



## Preoperative Diagnosis of Primary Malt Lymphoma in Graves' Disease

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### Abstract

Rare case of MALT lymphoma in Graves' disease with preoperative diagnosis through the use of ultrasound (US), Fine-Needle Aspiration Cytology (FNAC) and Core-Needle Biopsy (CNB). US showed solid hypoechoic nodule in hyperfunctioning goiter. FNAC diagnosed autoimmune chronic thyroiditis (Bethesda II), and then US-guided CNB resulted in a diagnosis of Lymphoproliferative Parenchymal Disorder (LPD). Immunohistochemistry was the clue for diagnosis of MALT lymphoma. CNB should be used as method of choice for differential diagnosis of thyroid LPDs.

**Keywords:** Core-needle biopsy; Lymphoma; MALT, Graves' disease; Thyroid surgery

### Abbreviations

MALT: Mucosa-Associated Lymphoid Tissue; US: Ultrasound Examination; FNA: Fine Needle Aspiration; FNAC: Fine Needle Aspiration Cytology; CNB: Core-needle Biopsy; AID: Autoimmune Disorders; PTL: Primary Thyroid Lymphoma; TSH: Thyroid Stimulating Hormone; FT3: Free Triiodothyronine; FT4: Free Thyroxine; TPOAb: Anti-thyroperoxidase Antibodies; ATA GL: ATA Thyroid US Classification; FLUS: Lesion of Undetermined Significance; N.V.: Normal Value

### Introduction

Non-gastric MALT lymphoma may arise from various anatomical sites, most commonly from the parotid and salivary glands (18% to 26%), eyes (7% to 14%), head and neck (11%), lung (8%), and breast (2% to 3%) [1]. The occurrence of Primary Thyroid Lymphoma (PTL) is also reported as increased in patients with Autoimmune Disorders (AID), usually in a background of Hashimoto's thyroiditis. So, even if an uncommon disease, PTL should be considered in the differential diagnosis of thyroid lesions because its preoperative identification may result in a complete cure with surgical treatment [2].

Aim of our clinical report is to describe an unusual case of PTL in Graves' disease and the efficacy of its preoperative diagnosis with the use of thyroid Ultrasound examination (US), US-guided Fine Needle Aspiration biopsy (FNA) and Core-Needle Biopsy (CNB).

### Case Presentation

A 43-year-old Italian woman was diagnosed as affected with Graves' disease in December 2015. Increased uptake at radioisotope thyroid scan, elevated serum thyroid hormones and suppressed Thyroid Stimulating Hormone (TSH) confirmed the clinical diagnosis. Medical treatment was well tolerated and provided a fairly good control of hyperthyroidism for several months.

In June 2017 the patient was referred to the thyroid outpatient clinic of our hospital for a clinical control. She was assuming methimazole (20 mg/day) and did not complain of local pressure or general symptoms. Her serum thyroid profile was as follows: TSH 0.01 (n. v. 0.20-4.0 µIU/mL), Free Triiodothyronine (FT3) 2.91 (n.v. 1.71-3.71 pg/mL), free thyroxine (FT4) 5.79 pg/mL (n.v. 0.70-1.48), anti-thyroperoxidase antibodies (TPOAb) 81U/mL (n.v. <35 U/mL). Serum determinations were performed with chemiluminescent assays (IMMULITE<sup>®</sup> 2000 immunoassay system, Siemens S.p.A. - Milano). Physical examination demonstrated a diffuse and slightly irregular enlargement of the gland without palpable nodules or regional lymph nodes. Ultrasonography (US) demonstrated a diffuse enlargement of the thyroid gland with a slightly hypoechoic appearance and increased

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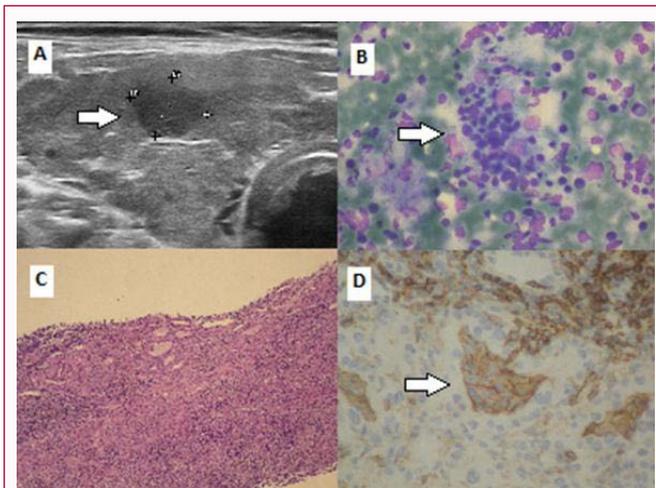
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**Figure 1A:** A solid, hypoechoic, nodule (21 mm × 14 mm × 16 mm in size) with fairly regular margins and no intranodular hyperechoic spot was present in the right lobe.

**Figure 1B:** Aspiration smear showing monomorphic population of atypical lymphoid cells infiltrating and growing into the thyroid follicle (MGG × 200).

**Figure 1C:** Core needle biopsy showed heavy lymphoid infiltrate with intraepithelial lymphocytosis and involvement of the thyroid epithelium by the neoplastic lymphocytes. Shown is a focus of intraluminal lymphoma cells, representing a so-called 'MALT ball'.

**Figure 1D:** Immunohistochemical findings disclose diffuse positive staining for CD20 (immunohistochemistry, × 200).

vascular signals. A solid, deeply hypoechoic, nodule (21 mm × 1 mm × 16 mm in size) with fairly regular margins and no intranodular hyperechoic spot was present in the right lobe (Figure 1A). No pathologic lymph node was observed.

