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SHORT COMMUNICATIONS AND CASE REPORTS

Primary thyroid lymphoma: case series with literature review

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Summary

Non Hodgkin's lymphomas (NHL) of the thyroid are rare thyroid neoplasms. The majority of histopathologic types are extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type and, diffuse large B-cell lymphoma (DLBCL). Most of them arise in a background of Hashimoto's thyroiditis and patients mostly present with a rapidly enlarging thyroid mass and with pressure symptoms. Treatment depends on the histological subtype and stage of the disease and includes radiotherapy and chemotherapy. The prognosis usually is favorable with proper treatment. Herein, we discuss the clinical diagnosis and treatment of thyroid lymphoma.

Key words: lymphoma, non-Hodgkin's lymphoma, thyroid lymphoma

Introduction

Primary thyroid lymphomas represent 1-5% of malignant thyroid neoplasms [1]. The most common type of primary thyroid lymphoma is the extranodal marginal zone B-cell lymphoma, MALT-type, followed by diffuse large B-cell lymphoma (DLBCL) [2]. The optimal treatment of thyroid lymphoma remains controversial. Some authors have advocated surgery for diagnosis only. This can be accomplished by fine needle aspiration core biopsy or open biopsy. The technique of fine needle aspiration cytology (FNAC) is a widely accepted and valuable method for investigation of thyroid lesions [2]. FNAC can be suggestive of thyroid lymphoma in 60% of the cases, although distinction of thyroid lymphoma from Hashimoto's thyroiditis is not always possible [3]. Others have favored a more aggressive surgical approach, showing that the amount of residual disease after debulking procedures directly correlates with the local and distant recurrences [4].

Treatment with radiotherapy directed to the neck alone has yielded inferior results when compared with radiotherapy that included the superior mediastinal lymph nodes. With the development of combination chemotherapy in the 1970s, combined modality treatment, including cyclophosphamide, adriamycin, vincristine and prednisone (CHOP) followed by involved field radiotherapy became more frequently used as initial treatment. Recent studies showed that patients who received combined modality treatment had a better outcome compared with those treated with radiation therapy or chemotherapy alone [5-8].

Immunophenotyping is used as an adjunct to pathological findings for diagnosis of malignant lymphomas because this procedure provides surface-marker characteristics. The addition of rituximab to CHOP increases the complete response (CR) rate and prolongs event-free and overall survival in patients with diffuse large-B-cell NHL, without clinically significant increase in toxicity [9].

Herein, we present 3 cases of thyroid lymphomas treated with the standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) regimen, followed by radiotherapy to the neck, including the upper mediastinum.

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Case presentations

Case 1

A 73-year-old female patient was admitted to the hospital with a rapidly growing cervical mass in the last 4 months. Her physical examination revealed a fixed and painless 15-20 cm large mass in the cervical region. In addition, there was a buccal lesion (3.5×3×5 cm). Her complete blood count (CBC), serum electrolytes, creatinine and liver function tests were normal. Serum LDH level was moderately high (907 U/L, normal 230-460). Her thyroid function tests were normal and antithyroglobulin or antimicrosomal antibodies were negative (TSH: 0.882 mU/L, FT3: 1.76 nmol/L, FT4: 1.2 nmol/L). A tru-cut biopsy of the thyroid and buccal lesion was carried out (Figure 1). Both lesions were diagnosed as DLBCL and immunohistochemical staining for CD20 was positive (Figure 2). Thoracic and abdominal computerized tomographies (CT) were negative for pathologic lymph nodes and organomegalies. The bone marrow biopsy was normal. The patient was diagnosed as stage IIE DLBCL and was treated with the 6 courses of R-CHOP, followed by radiation therapy to the neck, including the upper mediastinum. After the 3rd chemotherapy course, the thyroid mass showed an impressive regression (3×3.5 cm) and the buccal mass decreased (2.5×2.5×3.5 cm) and on completing the 6th course the patient was in CR.

