We describe two different cases of primary thyroid lymphoma (PTL). PTL is a rare malignancy. Nevertheless, it frequently presents diagnostic and therapeutic challenges. The first patient, a 79-year-old female, presented with a large, painless thyroid mass accompanied by severe obstructive symptoms of the upper respiratory and gastrointestinal track. The second patient (67-year-old female) presented with nodular goiter. Thyroidectomy - performed on the first patient for alleviation of obstructive symptoms - revealed the presence of a diffuse large B-cell lymphoma. Although she was administered standard chemotherapy she deceased four months later. In the second patient, primary thyroid lymphoma was an incidental finding following thyroidectomy performed for nodular goiter. These two cases illustrate the variable course of PTL, the possibility of which should be kept into consideration in clinical practice.

Key words: Hashimoto thyroiditis, nodular goiter, primary thyroid lymphoma, thyroid malignancies

Introduction

PTL is a rare disease representing 1–5% of all thyroid malignancies and 1-2.5% of all lymphomas [1]. Physicians treating thyroid cancer patients will have to consider the possible diagnosis of PTL in various clinical circumstances. Given the heterogeneous nature of the disease, neither diagnosis nor treatment is always straightforward [2]. We present two female patients with PTL who demonstrate the two ends of the clinical spectrum, as well as the histological variety and diverse outcome of the disease.

Case 1

A 79-year-old woman presented with a large goiter. The goiter was greatly hypoechoic on ultrasound, compatible with chronic thyroiditis. Thyroid function testing revealed subclinical hypothyroidism: FT4 18.0 pmol/l (normal 12.0-22.0), TSH 7.22 μIU/ml (normal 0.27-4.20), elevated the anti-TG antibodies 168.0 IU/ml (normal <115) and normal the anti-TPO antibodies, and the patient was started on L-thyroxine 50μg daily. On the third month of follow up, she complained of dysphagia, hoarseness and shortness of breath. On physical examination, the goiter was further enlarged, descending to the anterior chest wall. The patient was afebrile and no weight loss or night sweats were reported. Biochemical parameters were within normal range. A thyroid ultrasound revealed a solid mass on the right lobe measuring 21x26 mm and another solid mass on the left lobe measuring 26x38 mm. Both masses were intensely hypoechoic and heterogeneous and enlarged lymph nodes were observed on both sides of the neck. A fine needle aspiration cytology (FNAC) was performed and the cytologic analysis revealed follicular cells, immature lymphocytic ele-
Primary thyroid lymphoma

Case 1

Primary thyroid lymphoma was confirmed. Computed tomography (CT) of the neck confirmed the marked increase of the size of the thyroid gland, especially on the left lobe. The diameter of the trachea was decreased due to mass effect and neck nodes were enlarged.

Immediate thyroidectomy was undertaken. The left lobe measured 4.3×3.0×2.5 cm and was occupied almost entirely by whitish rubbery tumor; the right lobe measured 4.2×2.8×1.2 cm which was also occupied entirely by a similar whitish rubbery tumor. Combined histological and immune histological analyses were consistent with a diffuse large B-cell lymphoma of the follicular center/activated like-cell-non GCC, with a high proliferation index (Mib1/Ki-67: 90%), positive CD45Rb, CD10, CD75, CD79a, BSAP, BCL6, BCL2, MUM1, k-light chain, p53 and p63 and negative reaction of the neoplastic cells for CKAE1-3, EMA, HBME1, thyroglobulin and galectin-3. Figure 1 shows lymphoid infiltration of the thyroid follicle of this B-cell lymphoma in hematoxylin-eosin staining (H/E).

Staging was done according to the Ann Arbor staging system [3]. CT of the thorax, abdomen and pelvis and bone marrow aspiration were negative for other neoplastic foci. The patient had stage IIE disease (involvement of the thyroid and lymph nodes on the same side of the diaphragm). She underwent systemic chemotherapy with the R-CNOP chemotherapeutic protocol. Although the neck mass showed a significant regression after the first cycles of chemotherapy the patient deceased 4 months after initial diagnosis.

