Case report

Primary thyroid lymphoma: A case report and review of the literature

Rita Peixoto *, João Correia Pinto, Virgínia Soares, Pedro Koch, António Taveira Gomes

* Resident of General Surgery of Pedro Hispano Hospital, Matosinhos, Portugal
b Resident of Pathology of Pedro Hispano Hospital, Matosinhos, Portugal
c Endocrine Surgical Unit of Pedro Hispano Hospital, Matosinhos, Portugal
d Faculdade de Medicina da Universidade do Porto, Alameda Professor Hernâni Monteiro, 4200-319, Porto, Portugal

HIGHLIGHTS

• Primary thyroid lymphomas are very rare.
• New immunohistochemical and molecular techniques have improved the diagnostic accuracy with core biopsy limiting surgery.
• Surgery has a small role in PTL and when needed it should be performed by a specialized surgeon to decrease morbidity.

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ABSTRACT

Introduction: A rapidly enlarging mass of the anterior compartment of the neck with compressive symptoms may represent, among other diagnosis, a neoplasm of the thyroid gland. Presentation of case: We describe the case of a 59-year-old woman referred to the endocrine surgical unit because of compressive cervical symptoms for 3 months. The cervical ultrasound revealed a sub-sentral goiter with heterogeneous echo structure and the fine-needle aspirating cytology was inconclusive. Given the large impact of symptoms on life quality, she was submitted to a total thyroidectomy. Histological examination of the surgical specimen revealed the presence of a Diffuse Large B Cell Lymphoma of the thyroid.

Discussion: Primary thyroid lymphomas are rare and there are few randomized studies for diagnostic and therapeutic guidance. New immunohistochemical and molecular techniques have improved the diagnostic accuracy with core biopsy limiting the role of surgery. The treatment should first include the control of local disease with radiotherapy and/or surgery combined with chemotherapy to control obscure or disseminated disease. Palliative surgery may be needed to relieve airway compression symptoms. Under these circumstances, surgery should be performed by a specialized surgeon to decrease the associated morbidity. The prognosis of patients depends on the histological classification of the tumor and the stage of the disease.

Conclusion: Due to the rarity of the disease, each case must be evaluated and treated individually, since there is not a consensual therapeutic approach.

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1. Introduction

Primary thyroid lymphoma (PTL) is a rare entity and is defined as a lymphoma involving only the thyroid gland or the thyroid gland and regional lymph nodes without contiguity or metastasis of other areas at the time of diagnosis [1].

Since it is a rare entity, the diagnosis can be a challenge and may influence the treatment, as shown in this case report. The importance of recognizing primary thyroid lymphoma lies in the fact that this disease is quite curable without the need for extensive surgery if recognized early. We present a PTL case report submitted to surgery due to the lack of definitive diagnosis.
2. Case report

A 59-year-old woman was referred to the endocrine surgical unit due to compressive cervical symptoms. Her medical history included hypertension. There was no known history of cervical irradiation or family history of thyroid cancer. The patient mentioned that her child was diagnosed with a mucosa-associated lymphoid tissue lymphoma (MALT) of the parotid gland 3 months prior to our observation. She presented with a gradual onset of anterior cervical pain and dysphagia with 3 months of evolution and emergence of dysphonia 15 days before consultation. Laboratory tests showed normal thyroid function, with no significant deviations. The cervical ultrasound (Fig. 1) revealed an enlarged thyroid gland with heterogeneous echo structure, revealing a nodular lesion occupying almost the entire left lobe, migrating to the mediastinum, correlated with a substernal goiter. No enlarged lymph nodes were noticed.

Fine needle aspiration cytology (FNAC) of the thyroid gland was performed twice, proving both times to be inconclusive. The vocal cords were evaluated by laryngoscopy revealing paralysis of the left vocal cord with good compensation of the right cord and no involvement of the glottic lumen.

The patient was submitted to a total thyroidectomy with intraoperative findings of a globally hardened thyroid, showing a multinodular right lobe and an enlarged left lobe, with its inferior region located on the substernal region, strongly adherent to the trachea and esophagus with no evident cleavage plane. It was not possible to identify the left recurrent laryngeal nerve.

Macroscopically, the resected thyroid gland was enlarged and asymmetrical, weighing 43.4 g, while measuring 5.9 × 5.3 × 4.7 cm. The specimen was serially sectioned, revealing extensive multinodular whitish areas with a fleshy and firm cut surface.

