THYROID MALT LYMPHOMA IN PATIENTS WITH A COMPRESSION GOITER

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Abstract: Background. Mucosa-associated lymphoid tissue (MALT) lymphomas account for less than 1% of all primary thyroid malignancies. They typically arise as neoplastic transformations within areas of autoimmune thyroiditis. Although they tend to have an indolent course, these lymphomas present a diagnostic challenge requiring a high level of suspicion in patients at increased risk of development.

Methods. We retrospectively reviewed 3 cases of primary MALT thyroid lymphoma discovered in patients with a compressive goiter. This represents the experience at a single institution from 1996 to 2005. Hospital and clinic records were reviewed to identify the workup, treatment, and outcome.

Results. One of 3 patients underwent preoperative fine-needle aspiration (FNA). All patients underwent total thyroidectomy to relieve compressive symptoms, and the final pathology revealed MALT lymphoma. Two patients subsequently underwent radiation therapy. All patients are alive without evidence of disease recurrence.

Conclusions. These cases are notable for the unexpected presentation of MALT lymphoma within a compressive goiter.

Keywords: thyroid lymphoma; MALT; compressive goiter

Mucosa-associated lymphoid tissue (MALT) lymphomas were first described by Isaacson and Wright1 in 1983 in a small series of patients with gastrointestinal B-cell lymphomas. These lymphomas were recognized as extranodal marginal zone B-cell lymphomas in the Revised European-American Lymphoma (REAL) classification of 1994 and the World Health Organization (WHO) classification of 1999.2,3 They are low-grade B-cell lymphomas that occur primarily in the stomach but also in nongastrointestinal sites, such as the thyroid gland, salivary glands, ocular adnexa, skin, liver, conjunctiva, and prostate. MALT lymphomas are indolent lymphomas, although in approximately 30% of cases, dissemination to other mucosal sites, bone marrow, or lymph nodes is found at diagnosis.4

We performed a retrospective review of 3 cases of primary MALT thyroid lymphoma discovered in patients with a compressive goiter. This represents a single institution’s experience from 1996 to 2005. Hospital and clinic records were reviewed to identify the workup, treatment, and outcome.
CASE REPORTS

Case 1. A 49-year-old man initially visited his primary care physician with a complaint of shortness of breath and was treated with antibiotics for pneumonia. Dyspnea progressed over a number of months, and he presented to his local emergency department. He was found to have severe airway compromise for which emergency tracheotomy was performed to secure his airway. A neck CT revealed a large thyroid mass causing tracheal compression. The thyroid mass extended posterior to the pharyngeal walls and esophagus (Figures 1 and 2). His thyroid function tests were remarkable for low free T3, 1.5 pg/mL (normal, 2.3 to 4.2 pg/mL); low normal total T3, 0.8 ng/mL (normal, 0.80 to 2.00 ng/mL); and low free T4, 0.44 ng/dL (normal, 0.60 to 1.70 ng/dL). His thyroid-stimulating hormone (TSH) level was markedly elevated at 84.73 mIU/mL (normal, 0.320 to 5.00 mIU/mL). Incisional biopsy was performed at the time of the emergency tracheotomy and demonstrated sclerosing thyroiditis. These findings were confirmed by our pathology team. He was referred to our institution for further evaluation. On presentation to our clinic, he was able to phonate with a hoarse voice when covering his No. 6 Shiley tracheostomy tube. He denied dysphagia and appeared clinically euthyroid. His thyroid lobes were palpable to the angle of the mandible superiorly and as far as the level of the clavicles inferiorly. He was treated surgically for a compressive goiter with total thyroidectomy and was found to tolerate this procedure without complication. He was decannulated 3 weeks postoperatively. Final pathology on the surgical specimen revealed MALT lymphoma arising in the background of fibrosing chronic lymphocytic thyroiditis, with focal extrathyroidal soft tissue extension. He subsequently underwent postoperative radiation therapy to the thyroid bed (3060 cGy). After 24 months of follow-up, there is no evidence of disease recurrence.

