



Case Report

MALIGNANT LYMPHOMA OF THE THYROID GLAND: DIAGNOSTIC DILEMMAS

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ABSTRACT

Lymphomas comprise less than 5% of thyroid malignancies (1–3). Rare thyroid involvement and clinical symptoms usually suggest the presence of carcinoma. Only histological examination after surgical resection sets the final diagnosis which is extremely important with regard to the proper mode of treatment – conservative in lymphoma cases versus surgery in thyroid cancer. Here, we report a case of diffuse large B-cell lymphoma (DLBCL) manifesting as a primary disorder of the thyroid gland in 65-year old woman with primary diagnosis of thyroid cancer. We also reviewed cases of thyroid lymphoma reported in the English literature since 1962 in order to further characterize its clinicopathologic features.

Key words: primary thyroid lymphoma, lymphocytic thyroiditis, thyroid cancer

INTRODUCTION

Lymphomas rarely involve the thyroid gland. The majority of them are non-Hodgkin's lymphomas of B-cell origin that arise in the setting of thyroiditis (2, 4, 5). Although it is controversial whether these cases represent primary thyroid lymphoma or secondary thyroid involvement, the rarity of thyroid lymphoma may lead to it being missed or not being considered in the differential diagnosis of a thyroid mass. Most often diffuse large B-cell lymphoma (DLBCL) presenting in the thyroid can mimic primary thyroid carcinoma or thyroiditis, producing diagnostic dilemmas (2, 3, 5, 6, 9, 11).

Here, we report a case of diffuse large B-cell lymphoma (DLBCL) manifesting as a primary disorder of the thyroid gland. During operation a specimen has been sent for frozen section which showed totally effaced thyroid tissue. It has been assumed as a thyroid cancer and the patient was admitted at surgery for radical thyroidectomy.

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CASE REPORT

A 65-year old female was presented with a rapidly enlarging thyroid mass during the past 3-4 months and with a history of hypothyroidism, was sent to surgical department of University Hospital 'St.George' for excision. Examination revealed enlarged thyroid gland with a prominence of the right side. An ultrasound evaluation revealed a 'cold' nodule in a moderately enlarged heterogenous thyroid gland. Findings suggested adenoma on the background of fibrosclerosing thyroiditis. No peripheral lymph nodes were noted as enlarged, neither were spleen and liver changed. Laboratory parameters revealed increased thyroid stimulating hormone 7.250 mIU/l reference (0.490-4.670 mIU/l) and low peripheral hormonal levels of FT3- 1.55 pmol/l (reference 2.23-5.35 pmol/l) while the patient's vital blood indices remained unremarkable. A total thyroidectomy was performed

The entire thyroid was received in our surgical pathology department and weighed 50g. Grossly, the thyroid gland was very firm, measuring 4x3x1.5 cm (**Fig. 1**). The specimen was serially sectioned revealing grey cut

surface with a discrete nodular mass of 1.5 cm in diameter.



Figure 1. Grossly, the thyroid gland was very firm, measuring 4x3x1.5 cm.

MICROSCOPIC FINDINGS

Thyroid specimens were evaluated on formalin-fixed, paraffin-embedded and H&E-stained sections. For immunohistochemistry, 2-mm-thick paraffin sections of formalin-fixed tissue were deparaffinized and rehydrated, using standard protocols. Immunohistochemical studies were performed with monoclonal mouse anti-human CD20, CD3, CD30, CD15, pancytokeratin, followed by avidin–biotin peroxidase complex using a peroxidase-labeled detection system and manual immunostainer with antigen retrieval (all from DAKO, Denmark, Glostrup).

RESULTS

The frozen slide specimens showed totally effaced thyroid tissue with diffuse interstitial fibrosis, presence of necrosis and apoptotic figures. However, it clearly revealed large atypical cells (**Figure 2b**) in a background of mixed inflammatory cells - small lymphocytes and histiocytes mixed with variable numbers of benign thyroid follicular cells. (**Figure 2a**). The expressed parenchymal fibrosis (both grossly and morphologically) along with the history of hypothyroidism was suggestive of the fibrosclerosing variant of Hashimoto's thyroiditis and differentially interpreted as consistent with chronic lymphocytic thyroiditis.