The histological examination (Fig. 2) revealed partial effacement of the thyroid parenchymal architecture by a population of round-to-oval lymphoid cells, with large and pleomorphic nuclei, coarse nuclear chromatin, visible nucleoli and scarce eosinophilic cytoplasm. Infiltration of the follicular epithelium, creating lymphepithelial lesions, was noticed. The mitotic rate was 30 mitoses/10 HPFs, with atypical mitoses and foci of necrosis. Vascular invasion was seen, as well as infiltration of the surrounding fatty tissue and pre-thyroidal muscles. On the surrounding thyroid parenchyma,
Table 1
Ann Arbor classification on PTL.

| Ann Arbor stage | Localization                                      | Initial stage |
|-----------------|--------------------------------------------------|---------------|
| IE              | Involvement of Thyroid gland                     | 56%           |
| IIE             | Involvement of Thyroid gland + lymph node regions, on the same side of the diaphragm | 32%           |
| IIIE            | Involvement of Thyroid gland + lymph node regions, on both sides of the diaphragm and/or spleen | 2%            |
| IV-E            | Disseminated disease                             | 11%           |

extensive chronic lymphocytic thyroiditis (Hashimoto’s) coexisted. Immunohistochemical studies were performed on formalin-fixed and paraffin-embedded specimens and showed neoplastic cells diffusely immunoreactive to CD 20, with kappa light chains restriction and were negative for bcl-2, CD 10, lambda light chains and cytokeratin AE1/AE3. Proliferation index using Ki67 was 70%.

With these morphologic and immunohistochemical findings, a diagnosis of Diffuse Large B-Cell Lymphoma (DLBCL) in a background of chronic lymphocytic thyroiditis, was made. She was discharged on the third postoperative day, hemodynamically stable with normal serum calcium and maintaining dysphonia. The postoperative period was complicated with a readmission 10 days after discharge due to symptomatic hypocalcemia interpreted in the context of transitional iatrogenic hypoparathyroidism. The patient was reevaluated by laryngoscopy, maintaining left vocal cord paralysis and was proposed to speech language therapy. Despite the maintenance of dysphonia, the patient reported a significant improvement of the compressive symptoms.

The Positron Emission Tomography (PET) scan showed supradiaphragmatic lymph node involvement extending from the thyroid cartilage to the left mediastinum. After Oncology Group Consulting, she started R-CHOP chemotherapy (Rituximab - Cyclophosphamide, Doxorubicin, Vincristine, Prednisone).

Two years after de diagnosis the patient is disease-free.

3. Discussion and review of the literature

PTL is a rare condition. It is responsible for less than 5% of thyroid malignancies and no more than 2.5% of all lymphomas [2]. Most PTL are non-Hodgkin’s lymphomas. Similarly to this case report, 50–80% of the PTL are DLBCLs and 20–30% are mucosa-associated lymphoid tissue (MALT) lymphomas, most of these extranodal marginal type. Other rare subtypes include follicular lymphoma (12%), Hodgkin’s disease (7%), small lymphocytic lymphoma (4%) and Burkitt’s lymphoma (4%). There are some reports of T cell PTL [3].

The secondary thyroid lymphoma originates from a disseminated non-thyroidal neoplasia that metastasizes to the thyroid gland. It is clinically important to discriminate between primary or secondary lymphoma of the thyroid as the treatment and prognosis differ significantly. The secondary lymphoma of the thyroid invariably is a widespread disease and the mortality rate is higher, as opposed to primary thyroid lymphoma in early stages [4].

PTL is staged based on the Ann Arbor staging criteria (Table 1 [5]).

As a rule, the thyroid gland does not contain lymphoid tissue. Under pathological conditions, the appearance of lymphocytes may occur promoting the further development of the disease. The presence of autoimmune chronic lymphocytic thyroiditis (Hashimoto’s thyroiditis) is a well-established risk factor, presenting a 40–80-fold increased risk of developing PTL when compared to the general population [6]. According to some publications, Hashimoto’s disease is associated with more than 90% of the PTL [7]. This close relationship is probably due to chronic antigenic stimulation leading to malignant transformation [8]. In this clinical case, the previous diagnosis of Hashimoto’s thyroiditis was not known, but the thyroid histological examination proved the coexistence of this autoimmune disease.