Case 2. A 77-year-old woman was treated with thyroid hormone suppression therapy for 5 years for management of a large goiter. Despite adequate medical therapy, she continued to complain of intermittent dyspnea and dysphagia. On physical examination, she was noted to have a multinodular goiter without associated lymphadenopathy. Her voice was not hoarse, and she was not dyspneic. Fine-needle aspiration (FNA) of the goiter was performed at an outside institution prior to surgery, and, reportedly, no malignant cells were identified. Total thyroidectomy was performed without complication. The final pathology on the surgical specimen showed low-grade B-cell lymphoma consistent with monocytoid B-cell lymphoma or lymphoma of MALT. There was focal extrathyroidal soft tissue extension of the MALT lymphoma. After follow-up for 8 years and 3 months, there is no evidence of disease recurrence.

Case 3. A 37-year-old man with a goiter and presumed Hashimoto’s thyroiditis was treated with levothyroxine for 6 years. His goiter increased in size despite medical therapy, and he developed a globus sensation and positional shortness of breath. His thyroid function tests were within normal limits on thyroid supplementation. He had negative serum antithyroid antibodies.

FIGURE 1. Axial CT with contrast showing the trachea at the level of the tracheostomy with surrounding thyroid goiter.

FIGURE 2. Axial CT with contrast showing hypopharyngeal compression by thyroid goiter.
On physical examination, the right thyroid lobe was palpable from the hyoid to the clavicle and the left thyroid lobe was moderately enlarged as well. There was slight deviation of the larynx to the left, but both true vocal cords were mobile when visualized with flexible laryngoscopy. On CT scan of the neck, the thyroid gland was heterogeneously enhancing and contained multiple nodules. The right lobe measured 5.8 cm × 3.9 cm, and the left lobe measured 3.7 cm × 2.0 cm. He underwent an uncomplicated total thyroidectomy.

Low-grade MALT lymphoma in association with a background of fibrosing chronic lymphocytic thyroiditis was identified in the specimen, and focal extrathyroidal soft tissue extension was noted. The microscopic characteristics included sheets of plasmacytoid lymphocytes demonstrating lambda light chain restriction effacing the thyroid parenchyma. Follicular elements were separated by tumor cells and fibrosis, while many follicles contained tumor cells as well (Figures 3 and 4). The patient received postoperative radiation therapy, and there is no evidence of disease recurrence after 13 months of follow-up.

DISCUSSION

Nongastric MALT lymphomas have been difficult to characterize because they are widely distributed throughout the body and difficult to assemble as a large series at any specific site. For example, the International Extranodal Lymphoma Study Group (IELSG) analyzed a series of 180 patients with nongastric MALT lymphomas. Within the series, nongastric MALT lymphoma was located in a total of 12 different sites, and 10 patients (6%) had thyroid MALT lymphoma. Thyroid lymphomas, in general, are rare malignancies, accounting for approximately 1% to 5% of all thyroid malignancies and for 1% to 2.5% of all lymphomas. In a recent series of 26 patients with primary thyroid lymphomas, MALT lymphoma was the second most common histologic type (23%) after diffuse large B-cell lymphoma (50%). It is recognized that MALT lymphomas arise in areas of persistent antigenic stimulation or persistent autoimmunity where lymphoid tissue has been acquired and has subsequently undergone transformation. This pathogenic concept is borne out in the stomach in response to chronic *Helicobacter pylori* infection and in the salivary glands in the presence of Sjögren’s syndrome. Thyroid MALT lymphomas similarly arise in the presence of longstanding Hashimoto’s thyroiditis.