Case 2

A 67-year-old woman presented with a history of goiter since the age of 47 years. On physical examination, the thyroid was palpable and firm. She did not complain of pain or tenderness. Physical examination was otherwise normal. No cervical or systemic lymphadenopathy was recorded. The thyroid ultrasound revealed diffuse heterogeneous enlargement of the gland and a nodule of the right lobe measuring 3.3 cm. FNAC of the large nodule showed features of Hashimoto thyroiditis (HT). Due to the discomfort during swallowing and the patient’s strong preference, total thyroidectomy was performed.

Histology revealed that the left lobe measured 3.5×1.5×1.5 cm and the right lobe 2.5×2×0.5 cm. The palpable nodule corresponded to a hyperplastic nodule. A focus of papillary microcarcinoma was identified on the isthmus measuring 0.026 cm with no thyroid capsule invasion. The carcinoma had papillary and follicular architecture with positive reaction for HBME1, Galectin-3, CK19 and Cyc-D1. Moreover, microscopic histopathology revealed a focus of marginal zone incipient B-cell lymphoma / MALT lymphoma with positive immunohistochemistry for CD20 and negative for CD3, CD5 and TLC1. Background thyroid tissue showed diffuse lymphocyte infiltration and small follicles with scanty colloid, typical of HT. Figure 2 shows the lymphoid infiltration of the thyroid follicle by neoplastic lymphoid cells and expansion of the marginal zone with H/E stain.

Staging with CT of the neck, thorax, abdomen and pelvis and bone marrow biopsy showed no other evidence of disease. The patient’s stage was IE (lymphoma limited within the thyroid gland without apparent lymph node involvement). She is currently under levothyroxine treatment. None of the tumors has recurred during the 2-year follow-up period and thyroglobulin levels are 0.1 ng/ml. In this case, the final diagnosis was HT coexisting with papillary microcarcinoma and incipient primary MALT thyroid lymphoma.

Discussion

Surgery is the primary treatment for all differentiated thyroid malignancies. This does not
apply for two rare tumors, anaplastic thyroid carcinomas and PTLs. Radiotherapy is the treatment of choice for the former and chemotherapy and radiotherapy for the latter. Therefore, it is crucial for the clinician to make the correct diagnosis and avoid ineffective surgical procedures.

PTL may be suspected on the basis of clinical presentation. A rapidly growing painless goiter, frequently associated with obstructive phenomena, in a woman with HT in her sixth to seventh decade of life, is the typical presentation. Women are affected 3-4 times more often than men, the incidence increases with age, obstructive symptoms are present in half of the patients and anti-thyroid antibodies are usually increased. Commonly, patients are euthyroid, but overt or subclinical hypothyroidism may be observed in up to 40-60% of the patients [2,4]. A painful goiter mimicking subacute thyroiditis [5], or even hyperthyroidism [2,4], may rarely be encountered. Anaplastic thyroid carcinoma and sarcoma need to be included in the differential diagnosis.

Imaging of the thyroid does not provide specific diagnostic clues in cases of PTL. On ultrasound, PTL usually appears as a heterogeneous, intensively hypoechoic solid mass and it may show a nodular or diffuse pattern with enhancement of posterior echoes [6,7]. On CT scan, depending on the growth pattern of the lymphoma, a single or multiple nodules may be seen, or a heterogeneously enhancing mass compared to adjacent muscle [8,9]. Infiltrated lymph nodes may be observed. FNAC of the thyroid mass is a useful diagnostic tool. Nevertheless, its role is limited [10] and a rather large percentage shows inconclusive or false-negative results, mainly due to the similarities of the cells between HT and PTL. Ultrasound-guided core needle biopsy produces better results. In our first patient, FNAC was not diagnostic and the diagnosis was confirmed only after surgery, while in the second patient there was no evidence of malignancy in the ultrasound, due to the small size of the lymphoma.