Case 2

A 70-year-old female was admitted to the department of surgery with dyspnea and dysphagia. Her physical examination revealed a bulky cervical mass (15×15 cm) and upper airway obstruction due to external compression. Laboratory examinations showed a slightly elevated serum thyrotropin, normal serum triiodothyronine and thyroxin levels. She had subclinical hypothyroidism (TSH: 16 mU/L, FT4: 1.15 nmol/L, FT3: 1.72 nmol/L). Antithyroglobulin or antimicrosomal antibodies were negative and serum LDH level moderately high (597 U/L, normal 230-460). Because of rapid progression and the invasive nature of the mass, the patient underwent total thyroidectomy urgently based on the clinical diagnosis of malignancy. Pathological diagnosis was DLBCL of the thyroid with positive immunohistochemical staining for CD20. Thoracic and abdominal CTs revealed pathological lymph nodes (2 upper mediastinal 3×3 cm forming conglomerate and multiple paraaortic). Bone marrow biopsy was normal and the patient was staged as IIIE DLBCL. Postoperatively the patient was treated with 6 courses of R-CHOP at the end of which she attained CR. Because of the bulky cervical disease and upper mediastinal nodal conglomeration, chemotherapy was followed by radiation therapy to the superior mediastinal lymph nodes.

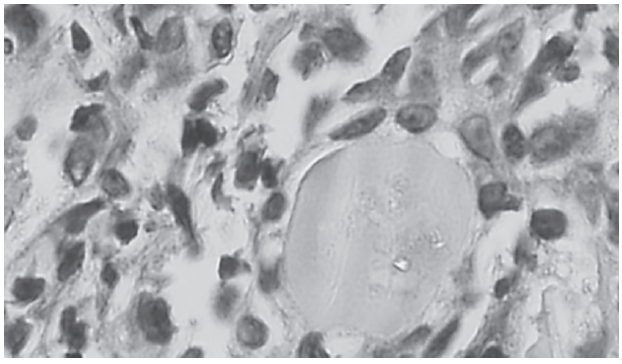

Figure 1. Neoplastic lymphoid cells in case 1 (H&E×200).

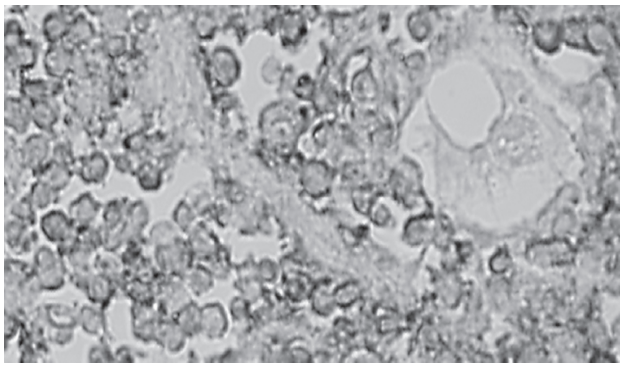

Figure 2. CD20 cytoplasmic staining of malignant lymphoid cells in case 1 (×100).

Case 3

A 58-year-old female was admitted to the department of surgery with dyspnea and dysphagia. She had a cervical mass measuring 10×10 cm for 5 months. Laboratory examinations revealed normal serum thyrotropin, triiodothyronine and thyroxin levels (TSH: 3.49 mU/L, FT4: 1.13 nmol/L, FT3: 2.75 nmol/L). Antithyroglobulin and antimicrosomal antibodies were negative, while serum LDH was slightly elevated (564 U/L, normal 230-460). The mass was rapidly enlarging causing dyspnea and suggesting malignancy. She was operated on with a preoperative diagnosis of thyroid anaplastic carcinoma. Postoperatively, pathological diagnosis was DLBCL of the thyroid. Immunohistochemical staining with CD20 was positive. Abdominal and thoracic CT revealed enlarged mediastinal (multiple, 2×2 cm) and abdominal (multiple paraaortic and iliac, 1.5×1.5 cm and 2×2 cm) lymph nodes and the

disease was staged as IIIE. The patient was treated with the 6 courses of R-CHOP, which resulted in CR. This was followed by radiation therapy to extranodal site and superior mediastinal lymph nodes.