However, focal collections of scattered large atypical cells admixed with variable numbers of small lymphocytes and histiocytes, plasma cells and large atypical mononuclear cells were embedded within the fibrotic stroma (**Figure 2b**, **2c**).

This finding raised the possibility of anaplastic thyroid carcinoma and as such was the specimen reported on the frozen section. Paraffin sections from the fixed thyroid displayed dissociated cell with the morphologic characteristics of immunoblasts and centroblasts. Immunohistochemistry was performed to prove that these large atypical cells were negative for pancytokeratin (**Figure 3**). The CD panel was applied to highlight the suspicion for diffuse large B-cell lymphoma (**Figure 2d**).

Some of the large cells demonstrated positivity for leukocyte common antigen (CD45) (data not shown). The antibodies to B-cell markers (CD20 at **Figure 2d**) showed that these atypical cells together with the lympho-plasmocytic population were predominantly B lymphocytes. Hodgkin's lymphoma was also included in the differential diagnosis but it lacked the characteristic features.

The lesion was classified as diffuse large B-cell lymphoma (DLBCL) on the background of lymphocytic thyroiditis (LT) and perithyroidal soft tissue infiltration.

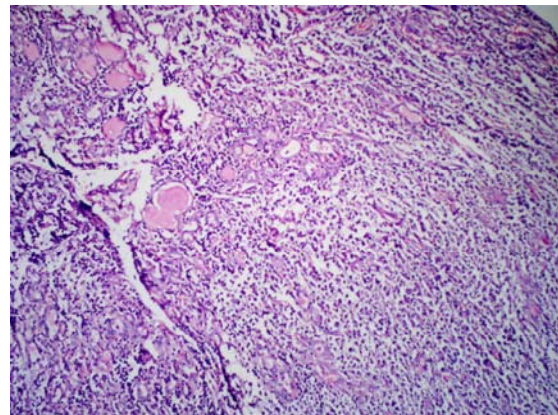


Figure 2. Histologic findings in thyroid nonHodgkin's lymphoma:

Figure 2 (a). Background of lymphocytic thyroiditis (H&E, original magnification x20).

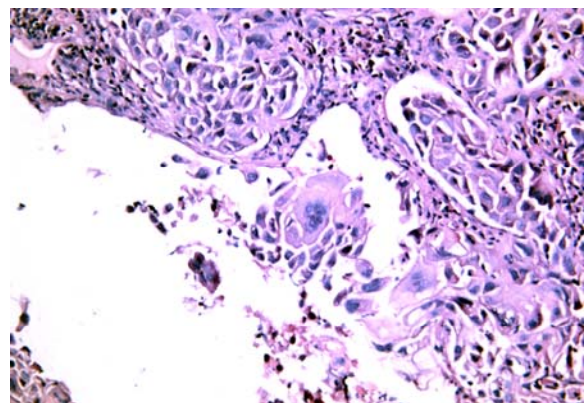


Figure 2 (b). Large atypical cells suggestive of anaplastic carcinoma (H&E, original magnification x20).

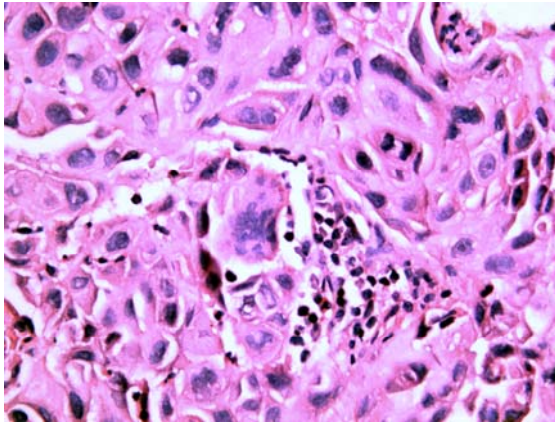


Figure 2 (c). Large atypical cells suggestive of anaplastic carcinoma (H&E, original magnification x40).

