain reaction (PCR)[12] which has the particularity of utility in the analysis of small specimens such as those obtained by FNA,[9] MALT lymphoma will be identified by the presence of immunoglobulin light chains, pan B- cell antigens, and BCL2 and absence of CD5, CD10 and CD23,[12] on PCR, it highlights a monoclonal rearrangement of genes that code for IG,[3] we can also detect a number of specific chromosomal translocations associated with MALT lymphoma: t(11,18) (q21,21); t[14,18] (q32,21), t[3,14] (p14,q32) and t[1,14] (q32,q21).[10]

MCL are characterized by the chromosomal translocation t(11,14)(q13,32). Chromosomal translocation that juxtaposes BcL-1 gene and Ig H gene enhancer and results in overexpression of BcL-1 encoded cyclin D1 protein.[17]

Some authors insist on the immunohistochemical examination in case of lymphoma accompanied with Hashimoto's thyroiditis because of the probability of coexistence either the neoplastic and reactive lesions.[15]

Nevertheless, most of the authors indicate the superiority of the needle biopsy or surgical biopsy guided by ultrasound study; compared to the FNA; for diagnosis and subtyping.[10] The open surgical biopsy is performed when definitive diagnosis on the identification of the subtype was not possible by the less invasive technique.[12] Concerning our population, diagnosis was confirmed by a core biopsy and an immunohistochemical examination.

Once the diagnosis of lymphoma was confirmed, the first step consists of a systematic evaluation to identify it as primary.[13] including physical examination, a full biochemical investigation, and evaluation of the gastrointestinal tract (gastroscopy, colonoscopy), a bone marrow biopsy and scanning of neck, chest and abdomen.[13]

The second step is the staging of the tumor according to the system proposed by Ann Arbor and modified by Myssof.[10,13]
Stage I: disease localized to the thyroid Stage II: disease localized to the thyroid and regional lymph node basins.
Stage III: disease involvement on both sides of the Diaphragm.
Stage IV: Disseminated disease.

Currently, there are no randomized clinical trials defining a standard treatment[11,14] which implies a therapeutic adjustment for each patient considering that generally, the management of extra-nodal lymphoma in the head

and neck follows the same broad principles as the management of lymphoma in other sites.[1,12,13]

Also, there are no trials which compared single versus multimodality therapies for primary thyroid lymphoma and its subtypes[12]

The treatment modality depends on clinical stage grade of lymphoma and the health conditions of the patient.[2]

Three modalities of treatment could be proposed: surgery, radiotherapy, and chemotherapy.

Surgery is mostly indicated in the achievement of histological diagnosis, in localized thyroid MALT lymphoma and as a palliative treatment when it is about a compressive goiter.[12] In this last situation, intervention should be indicated with caution when setting of initial airways obstruction because of its high morbidity.[12] Some authors reported good responses of the administration of corticosteroids and chemoradiotherapy, thus avoiding surgical complication.[12] We also adopt this strategy, then in the absence of compressive symptoms necessitating an urgent tracheotomy for saving a life, medical treatment can lead to the release of the obstruction and so avoiding tracheotomies complication on a vulnerable patient.

Whereas surgical intervention of the thyroid is contraindicated in lymphoma with higher than stage I, in bulky tumors and mixed tumor.[12] Radiotherapy could be used as an adjuvant treatment to prior surgery or chemotherapy, treating potential microscopic residual disease. The decision of using it should take in consideration initial tumor bulk, response to systemic therapy and the morbidity of irradiation.[19] This therapeutic modality may also be used as salvage therapy for localized recurrences after surgery or chemotherapy.[19]

Excellent control can be achieved using low doses 30 Gy which mostly played in the regimen « extended field radiotherapy » including the mediastinal nodes and sometimes the axillary lymph nodes.[12] There is no clear evidence that IMRT results in a superior outcome since it is low doses that are required.[1] Chemotherapy is indicated in high-grade lymphoma and the advanced stage of the low-grade disease, i.e., stage III, and IV.[13]

High-grade lymphoma is primarily treated by chemotherapy based on the regimen R-CHOP (Rituximab-cyclophosphamide-doxorubicinvincristine-prednisolone) with 6 cycles, followed by radiotherapy.[1,9] Moreover, some studies noted the superiority of the combination chemoradiotherapy compared to chemotherapy alone and were in some review significantly associated with better disease-free survival.[12,20] Indolent lymphoma; MALT and follicular lymphoma; are often confined disease, plus, known by their benign pathological behavior and good response to local treatment; therefore, a single modality, i.e., surgery or radiotherapy alone, or even associated can lead to local control.[1,5,11,12,13]

In our study, the 2 cases subtyped DLBCL lymphoma were treated by chemotherapy using CHOP regimen for one case, the other one have beneficied of a total thyroidectomy; because clinical presentation was a moderate goiter, thus a preliminary biopsy doesn't seem necessary; once the definitive histologic examination confirmed the lymphoma diagnosis, treatment was completed by chemotherapy cure. The man diagnosed with Mantle cell lymphoma was treated by CHOP regimen chemotherapy Finally, the case of MALT lymphoma was controlled by a total thyroidectomie.

The prognosis of this entity is closely dependent on the age of the patient and his health status, the clinical stage of the disease and the histologic type. In fact, the only largest population-based study of thyroid lymphoma using the surveillance, epidemiology, and End Results database of the national cancer institute, Groffe-Baker et al. reported on multivariate analysis factors associated with decreased 5-year disease: age >= 80 years, advanced stage. Besides, some authors mentioned that some histologic findings like a vascular invasion, abundant apoptosis, high mitotic rate, and peri thyroidal soft-tissue invasion are associated with poor prognosis.[9,13] We report through our study that two patients having DLBCL dead, one because of the bad general health condition and advanced age, the other because of non tolerance of the chemotherapie. The remaining cases did not show any relapse.

CONCLUSION

Primary thyroid lymphoma is an uncommon pathologic entity. We incriminate Hashimoto's thyroiditis as the most risk factor Clinically, characterized by a rapid indolent enlarging neck mass, frequently associated with the upper airway obstruction, so raising the question of differential diagnosis with anaplastic cancer. Improvements in The FNAC and the core biopsy let an open surgical biopsy required only when subtyping was not possible through these less invasive techniques. The treatment is based on combination chemoradiotherapy. The prognosis is primarily dependent on age, staging and disease spread, then the histologic subtype.

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