Primary thyroid lymphoma: a rare but challenging diagnosis

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Introduction Primary thyroid lymphoma accounts for 2% to 5% of all thyroid neoplasms and occurs mostly in elderly women with prior long-lasting autoimmune lymphocytic thyroiditis. The lymphoma usually presents as rapidly growing thyroid mass, with increasing dyspnea due to tracheal compression, sometimes accompanied by enlargement of regional lymph nodes. Consequent respiratory disturbances and decreased venous reflux from the head and neck (superior vena cava syndrome) require early diagnosis and immediate treatment. A fine-needle aspiration biopsy (FNAB) is recommended as the first-line diagnostic procedure, but owing to its low sensitivity and specificity, a core needle biopsy or open surgical biopsy is often necessary. Since the histopathological diagnostic workup is time-consuming, some patients have to be treated before establishing a definite diagnosis. Tracheal compression may be relieved surgically or conservatively, usually with corticosteroids. The definitive treatment is based on chemotherapy with radiation therapy; only in selected cases of mucosa-associated lymphoid tissue (MALT) lymphoma at an early stage, radical surgery may be sufficient. Surgery plays an important role in sampling the specimen and when conservative treatment of tracheal stenosis fails.

Patients and methods We identified 10 cases of primary thyroid lymphoma treated in our department between 2007 and 2015: 9 women and 1 man, aged 51 to 90 years (mean age, 70 years), 7 with diffuse large B-cell lymphoma (DLBCL) and 3 with marginal zone lymphoma (MZL), 5 in stage IE and 5 in stage IIE according to the Ann Arbor staging system for lymphomas. All patients underwent standard preoperative tests for thyroidectomy: blood type, electrocardiogram, chest and neck X-ray, complete blood count, clotting screening, basic metabolic panel, as well as measurement of thyroid-stimulating hormone and free thyroid hormone (free triiodothyronine and free thyroxine) levels. The characteristics of the patients are presented in Table 1. The extent of the operation was described as: total thyroidectomy, subtotal thyroidectomy, isthmectomy or debulking for decompression of the trachea, an open surgical biopsy (or partial/wedge thyroid resection), and a biopsy of regional lymph nodes. Only total and subtotal thyroid resection was considered as curative surgery; all other procedures were described as palliative or diagnostic ones.

This study was approved by the appropriate ethics review board. The patients provided written informed consent to participate in the study.

Results Initial diagnosis of primary thyroid lymphoma was made on the basis of clinical symptoms and ultrasonography. Computed tomography (CT) was performed in 3 cases, showing an extensive tumor involving the thyroid gland. All patients presented with rapidly growing mass of the thyroid gland as a dominant symptom, 2 patients had hoarseness due to recurrent laryngeal nerve (RLN) palsy, and 8 patients had dyspnea due to tracheal compression. One patient with DLBCL showed symptoms of imminent respiratory failure and another patient with DLBCL underwent endotracheal intubation in another hospital before admission to our center. General symptoms including fever, night sweating, and weight loss were reported by 2 patients with DLBCL. Two cases of lymphoma were diagnosed in a histopathological examination after thyroid resection. One female patient was admitted to our department in emergency with severe respiratory distress due to tracheal compression, and in the remaining cases, admissions were planned.

Considering the clinical pattern, tumor size, and infiltration of the surrounding structures in all patients, we planned to perform at least open...
of 2 to 5 years), 1 patient (90 years old) died in the early postoperative course (at day 10 after surgery, due to progressive heart failure), 2 patients (aged 84 and 86 years) were discharged to the unit of internal medicine in their regional hospital with our recommendation for further treatment in a hematological/oncological center and were lost to follow-up. Two patients with DLBCL stage IIE died 1 and 3 years after surgery for progressive disease.

Discussion Thyroid lymphomas usually occur as rapidly growing neck tumors, mimicking thyroid anaplastic cancer. Some patients present with so-called B-cell symptoms: fever, sweating, especially nocturnal, weight loss, and enlarged cervical lymph nodes. Compression from rapidly growing mass results in narrowing of the tracheal lumen, stridor, and in some cases, unilateral or bilateral RLN palsy. Both dysphagia and superior vena cava syndrome are rare. Clinicaly, it is impossible to distinguish thyroid lymphoma from cancer or sarcoma. There is usually a history of Hashimoto disease or other autoimmune thyroiditis.