Regarding pathogenesis, there is a clear statistical association with HT. The estimated risk of developing a thyroid lymphoma is increased up to 80-fold in patients with HT [1]. Nevertheless, the risk of developing PTL in the background of HT seems to be quite uncommon. Normally, the thyroid does not contain lymphoid tissue, but it acquires a lot in the course of the development of HT. Lymphoid infiltration of the thyroid gland and the chronic stimulation of lymphocytes through antithyroid antibodies have long been assumed to contribute to the development of lymphoma. Recently, more specific molecular mechanisms, such as the aberrant somatic hypermutation, provide a possible causative link between the presence of HT and PTL [11]. Somatic hypermutation, as a physiologic process, is the introduction of point mutations in the V region of the immunoglobulin genes in B lymphocytes, aiming at enhancing affinity of antibodies for antigens. However, it may aberrantly occur in several proto-oncogenes too, in B cells, leading to the development of B-cell lymphomas. Indeed, aberrant somatic hyperstimulation has been reported in both thyroid lymphomas and HT [12]. Further, clonal B cell populations, frequently observed in HT, may show high sequence homology in their rearranged immunoglobulin heavy chain gene with lymphoma’s cells, implicating the HT’s lymphocytes as the precursors of the lymphoma’s cells [13].

The most frequent histological subtype of PTL is the diffuse large B cell lymphoma accounting for approximately 70% of the cases, followed by MALT lymphoma and follicular lymphoma that amount to 10% each. Other types, like small lymphocytic lymphoma, Burkitt’s lymphoma, and Hodgkin’s disease are less frequent [14].

The Ann Arbor staging system which includes 4 stages, I through IV, has been used for survival prognosis [3]. The 5-year disease-specific survival is reported over 80% for stages I, 50-80% for stage II and up to 64% for combined stages III/IV [1,14]. Stratifying patients by histological subtype, the 5-year disease-specific survival is reported approximately 75% for the diffuse large B cell lymphoma and over 96% for MALT lymphomas [1,14].

Stage of disease higher than IE, older age, diffuse large-B-cell, follicular or mixed (diffuse large-B-cell and MALT lymphomas) subtypes and lack of radiation or operation are reported as the most important factors adversely affecting survival [14]. Chemotherapy followed by external radiotherapy is the most effective treatment and the combination of both has significantly ameliorated the prognosis [15]. Surgery is considered useful only as an open biopsy procedure or as palliative, debulking treatment in the presence of severe obstructive symptoms [1]. Patients with stage I MALT lymphomas, which usually have the most indolent course, may be treated with surgery or radiation alone [16].

Incidental thyroid lymphomas in thyroidectomies performed for other reasons, as was the case in our second patient, are not specifically reported in the literature. In a pathological study of
Primary thyroid lymphoma

PTL [17], lymphoma size as small as 0.5 cm was reported, that definitely would have been undiagnosed prior to surgery.

Simultaneous occurrence of both papillary carcinoma and PTL in HT is uncommon. Most of the patients had MALT lymphoma, while HT was always present, whenever recorded. It is unknown if there is a causal relationship between the two malignancies or their simultaneous development in the same thyroid is random, given the high prevalence of papillary microcarcinoma in the general population. Interestingly, in a recent study of the prevalence of BRAF and RAS mutations in PTL, 24% and 8% of diffuse B cell thyroid lymphomas had mutations of the BRAF and NRAS genes, respectively [18]. It may thus be conceivable that a common etiopathogenic factor may trigger such mutations in thyroid cells and ultimately lead to the development of two histologically totally unrelated malignancies. HT may be considered as a candidate factor, since its relation to thyroid lymphoma is rather clearly established as mentioned above, although this is not the case for differentiated thyroid carcinoma and HT, where controversy about a reciprocal correlation still exists [19,20].

In conclusion, our two cases confirm the heterogeneous nature of PTL. The extensive disease of the first patient with the more aggressive histologic subtype, the diffuse large B cell, and the more advanced stage IIE, predicted an adverse outcome. The second patient, on the other hand, diagnosed incidentally with an incipient lymphoma, due to the limited extension of the disease, the early stage IE, and the MALT subtype, is free of disease 2 years later, without any further treatment.

References

17. Derringer GA, Thompson LD, Frommelt RA, Bijwaard