MALT lymphomas of the thyroid gland usually occur in middle-aged to older individuals, with a 2–4:1 female-to-male ratio. Patients may present with a neck mass with or without dysphagia, dyspnea, anterior neck pain, or other compressive symptoms. As previously noted, these indolent tumors classically arise in a background of longstanding chronic lymphocytic thyroiditis. The estimated risk of the development of thyroid MALT lymphoma in this patient population is sig-
nificantly higher than in the general population. However, because autoimmune thyroiditis is one of the most common thyroid conditions, with 10% to 15% of all adults having antithyroid antibodies, the development of MALT or other thyroid lymphoma is a decidedly rare occurrence. MALT lymphomas may present 20 to 30 years after the onset of autoimmune thyroiditis and may manifest through the sudden enlargement of a preexisting thyroid mass.7

The use of FNA for the primary diagnosis of lymphoma8 remains controversial. Sangalli et al9 reviewed 17 primary thyroid lymphomas to analyze the utility of FNA for thyroid lymphomas. These investigators found 10 cases of MALT type, with 4 diagnosed correctly by FNA, 4 diagnosed as suspicious for lymphoma, and 3 diagnosed as Hashimoto’s thyroiditis. Similarly, in a retrospective review of 23 cases of primary thyroid lymphoma, Cha et al10 found that MALT tumors were inconsistently diagnosed with FNA, even with advanced ancillary techniques such as immunophenotyping.

Although FNA was historically of little value in the diagnosis of lymphoma, in reports on the addition of flow cytometry (FCM) to the analysis of the aspirate, FNA has proved useful. A number of series have been published documenting the value of FNA in the diagnosis and subclassification of non-Hodgkin’s lymphoma when combined with FCM.8 Advances in the FCM technology have allowed for the detection of abnormal coexpression of antigens important to diagnose and characterize lymphomas. In the REAL classification system, greater emphasis is placed on subclassification based on cytomorphologic analysis and immunophenotyping, as compared with the emphasis placed on lymph node architecture in the Working Formulation classification system. With careful cooperation between the cytopathologist, hematopathologist, and oncologist, a focused antibody panel can be applied during FCM. This focused FCM approach is critical given the limited FNA sample size and the need for a large number of cells for FCM. As compared with other small cell lymphomas, MALT lymphomas have been cytomorphologically distinguished as small, round cells with scattered immunoblast-like nucleolated large cells and immunophenotypically distinguished based on leukocyte antigens.

Patients with Hashimoto’s thyroiditis may be followed by a physician for many years before a thyroid MALT lymphoma is identified. Thieblemont et al5 sought to find a simple test to identify the evolution from chronic lymphocytic thyroiditis to MALT lymphoma. Thyroid function tests and tests for serum monoclonal immunoglobulins were unable to detect this evolution. They concluded that there was no simple blood test to replace the role of open biopsy to monitor the possible evolution of lymphocytic thyroiditis to lymphoma.

Imaging studies performed in the evaluation of a thyroid mass or goiter include ultrasound, radioactive iodine and technetium scans, CT, and MRI. On ultrasound, thyroid lymphomas typically have a nonspecific hypoechoic pattern, and radionuclide studies similarly show generalized heterogeneity.11 In a series of 9 patients with primary thyroid lymphoma, the most common CT appearance was a homogeneous mass diffusely affecting both lobes of the gland, isointense to muscle with a low invasive tendency and a low frequency of necrotic degeneration and calcification.12 MRI may complement other imaging studies by detecting surrounding extrathyroidal soft tissue involvement.

Overall, imaging studies are of limited value in diagnosing MALT thyroid lymphoma, although CT is required for staging and treatment planning once the diagnosis has been made. Disease is staged according to the Ann Arbor classification modified by Mussoff, in which stage IE disease corresponds to disease confined to the thyroid, stage IIE corresponds to disease confined to the thyroid gland and regional lymph nodes above the diaphragm, stage IIE corresponds to disease confined to the thyroid and lymph nodes above and below the diaphragm and/or spleen, and stage IV corresponds to disseminated nodal and/or additional extranodal involvement.13 Stages IE and IIE are considered locoregional disease, whereas stages IIE and IV are considered advanced disease. Cervical lymph nodes were noted to be the most commonly involved site at the time of diagnosis, with other nodal sites such as mediastinal nodes, or extranodal sites including the gastrointestinal tract, bone marrow, lung, bladder, liver, and spleen reported to be involved as well.

