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# Primary thyroid lymphomas. Experience in hospitals of Castilla-La Mancha[☆]

## Linfomas primarios tiroideos. Experiencia en hospitales de Castilla-La Mancha

Primary thyroid lymphoma (PTL) is a rare disorder circumscribed to the thyroid gland and locoregional lymph nodes. Disease involvement of other locations should be discarded at the time of diagnosis.[1] It accounts for less than 2–5% of all thyroid gland neoplasms and less than 2.5% of all extranodal lymphomas.[2] Primary thyroid lymphoma shows a greater prevalence in women (a 4:1 proportion), and in most cases develops between 60 and 75 years of age, with a mean age of 67 years.[3] Clinical presentation most often is in the form of a rapidly growing mass that may be painful, and which causes compression symptoms (dyspnea, dysphagia, aphonia, stridor and cough). Associated systemic manifestations (fever, nocturnal perspiration and weight loss) are observed in 10–20% of all cases of PTL.[4,5] The patients usually show a euthyroid profile at the time of diagnosis, though 10% can present primary hypothyroidism.

The present study describes our experience with the management of PTL at three hospitals in Castilla-La Mancha (Spain). We selected those patients with a histological diagnosis of PTL or who presented that diagnosis in the hospital discharge report in the period between 1990 to date, and a retrospective analysis was made of the case histories. Seven patients – all women – with a mean age of 59 years met these characteristics. In all cases PTL presented as a rapidly growing (evolutive course 1–12 weeks), painless thyroid nodule associated with compressive symptoms. Six of the patients (85.7%) presented associated chronic autoimmune thyroiditis, and four (57%) had primary hypothyroidism. The results of the imaging studies are shown in Table 1. Fine needle aspiration biopsy (FNAB) under ultrasound guidance was performed in 6 cases (85.7%). The cytological findings are reported in Table 1. Two patients (including one after FNAB) underwent a core needle biopsy (CNB). Surgical treatment was decided upon in 71% of the cases: total thyroidectomy (TT) in four patients and hemithyroidectomy in one case. Systemic chemotherapy (CT) was provided in all cases. The treatment schemes are shown in Table 1. Three patients (42.8%) also received radiotherapy (RT). No cases of death or PTL relapse were recorded.

Primary thyroid lymphomas are infrequent. Most PTLs are non-Hodgkin lymphomas (NHLs). In turn, 50–80% are diffuse large B cell lymphomas (DLBCLs) and 20–30% are mucosa-associated lymphoid tissue (MALT) lymphomas. Other histological subtypes such as follicular lymphoma, small cell lymphocytic lymphoma, Burkitt's lymphoma (BL), Hodgkin's lymphoma or T cell lymphoma are extremely infrequent.[4] In our series, one patient presented BL, and in two cases coexisting papillary thyroid carcinoma (PTC) was also observed. Although PTC accounts for 85% of all thyroid follicular epithelial cell cancers, the association of PTL and PTC is exceptional, with very few cases reported in the literature to date.[6,7] The risk of suffering PTL increases 80-fold in the presence of chronic autoimmune thyroiditis, though the progression of this disorder to lymphoma is infrequent.[1] On the other hand, the relationship between chronic autoimmune thyroiditis and PTC remains subject to controversy, though the coexistence of both conditions is a clinical reality of still uncertain meaning.[8] A firm diagnosis of PTL often requires surgical biopsy, since most of the cytological explorations show low sensitivity.[4] The role of FNAB in the diagnosis of PTL is limited by the difficulty of establishing a differential diagnosis between lymphoma and lymphocytic infiltration of the thyroid gland. However, the sensitivity of FNAB has increased considerably with the introduction of other techniques such as flow cytometry, immunohistochemical studies or molecular techniques. In our series, a firm diagnosis after FNAB was only obtained in one case (case 2). This was a patient with BL, which represents a more aggressive variant. In case 1 we performed flow cytometry of the FNAB material, and this technique helped to complete the diagnosis of B cell NHL, although lymph node biopsy was also finally performed to establish the definitive histopathological diagnosis. In cases 3 and 5 we performed molecular biological techniques with the CNB material, with confirmation of the histopathological diagnosis without the need for surgery. Staging is made based on the Ann Arbor classification: IE (disease limited to the thyroid gland), IIE (involvement of the thyroid and locoregional lymph nodes), IIIE (lymph node involvement on both sides of the diaphragm) and IVE (diffuse disease). Ninety percent of all PTLs are diagnosed in early stages of the disease,[9] as was confirmed in our series.