The diagnosis of primary thyroid lymphoma is difficult. Rapid progression of clinical symptoms requires that the diagnosis is established in the shortest possible time. Imaging does not allow a definite diagnosis but rather only a suspicion of cancer or lymphoma. Most authors emphasize the need for limiting the extent of surgery, especially to avoid tracheostomy, in favor of medical treatment and endoscopic stenting of tracheal stenosis. Debunking and cytoreductive surgical biopsy and possible tracheal decompression. In 2 cases, the symptoms of severe tracheal compression, resting dyspnea, and dysphagia required introduction of corticosteroid therapy on admission. In one of those cases, mild local improvement was achieved, while in the other patient, we observed rapid local response with almost complete tumor regression and symptom relief after 48 hours of treatment. Both patients avoided tracheostomy.

Extensive thyroid resection was performed only in patients in stage IE of lymphoma. There was no correlation between the Ki-67 index and the extent of the tumor and possible resection. The postoperative course was uncomplicated in 7 patients, with no cases of respiratory distress after nonradical or partial thyroid resection. In the patient who underwent tracheostomy, problems with correct tube positioning occurred as a result of extensive infiltration in the anterior or mediastinum and backward displacement of the tube. This led to the leaning of the tip of the tube onto the posterior tracheal wall and resulted in obturation of the tube. Typical local complications of tracheostomy also occurred in this case. In one patient after the lymph node biopsy, the compressive symptoms increased with severe resting dyspnea and imminent respiratory failure. High doses of methylprednisolone resulted in rapid tumor regression and symptom relief within 24 hours.

After confirmation of the diagnosis, patients were referred to the Department of Hematology for further treatment. To our best knowledge, 5 patients are still alive with remission (follow-up of 2 to 5 years), 1 patient (90 years old) died in the early postoperative course (at day 10 after surgery, due to progressive heart failure), 2 patients (aged 84 and 86 years) were discharged to the unit of internal medicine in their regional hospital with our recommendation for further treatment in a hematological/oncological center and were lost to follow-up. Two patients with DLBCL stage IIE died 1 and 3 years after surgery for progressive disease.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>HD</th>
<th>FNAB</th>
<th>H-P</th>
<th>Surgery</th>
<th>Ki-67</th>
<th>Bcl-2a</th>
<th>Stage</th>
<th>Dyspnea</th>
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<tr>
<td>1</td>
<td>F</td>
<td>73</td>
<td>Yes</td>
<td>Nondiagnostic</td>
<td>MZL</td>
<td>Subtotal thyroidectomy</td>
<td>&gt;70%</td>
<td>+</td>
<td>IE</td>
<td>+++ / steroid therapy</td>
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<td>86</td>
<td>No</td>
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<td>DLBCL</td>
<td>Thyroid biopsy</td>
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<td>NA</td>
<td>IIE</td>
<td>+</td>
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<tr>
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<td>NA</td>
<td>Lymphoid cells</td>
<td>MZL</td>
<td>Thyroid biopsy / tracheal decompression</td>
<td>&gt;55%</td>
<td>+</td>
<td>IE</td>
<td>-</td>
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<td>83</td>
<td>No</td>
<td>Nondiagnostic</td>
<td>DLBCL</td>
<td>Thyroid biopsy</td>
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<td>+</td>
<td>IE</td>
<td>+</td>
</tr>
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<td>5</td>
<td>F</td>
<td>90</td>
<td>No</td>
<td>Not performed</td>
<td>DLBCL</td>
<td>Debulking resection</td>
<td>90%</td>
<td>+++</td>
<td>IIE</td>
<td>+ + +</td>
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<td>DLBCL</td>
<td>Nodular biopsy</td>
<td>70%</td>
<td>+++</td>
<td>IIE</td>
<td>-</td>
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<td>84</td>
<td>No</td>
<td>Not performed</td>
<td>DLBCL</td>
<td>Tracheal decompression; tracheostomy</td>
<td>&gt;90%</td>
<td>+++</td>
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<td>+++ / intubation / emergency admission</td>
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<td>F</td>
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<td>No</td>
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<td>Nodular biopsy</td>
<td>70%</td>
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<tr>
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<td>Yes</td>
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<td>Thyroidectomy</td>
<td>5%</td>
<td>+</td>
<td>IE</td>
<td>+</td>
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</tbody>
</table>

a +, weak staining; +++, strong staining
b +, mild dyspnea; +, moderate dyspnea; +++, severe dyspnea