On the basis of current Thyroid Guidelines recommendations [3], was performed an US-guided FNA that provided a cytological sample characterized by scanty colloid, rare thyrocytes, numerous small and medium-size lymphocytes, and a few plasmacytoid lymphocytes (Figure 1B). As the sample was consistent with, but not conclusively diagnostic for, autoimmune chronic thyroiditis (Bethesda II cytological classification), after one month was performed an US-guided CNB that resulted in a micro histological sample diagnostic for a lymphoproliferative parenchymal process (Figure 1C). Immunohistochemical assessment revealed positivity for CD43, CD3, CD5, and CD4 with rare CD8 elements. B immunophenotyped (CD20+) elements were present, as well (Figure 1D).

In October 2017 the patient underwent total thyroidectomy. Preoperative US staging and intraoperative evaluation of the neck excluded the presence of regional lymphadenopathy. Pathologic examination of the gland confirmed the presence of a 2 cm tumor consisting of polymorphic lymphoid population CD20+ CD3- (CD3+ in T component) CD5-. These findings, the destruction of normal thyroid gland architecture induced by lymphoid cell, and the results of flow-cytometry (kappa light-chain restriction) confirmed the diagnosis of Malt Lymphoma. No infiltration of the thyroid capsule was observed and the remaining glandular parenchyma showed a diffuse nodular hyperplasia (Table I). PET/TC scan and endoscopic examination of the digestive tract excluded further localizations of the disease. So, according to the Ann Arbor staging system [1], the conclusive diagnosis was stage I Malt Lymphoma (disease localized to the thyroid gland). After surgical therapy the patient was started on levothyroxine 100 mcg/day with no need of additional treatments. No evidence of relapse was present at the six-month follow-up.

**Table 1:** Diagnostic course.

Diagnostic course
1. Hormone levels
2. Ultrasonography
3. FNAC
4. Core biopsy
5. Immunohistochemistry studies
6. Pathologic specimen's examination

## Discussion

Thyroid MALT lymphoma is a rare thyroid neoplasia that is reported to represent about 0.6% of all thyroid tumors and less than 2% of the extranodal lymphomas [1]. Primary thyroid extranodal marginal zone lymphomas is usually diagnosed in the 5<sup>th</sup> to 7<sup>th</sup> decades of life and almost always arise in the background of chronic lymphocytic thyroiditis (Hashimoto's thyroiditis). The natural history of the disease, indeed, is supposed to involve the chronic stimulation of the gland often associated with autoimmune diseases and lymphocyte infiltration [4]. Malt lymphoma traditionally develops after an at least 10-year history of Hashimoto's thyroiditis [5]. Large cell lymphoma probably develops from low-grade MALT malignant lymphoma, advancing a morphological conversion from chronic lymphocytic thyroiditis to low-grade MALT lymphoma, and subsequently, to high-grade large-cell lymphoma [6].

The preoperative diagnosis of thyroid lymphoma is generally difficult in the absence of clinical signs or symptoms and the present case is of interest because it showed a few unusual features:

- The association of MALT lymphoma with Graves' disease is exceedingly rare and nearly all the reported cases concern Japanese patients [7]. Our patient is the second case, after a former French patient [8], diagnosed in Europe. So in patients with Graves' disease thyroid lymphoma is rarely considered in the differential diagnosis of thyroid nodules.

- Thyroid lymphoma is frequently difficult to differentiate from chronic thyroiditis at US examination. Nodular lymphoma has a profound hypoechoic pattern and the border between lymphoma and non-lymphomatous tissue is usually lobulated or irregular [9]. In our case, conversely, lymphoma had a distinct and regular border between the tumour and the non-lymphomatous thyroid gland and its internal echoes were of uniform low intensity without evidence of necrosis or calcifications. These findings were consistent with an intermediate risk thyroid nodule at the ATA Thyroid US Classification and were not predictive of a lymphomatous lesion [3].

- FNA has an established role in the management of thyroid nodules and goiters but it is often inconclusive in the differential diagnosis between thyroiditis and lymphoma [3,10]. In this case cytological findings were not diagnostic and the nature of the nodule was reliably established only with the micro-histological sample obtained with US-guided core-needle biopsy. Cutting-needle biopsy is rarely employed as the initial diagnostic procedure, because of the risk of bleeding and cervical pain. However, a repeat biopsy that offers a microhistologic sample may provide a more reliable information about thyroid architecture in lesions that are read as follicular lesion of undetermined significance (Bethesda Class III and IV), and in case of suspected lymphoma [11].

The importance of a timely preoperative diagnosis is relevant

in the management of thyroid lymphoma. About 80% of patients with primary thyroid lymphoma have an I or II stage of the disease [12]. Prospective randomized trials have shown an advantage in combining chemotherapy with radiotherapy for patients with stage I and II intermediate- and high-grade NHL, while Mucosa-Associated Lymphoid Tissue (MALT) lymphomas demonstrate a more indolent behavior. The stage IE of this subgroup responds well to total thyroidectomy or radiation with a complete response rate of more than 90% [13]. Surgery is recommended as the primary therapy in the management of localized MALT lymphomas and in stage IE cure is attained with a complete thyroid resection with minimal morbidity and low risk of recurrence [14].

## Conclusion

This is the second European case of primary thyroid MALT lymphoma in patients with Graves' disease. Clinical and US examination and US-guided FNA did not provide a conclusive diagnosis of the nodular lesion within the hyperfunctioning thyroid gland. Immunohistochemical staining and flow-cytometry on a micro histological sample obtained with US-guided core-needle biopsy were the clue for the differential diagnosis. This procedure allowed an appropriate surgical indication and an effective treatment for the patient preventing the risk of diagnostic delay and the probability of a second definitive surgery.

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