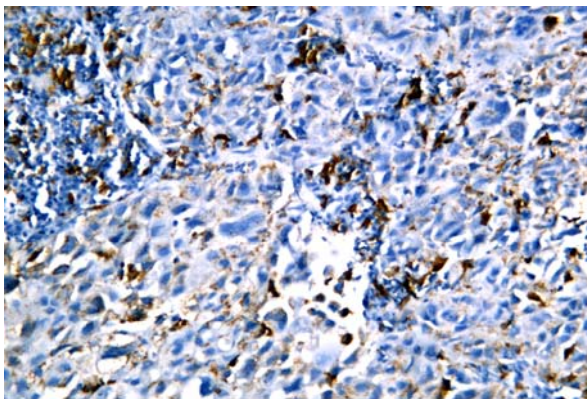


Figure 2 (d). The large atypical cells with present adjacent lymphoblasts both showing CD20 positivity (immunoperoxidase, original magnification x 20).

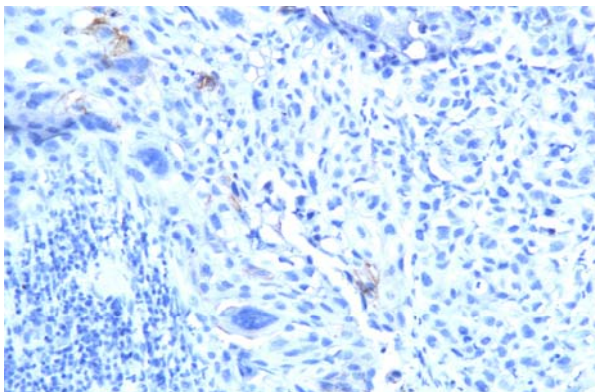


Figure 3. Pancytokeratin negativity for both large anaplastic and lymphoid cells.

DISCUSSION

Primary lymphomas of thyroid gland are rare – 1% to 5 % all malignant neoplasms arising in the gland and 2.2% to 2.5% of all extranodal lymphomas (3). They are divided into non-Hodgkin lymphoma of the B and T cell types and Hodgkin lymphoma. Mucosa-associated

lymphoid tissue (MALT) lymphomas are a subset of B-cell non-Hodgkin lymphoma and they are listed as marginal zone B cell lymphomas of the MALT type according to the revised European-american lymphoma classification (1, 2, 4-12) and the World Health Organization of hemopoetic and lymphoid tissue neoplasms. Most of them are large B-cell lymphoma non-Hodgkin lymphoma.

In certain cases, it is difficult to cut a primary involvement of the gland. The question thus arises as to whether lymphoma of the thyroid gland represents a primary event or reflects secondary involvement by nodal or thymic lymphoma.

Co-existence of lymphoma and carcinoma of thyroid is even rarer. It is usually as a result of chemo- and radiation therapy of preexisting neoplasm of the gland. In medical press such reports are infrequent (1). It is presumed that extra nodal primary lymphoma are more common in gastrointestinal tract (6,8), nasopharyngeal region (9,10), central nervous system (11), kidney (12) or other sites (2–12). Although the most common lymphoma type in thyroid is diffuse large B-cell lymphoma (DLBCL) followed by extra nodal marginal zone lymphoma only few cases have been reported in the literature (10, 12). Other small B-cell lymphomas (such as follicular lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma along with single cases with T-cell and Hodgkin lymphoma have been reported in thyroid gland.

Diffuse large B-cell lymphoma (DLBCL) is predominantly a nodal-based disease characterized by the large atypical lymphoblasts in a background of non-neoplastic reactive cells.

The vast majority of thyroid lymphomas arise on the background of chronic lymphocytic thyroiditis. These patients have a threefold risk of developing lymphoma and an 80-fold increased risk of thyroid lymphoma. Primary thyroid lymphoma occurs more often in women (4-5:1 female to male) and an increased risk with age (63-64 yrs). The association between non-Hodgkin's lymphoma and a pre-existing lymphocytic or Hashimoto's thyroiditis has been well-recognized (5, 13). The thyroid gland contains no native lymphoid tissue; intrathyroidal lymphoid tissue can develop in various pathological conditions, but