Large epidemiological studies have shown a consistent increased risk for developing lymphoma in the setting of autoimmune disorders. It is known that this link appears to be stronger for some autoimmune diseases and certain non-Hodgkin lymphoma subtypes e.g. Sjögren’s syndrome and extra-nodal marginal zone lymphoma of the salivary gland, and thyroid MALT lymphoma in a background of Hashimoto’s thyroiditis [9]. Interestingly, the patient’s daughter was diagnosed with a MALT parotid lymphoma recently but we did not find any correlation between this two cases.

PTL is more prevalent in female patients (F:M ratio - 3:4:1), representing this case report one example of this majority, and present more frequently in the seventh decade of life (mean age of 67 years), as a cervical mass with a quick and painless growth [10]. 30% of patients are diagnosed with symptoms and signs of compression of adjacent structures such as dyspnea, dysphagia, stridor, hoarseness, coughing or choking [11]. Most individuals are euthyroid at presentation, but 10% may be hypothyroid. Additionally, up to 10–20% of patients may be diagnosed with the presence of B symptoms (fever, night sweats or weight loss) [7,10].

FNAC has a leading role in the diagnosis of thyroid nodular disease. On the other hand, its role in the diagnosis of PTL is of limited value because the differential diagnosis between thyroid lymphoma, lymphocytic thyroiditis and even anaplastic carcinoma thyroid is difficult in some cases, representing a real challenge for cytological interpretation. As reflected in this clinical case, the differential diagnosis of a preexisting autoimmune thyroiditis and PTL is often impossible, showing that lymphoma may be an underdiagnosed entity. The features that favor the diagnosis of DLBCL are lack of cellular cohesion, pleomorphism with many showing prominent nucleoli, numerous mitotic figures and presence of lymphoglandular bodies in the background. The closest differential diagnosis includes anaplastic carcinoma of the thyroid gland that show cell clustering and nuclear molding and absence of lymphoglandular bodies [12]. Differentiating these two entities is very important as the treatment for DLBCL usually implicates only chemotherapy while surgical resection is needed for anaplastic carcinoma when resectable. In this clinical case, the lack of cytological diagnosis allied with a rapid enlarging neck mass raised the possible diagnosis of an undifferentiated thyroid carcinoma with surgical indication.

Although there are no randomized studies to evaluate the accuracy of FNAC in the diagnosis of PTL, several small retrospective studies have demonstrated increased sensitivity and specificity with the introduction of other techniques such as flow cytometry, immunohistochemical studies or using molecular techniques such as polymerase chain reaction (PCR) [13]. Ultrasound-guided fine needle aspiration also increases the sensitivity of this technique since it is possible to prevent the biopsy of necrotic tissue regions and minimizes the risk of trauma of the adjacent structures. When FNAC is not diagnostic, a corebiopsy, incisional biopsy or even a thyroidectomy may be required [14]. Demhar et al. [15] recently demonstrated that corebiopsy diagnoses and classifies 95% of lymphomas, but there are no definitive data specifically for PTL.
This technique may be helpful in patients in whom FNAC was not diagnostic but the suspicion is high.

Although less performed nowadays because of the advances in immunohistochemical and molecular techniques, incisional biopsy (IB) also has its place in the diagnosis of PTL. IB may be required in cases where the therapeutic strategy depends on the histological subtype, such as the large B-cell lymphoma vs MALT lymphoma [16]. In the absence of prospective or randomized studies about the role of IB in PTL, it is clear that this method should be used only when less invasive techniques are not sufficient for diagnosis.

The therapeutic approach in PTL is controversial because it is a rare disease and, therefore, there are no prospective large-scale studies. Currently, most authors propose a multidisciplinary approach. The local control of the disease can be achieved by radiotherapy, surgery or both. Chemotherapy is used for control of hidden or disseminated disease, improving the long-term outcome [6].

The surgical treatment in PTL is questionable. The largest study to date regarding this issue was conducted by Mayo Clinic analyzing 62 patients with PTL [17]. The combination of total thyroidectomy with adjuvant radiotherapy did not demonstrate increased survival compared to a biopsy associated to radiotherapy in stages IE or IIE. The same authors decline thyroidectomy emphasizing the possible morbidities associated and the absence of an improvement in survival rate. Surgery may play a role in MALT lymphomas. Typically, MALT lymphomas are incidental findings when performing a thyroidectomy for another reason and usually they are confined to the thyroid gland (stage IE), with no need of adjuvant therapy. Derringer et al. [11] included in their study 16 patients with MALT lymphoma that were only treated with surgery and the overall survival after 7 years was 100%. However, surgery is not a treatment option for MALT lymphomas more advanced than IE stage, bulky tumors larger than 10 cm and mixed lymphomas [13]. In other series, the therapeutic strategy focused solely on radiotherapy and with favorable results too [18,19]. When used appropriately, radiotherapy can locally control the disease in a high percentage of patients (70–100%) with a follow-up up to 4 years. Given that MALT lymphomas do not represent the most part of PTL, surgery is not the primary treatment.