Discussion

Thyroid NHL are uncommon thyroid neoplasms, mainly diagnosed in 50-80 years old persons with a predilection for women [1]. They are typically presented as a rapidly enlarging, painless mass, which can cause dysphagia (40-50%), voice changes (25-30%), dyspnea (21%), hoarseness (21%), stridor (11%) [3,4] and occasionally symptoms of upper airway obstruction. Primary thyroid NHL poses a diagnostic and therapeutic challenge because it can be confused with anaplastic thyroid carcinoma due to similar symptoms [3]. NHL typically arise in previously normal thyroid tissue, in contrast to anaplastic carcinomas that usually arise in a previously detected nodule. It is essential to differentiate small cell anaplastic carcinoma and NHL [1].

Most patients have a history of thyroid enlargement, and usually there is an association with a previous diagnosis of autoimmune thyroiditis (Hashimoto's disease) with or without hypothyroidism [4].

In terms of predicting prognosis, the aggressive thyroid NHL types (most commonly DLBCL) can be classified using the International Prognostic Index (IPI) [10]. IPI provides more precise and reproducible information. Also tumor size larger than 10 cm, the presence of dysphagia and T-cell lymphoma have been proven poor prognostic factors for thyroid NHL [8]. Ultrasound, CT, and magnetic resonance imaging have been advocated for the assessment of local invasion and distant spread.

According to the National Cancer Institute Working Formulation which was reported in 1982, about 70% of the thyroid lymphomas are classified as intermediate-grade lymphomas, with the remaining cases divided among low-grade, high-grade, and undefined [8]. This classification is based on the tumor growth pattern (follicular or diffuse) and the size of the tumor cells. In contrast, using the Kiel classification, about 65% are low-grade lymphomas, 30% high-grade, and 5% undefined [11]. In a series of thyroid lymphomas, 83% of the cases showed high-grade and the remainder low-grade morphology. It is likely that high-grade lymphomas may arise from transformation of low-grade marginal zone lymphomas, given the high frequency of tumors with both histologies sharing identical immunoglobulin light chain restriction.

FNA biopsy is usually recommended as initial diagnostic procedure. Matsuzuka et al. reported a series of 119 patients with thyroid lymphoma and found that FNA was suggestive of lymphoma in 78% of the cases [6]. Skarsgard et al. reported that FNA was suggestive but not diagnostic in their series of 27 patients [8]. FNA in combination with immunophenotyping has been successfully used to diagnose thyroid lymphoma without the need for further invasive procedures [12]. FNA is an appropriate initial step when there is a high index of suspicion of NHL. If lymphoma is suspected by cytologic study, an open procedure is generally indicated to obtain sufficient tissue for accurate histologic and immunologic classification [8]. Two of our patients had a rapidly progressive respiratory distress caused by a massive anterior neck mass with tracheal compression. Surgical debulking should be considered in life-threatening situations, such as in patients who present with symptoms of upper airway obstruction [13]. However, the role of surgery in the treatment of this tumor is controversial. Some authors suggest that extensive thyroidectomy should be the initial treatment of choice. With this approach the extension of the tumor can be determined more accurately and the thyroid can be removed more efficiently. This may provide less local and distant recurrence rates, and longer remission [4]. Also, according to one report, the prognosis after surgery was favorable when complete resection was possible [4]. The patients who had all macroscopic tumor removed before radiation therapy achieved better local control and higher survival rate compared with those with persistent macroscopic disease at the start of radiation [14]. However, Pyke et al. [15] reviewed the necessity for surgery in addition to biopsy in 62 cases of malignant lymphoma of the thyroid tested at the Mayo Clinic, and found that the remission rate did not differ significantly between the surgery+radiochemotherapy group (85%) and the biopsy+radiochemotherapy group (88%). They concluded that highly invasive surgery is unnecessary when dealing with this kind of tumor.