most commonly occurs in the setting of autoimmune thyroiditis. This acquired lymphoid tissue represents mucosa-associated lymphoid tissue and can lead to an extranodal marginal zone B-cell lymphoma. (3, 4). The development of extranodal marginal zone B-cell lymphoma in the thyroid gland is often characterized by an indolent course, but transformation to an aggressive lymphoma can also occur (3, 4, 5, 12, 13). In contrast, any association between LBC lymphoma and underlying thyroiditis has been difficult to document because of the small number of cases. Of the 21 patients (12), seven patients had a well-documented clinical history of chronic thyroiditis several months to years prior to the presentation of Hodgkin's lymphoma. In three of these seven cases and in three additional cases occurring in euthyroid patients, lymphocytic or Hashimoto's thyroiditis were demonstrated histologically in areas uninvolved with Hodgkin's lymphoma. In contrast to systemic Hodgkin's lymphoma, which has an equal male to female ratio, thyroid Hodgkin's lymphoma shows a striking female preponderance, seen in autoimmune thyroiditis as well as other thyroid disorders.

Distinguishing severe chronic thyroiditis from lymphoma puts us as pathologists in great difficulty when the inflammatory exudates is so expressed that it effaces the normal thyroid architecture. Moreover, such thyroiditis lead to cellular aggregates that could be classified as lymphoepithelial lesions. In fact, lymphocytic thyroiditis is present in the background of 94% in thyroid lymphomas.

The most common presenting symptom is that of enlarged thyroid. Patients with thyroid lymphoma are most often euthyroid. If hypothyroidism is present (as in our case) it is secondary to pre-existing thyroiditis. Morphologically, in chronic lymphocytic thyroiditis, the lymphocytes are a mixture of B and T cells but mostly T-cells. Scattered larger lymphoblasts, immunoblasts and plasma cells are also present in cases with chronic lymphocytic thyroiditis.

Germinal centers are often prominent. Overall, chronic lymphocytic thyroiditis can be so severe that it can mimic thyroid lymphoma. Use of immunohistochemistry and clonality to confirm diagnosis is a must.

While the lymphocytic thyroid infiltrates may represent a reactive process secondary to

the Hodgkin's lymphoma, it appears that at least a subset of thyroid Hodgkin's lymphoma are associated with antecedent autoimmune thyroiditis.

The rarity of the disease has led to difference in therapy-effectiveness observations. There is a disagreement in literature regarding the use of thyroidectomy as primary therapy for thyroid lymphoma (7, 8, 9, 12, 13). Surgical intervention is rarely required in the treatment of lymphoma. However, in some patients presented with symptoms that compromised their airway or caused severe pain surgical therapy is necessary to ease these symptoms. The most effective therapy is systemic chemotherapy in combination with local radiation.

In thyroid lymphoma, the majority of patients presented with Stage IIE disease, with mediastinal and/or regional lymph node involvement.

Most of the thyroid lymphoma patients presented with low-stage disease, responded well to chemotherapy with or without radiation therapy and had a favorable clinical outcome (2-5, 9, 13, 14). Besides, prognosis of thyroid lymphoma depends on its type - diffuse large B-cell lymphoma are more aggressive (50% present with disseminated disease), whereas extra-nodal marginal zone lymphoma have a good prognosis. Surgical intervention did not appear to be associated with adverse outcome in both Hodgkin and non-Hodgkin's patients.

Though the first manifestation of diffuse large B-cell lymphoma (DLBCL) lymphoma may be a disorder of an extranodal site, such as the gastrointestinal tract, nasopharyngeal region, central nervous system, kidney or other sites (2-6).

Statistically, stages greater than I, presence of DLBCL, rapid clinical growth, abundant apoptosis, presence of vascular invasion, high mitotic rate, and infiltration of the perithyroidal soft tissue were significantly associated with death.

Despite their histologic heterogeneity and frequent simulation of other lymphoma subtypes, virtually all thyroid lymphomas are lymphomas of MALT-type arising in the setting of lymphocytic thyroiditis. Diffuse large B-cell lymphomas and marginal zone lymphomas are common. Overall, thyroid

lymphomas have a favorable outcome with appropriate therapy, but prognosis depends on both clinical stage and histology (2, 3, 5, 8, 9). Marginal zone lymphomas and stage I tumors have an excellent prognosis, whereas tumors with a large cell component or diffuse large B-cell lymphomas or stage greater than I have a poor outcome.

The patient was treated with surgical excision and chemotherapy and was alive after 7 months of follow-up.

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