Treatment recommendations for patients with MALT lymphomas of any site are still evolving, and this is true for thyroid site-specific MALT lymphoma as well. MALT lymphomas tend to remain localized for a long time, and consequently local treatment options like surgery or radiation therapy have been effective.14,15 In their series of 103 patients with stage IE and IIE MALT lymphoma, Tsang et al16 noted excellent local control and curative potential in 13 patients with disease
arising in the thyroid gland. All 13 patients were treated with 30 to 35 Gy of radiation therapy; 1 of these also received preirradiation chemotherapy. The disease control rate for these patients was 100%. In the Theiblemont series of 7 patients with thyroid MALT lymphoma, all were treated with surgical excision, with a disease control rate of 100%. Notably, the diagnosis of MALT lymphoma may not be made until after thyroidectomy. In this case, adjuvant external beam radiation therapy should be considered if there is any question of incomplete surgical resection. Additionally, although most patients present with stage IE or IIE disease, it is recommended that patients found to have disease extending beyond the locoregional nodal basin undergo multimodality chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone.17

Recently, attention has turned to frontline treatment of nongastrointestinal MALT lymphoma with chemotherapy. This therapy is advantageous for the ability to avoid surgical risk or the risk of radiation-induced toxicity. In a series of 31 patients with stage IE nongastrointestinal MALT lymphoma, 3 patients had disease of thyroid origin, and all disease was considered nonbulky (ie, < 7 cm).15 Two of these 3 patients were treated with first-line chemotherapy consisting of flutarabine and mitoxantrone, and 1 patient was treated with first-line cyclophosphamide, vincristine, and prednisone. All 3 patients had a 100% disease control rate.

Malek et al14 recommend the inclusion of the tumor size when deciding on treatment for localized disease. They advocate multimodality therapy consisting of either surgery followed by radiation therapy or chemotherapy followed by radiation therapy for bulky MALT lymphoma of the thyroid. These investigators defined the disease as bulky if > 7 cm in greatest dimension.

In general, most patients with MALT lymphoma restricted to the thyroid gland have an excellent prognosis whether they are treated with thyroidectomy, radiotherapy, or chemotherapy as their frontline treatment. Most series report a 5-year overall survival rate of > 90% for thyroid lymphoma of the MALT subtype.4–6,16,18 Randomized clinical trials comparing the different treatment options have not been performed to compare the 3 therapies. Given this situation, treatment protocols should be tailored to the individual patient, with attention paid to surgical risk and the toxicity of radiotherapy or chemotherapy. For patients with a compressive goiter and an established diagnosis of localized thyroid MALT lymphoma, thyroidectomy with an attempt at resection of all disease is a reasonable option. However, the 3 cases presented in the present study demonstrate that establishing the diagnosis of thyroid MALT lymphoma preoperatively in a patient with goiter is difficult. Until diagnostic techniques are further refined, one must maintain an index of suspicion for the diagnosis and use individualized therapy that will have the lowest risk for that patient.

**CONCLUSION**

Thyroid MALT lymphomas are uncommon thyroid malignancies that typically arise in the presence of longstanding lymphocytic thyroiditis. They generally have an indolent course. Historically, the diagnosis was difficult to make without excisional biopsy, although advances in immunohistochemistry and FCM are improving the utility of FNA for primary diagnosis. A high index of suspicion is recommended in patients with a compressive goiter who have a longstanding history of lymphocytic thyroiditis, particularly if the goiter enlarges suddenly. Thyroidectomy should be recommended in this clinical scenario as an alternative to conservative therapy, to establish a diagnosis and treat the compressive symptoms. However, for thyroid MALT lymphoma in a patient without compressive symptoms or sudden enlargement, treatment should be tailored to the patient, with consideration of tumor size, disease dissemination, and contraindications to any of the 3 treatment options. Radiation therapy is a reasonable primary therapy for patients with stage IE and IIE, nonbulky disease and as adjuvant therapy for patients with thyroidectomy and suspected residual disease. Excellent cure rates have also been noted with first-line chemotherapy in patients with locoregional disease, stages IE and IIE. Although chemotherapy has been recommended for patients with advanced disease (stages IIIE and IV), prognostic data are unavailable because of the rarity of this condition.

**REFERENCES**