The role of chemotherapy as more efficient than radiotherapy in the treatment of this tumor is also controversial. The 21 patients treated between 1985 and 1992 initially with chemotherapy except stage IEA (< 5 cm diameter) had a 5-year survival of 69% compared with 46% for the 14 patients treated between 1973 and 1984 with initial radiotherapy [16]. In another study 5-year freedom from relapse was 76% after adjuvant CHOP compared with 45% after radiation alone [17]. However, Vigliotti et al. noted that patients with stage IIE disease are less responsive to radiotherapy alone, especially when the mediastinum is involved (5-year disease-free survival of 75%), but they pointed out that this approach was more effective than chemotherapy

alone (5-year disease-free survival of 30%) [18]. Chak et al. reported excellent therapeutic results with irradiation alone in early-stage lymphoma [1]. Patients treated with chemotherapy alone had local recurrence [1]. A 25% incidence of local recurrence has also been reported in a series of patients with extranodal lymphoma after chemotherapy [19]. Radiotherapy will effectively control disease locally and rapidly relieve symptoms with little morbidity and chemotherapy is effective in preventing distant recurrence in patients who receive involved field radiation [5].

There are no published randomized trials directly comparing radiation alone to radiation plus chemotherapy for clinically localized thyroid lymphoma. However, contemporary results of multiple series combining radiation and chemotherapy in 211 patients with stage IE or IIE thyroid NHL have been summarized. Distant and overall recurrence rates were significantly lower in patients who received combined therapy than in those who received either radiation or chemotherapy alone [5]. In general, radiotherapy followed by CHOP chemotherapy is superior to chemotherapy alone in patients with localized extranodal NHL, and this regimen may also be preferable for patients with thyroid lymphomas [13]. In a large series of 119 primary B-cell NHL of the thyroid described by Matsuzuka and coworkers, a regimen consisting of one course of CHOP followed by radiotherapy and then an additional 5 courses of CHOP resulted in 100% 8-year survival in 16 cases [6]. In one series of 51 patients with localized (stage I or II) thyroid NHL, 5-year failure-free survival rate was 76.50%, and 91% for patients treated with radiation, chemotherapy, or combined modality therapy [20]. The local and distant relapse rates were significantly lower in those patients receiving combined modality therapy compared to chemotherapy or radiation alone [5-8].

Recently, R-CHOP chemotherapy was compared to CHOP alone in a randomized study of patients with diffuse large-cell NHL who were older than 60 years. The study showed an improvement in the CR rate, failure-free survival and overall survival for patients treated with R-CHOP [10].

Currently, it's our institution policy that all patients with a thyroid mass should undergo needle or preferably core needle biopsy as the initial diagnostic procedure. After confirmation of diagnosis and after full staging workup, patients are treated with combined modality therapy in the form of 4-6 cycles of R-CHOP chemotherapy followed by consolidation radiotherapy to a total dose of 30-36 Gy in 3.5-4 weeks.

In our case series, combined modality treatment (R-CHOP+RT) attained excellent results with all patients being alive and in CR 3 years after diagnosis.

In conclusion, thyroid NHL is primarily a disease of older women. There is a strong association between thyroid lymphoma and Hashimoto disease, and the presence of underlying thyroiditis appears to be a favorable prognostic factor. Prognosis depends on the histologic type and stage. It should be recognized that early diagnosis and correct treatment lead to favorable prognosis. The combination of immunochemotherapy with RT seems to be a highly effective treatment modality for B-cell NHL of the thyroid, but the rarity of this type of lymphoma calls for a large multicentric randomized trial in an attempt to better define several aspects of this disease, including predictive, prognostic and therapeutic issues.

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