In this case report, the patient underwent a total thyroidectomy as there was no definitive diagnosis preoperatively and she presented compressive symptoms that interfered decisively on her life quality. Palliative surgery may be needed to relieve symptoms of compression of the airway, especially those who do not respond quickly to non-surgical treatment. Under these circumstances, surgery should be performed by a specialized surgeon to reduce the associated morbidity. There are no randomized studies on this subject. Meyer-Rochow et al. [20] suggested that patients with obstructive symptoms, radiotherapy and chemotherapy can exacerbate symptoms because of tissue edema, and therefore a palliative reducing size surgery prior to adjuvant treatment should be considered in selected patients. A small series published by Sippel et al. [21] of 27 patients with thyroid lymphoma showed that palliative resection has good results when performed by experts, with improvement of obstructive symptoms in all of them. Still, it was reported the death of 1 patient with acute myocardial infarction and 5 patients required tracheostomy due to tracheal invasion, edema or difficulties in airway extubation in the postoperative period. According to Mack et al. [16] there are not enough studies to support palliative surgery for airway symptoms control so it is not recommended.

Chemotherapy as a single modality to treat PTL is not recommended since it has inferior results when compared to its association with radiotherapy (RT). Classically, most of the PTL subtypes, including DLBCL and excluding the MALT lymphoma, are treated with the combination of chemotherapy and radiotherapy, even at early stages [22]. The use of local treatment only with RT or surgery eventually has high success rates in low stage MALT lymphomas [23]. Typically, the PTL respond rapidly to combined chemotherapy regimen, commonly the CHOP scheme [11]. The combined therapy (chemotherapy + RT) is associated with a significantly lower risk of spread disease in locally advanced tumors compared to patients treated only with radiotherapy. In a retrospective study of Doria et al. [24], in 211 patients in stage IE and IIE, relapse rates were 7.7%, 37.1% and 43% for chemoradiation, radiotherapy and chemotherapy alone, respectively. Local recurrence rates were 2.6%, 12.6% and 23%, respectively, showing the benefit of combination therapy over isolated locoregional therapy (surgery, radiotherapy or surgery and radiotherapy) alone or single systemic therapy. The introduction of Rituximab, a monoclonal antibody anti-CD20, represented a significant advance in the treatment of Diffuse Large B Cell lymphomas, improving disease-free and overall survival. Many schemes to treat this thyroid lymphoma include rituximab in combination with chemotherapy or as a maintenance scheme [25].

The prognosis depends on the histological classification of the tumor and the stage of the disease [6]. MALT lymphomas, due to its more indolent behavior and more favorable response to therapy, have a better prognosis than DLBCL. The 5-year-survival rate in patients with intrathyroidal disease is 90% and decreases to 35% in patients with extrathyroid disease [6]. Clinical factors that predict a worse prognosis include tumor size over 10 cm, advanced stage (greater than stage IE), presence of obstructive local symptoms, rapid tumor growth, mediastinal involvement, age > 60 years and elevated LDH and β2microglobulin levels [26].

4. Conclusion

PTL is a rare disease and the pre-operative diagnosis is not easy even though the use of immunohistochemical and molecular techniques has improved the sensitivity of the results.

Surgery is not the first line therapy for this entity and should be reserved for selected cases.

Large-scale randomized studies are needed to standardize internationally guidelines but due to the rarity of the disease, this may not be possible and each case should be evaluated and treated individually, since there is not a consensual therapeutic approach.

Ethical approval

This is a case report, without clinical research involved.

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Author contribution

Rita Peixoto — data collection, writing the paper.
João Correia Pinto — writing the paper (pathology description and discussion).
Virginia Soares - data analysis or interpretation, writing the paper.
Pedro Koch - data analysis or interpretation.
António Taveira Gomes - data analysis or interpretation.

Conflicts of interest

The authors declare that they have no conflict of interest.
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