Surgery has been the traditional treatment for PTL. Surgery was decided upon in 5 of our patients. In all patients,

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**Table 1** Characteristics of the cases of primary thyroid lymphoma.

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 |
|---|---|---|---|---|---|---|---|
| Year of diagnosis | 2016 | 2005 | 2015 | 2005 | 2008 | 2010 | 1992 |
| Neck ultrasound | Hypoechogenic nodule 42 mm × 26 mm | Solid nodule 50 mm × 40 mm | Solid nodule 51 mm × 57 mm × 80 mm | Solid nodule 49 mm | Not performed. Neck CT: mass in LTL-isthmus. Size not indicated | MNG | Multiple hypoechogenic nodules, some containing calcium |
| Adenopathies | Yes | No | Yes | No | No | No | Yes |
| FNAB result | Atypical lymphoid proliferation | High grade lymphoma | Atypical lymphoid proliferation | Atypical lymphoid proliferation | Not performed | Hashimoto thyroiditis and papillary type proliferation with atypias | Inconclusive |
| CNB<br>Lymph node biopsy | Lymph node biopsy: non-classifiable B cell NHL (intermediate between DLBCL and BL) | | CNB: low grade lymphoma | | CNB: DLBCL | | |
| Surgery | Post-CT TT | TT | No | HT | No | TT | TT |
| HP result (in case of surgery) | Chronic thyroiditis and atypical lymphoid proliferation areas | BL | | DLBCL | | DLBCL<br>Multifocal PTC | High grade B cell NHL micro-PTC (7 mm) |
| Stage (Ann Arbor) | IIE | IE | IIE | IE | IE | IIE | IIE |
| CT/scheme/ | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| No. of cycles | 1 R-CHOP<br>4 R-DA-EPOCH | 2 CODOX-M-R | 6 R-Bendamustine | 5-R-CHOP | 5 R-CHOP + liposomal adriamycin | 3 R-CHOP | 6 R-CHOP |
| RT/dose | No | No | No | Yes. 30 Gy | Yes/unknown | No | Yes/unknown |
| Survival (months) | 13 | 138 | 21 | 146 | 100 | 87 | 280 |

HP: histopathology; CNB: core needle biopsy; MNG: multinodular goiter; CODOX-M-R: cyclophosphamide, doxorubicin, prednisone, vincristine, methotrexate, rituximab; PTC: papillary thyroid carcinoma; HT: hemithyroidectomy; BL: Burkitt's lymphoma; DLBCL: diffuse large B cell lymphoma; B cell NHL: B cell non-Hodgkin lymphoma; LTL: left thyroid lobe; FNAB: fine needle aspiration biopsy; CT: chemotherapy; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DA-EPOCH: rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; RT: radiotherapy; CT: computed tomography; TT: total thyroidectomy.

surgery was performed before systemic CT, except in case 1, where TT was performed after systemic CT, due to the suspicion of persistent disease as suggested by thyroid gland uptake in the positron emission tomography–a computed tomography (PET-CT) scan with 18-fluorodeoxyglucose ($^{18}$FDG)–though the final histopathological diagnosis was chronic thyroiditis, meaning that persistent tumor disease after the treatment provided could be discarded. In the remaining cases surgery was performed with therapeutic intent (one patient presented BL, which represents a more aggressive variant; in other cases the cytological study proved inconclusive; and in the last case the FNAB findings suggested PTC, with TT being recommended). The current treatment of choice is systemic CT based on the CHOP scheme (adding rituximab in B cell NHL), with or without associated RT,[10] although no randomized prospective trials have been carried out, since PTL is a rare disease. In our series, a more intensive CT scheme was decided upon in two patients, since the lymphomas in these women were associated with a less favorable prognosis. The prognosis of PTL depends on the histological type and on the stage of the disease. Mucosa-associated lymphoid tissue (MALT) NHLs show a better prognosis, since their behavior is less aggressive. On the other hand, the 5-year survival rate is 80% in the case of stage IE disease and 50% and 35% in stage IIE and III-IVE disease, respectively.[1,11] It should be noted that all of our patients showed disease remission, with a survival rate of 100%.

In conclusion, although PTL is very infrequent, it should be suspected in women with rapid thyroid growth associated with compressive symptoms. Most are B cell NHLs that are diagnosed in early stages of the disease, and in such cases the survival rate is high. The treatment of choice is systemic CT, while surgery plays a fundamentally diagnostic role.

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