Abbreviations: DLBCL, diffuse large B-cell lymphoma; F, female; FNAB, fine-needle aspiration biopsy; HD, Hashimoto disease; H-P, histopathology; M, male; MZL, marginal zone lymphoma; NA, not available; +, weak staining; +++, strong staining
operations are not recommended since the principal methods of the treatment of primary thyroid lymphoma are chemotherapy and radiation therapy, and the risk of additional postoperative complications is high. Thyroid resection, with possible adjuvant radiation therapy, is acceptable as a curative procedure only in selected cases of MALT lymphomas (stage IE) limited to the thyroid gland without extending through its capsule. It was also reported that thyroidectomy in cases of lymphatic tumors unreasonably exposes the patient to the risk of thyroid resection, especially to RLN palsy. DLBCL usually extends widely to the adjacent structures, making the radical resection impossible, while debulking surgery does not improve the results of treatment but increases the risk of local complications. The first-line diagnostic technique is neck ultrasound to visualize the thyroid gland and cervical lymph nodes. Scintigraphy is useless because lymphomas are not capable of iodine uptake. The technique of choice in imaging examination in all cases of rapidly growing neck masses is CT with visualization of the tumor size as well as its relation to vital structures of the neck and their possible infiltration. Magnetic resonance imaging has no advantage over CT and is used mostly in radiation therapy planning.

A preoperative biopsy may help establish the diagnosis of lymphoma in some cases, especially DLBCL, while diagnosis of MALT lymphoma is less certain with biopsy. This makes an open surgical biopsy or core needle biopsy the most important method in the diagnostics of thyroid lymphoma. The role of FNAB, which is still the basis for preoperative diagnosis of thyroid tumors, has not been established in thyroid lymphomas. The diagnostic efficacy of FNAB can be improved with flow cytometry and immunocytochemistry; however, they require enough cellular material, strict cooperation between a pathologist and a clinician during the procedure, and adequate diagnostic facilities of the center. Since flow cytometry is performed in unfixed material, the next biopsy may be needed to confirm the diagnosis of lymphoma established on the basis of routine FNAB. In our experience, FNAB was not useful, and even confusing in some cases. In patients scheduled for open surgical biopsy, repeated FNAB was not performed. We did not use flow cytometry either, as it is not routinely available in our center.

All the above reasons suggest surgery as the technique of choice to establish a definite diagnosis. Unreasonable cytoreductive procedures as well as tracheostomy should be avoided since they affect the radiation therapy and response evaluation in imaging examinations. Radical resection is rarely possible for technical reasons and additionally exposes the patient to complications. Surgery may be curative only in rare cases of thyroid-limited MALT lymphoma (stage IE); in more advanced cases of MALT lymphoma and in all other histological types of lymphoma, surgery is diagnostic or palliative. In patients with a suspicion of lymphoma, corticosteroids may lead to a rapid decrease of the tumor mass and improve the patient’s quality of life. Tracheostomy should be considered a last resort treatment, especially in the era of endoscopic stenting both in the alimentary tract and in the airways. In our study, tracheostomy was performed only once because the patient’s state did not allow us to apply other treatment methods. In other cases, surgical reduction of the tumor mass or corticosteroids allowed us to avoid tracheostomy.

Only 2% to 3% of all lymphomas are found in the thyroid gland, mostly non-Hodgkin B-cell lymphomas, with the most common DLBCL, followed by MZL or MALT lymphoma. The latter is associated with long-lasting autoimmune thyroiditis. Hashimoto disease cannot be confirmed in all cases, as some patients do not present symptoms of hypothyroidism, and, in some cases, there are no signs of lymphocytic thyroiditis in histological specimen. Development of MALT lymphoma in the organs that physiologically do not contain lymphoid tissue has to be preceded by lymphocytic proliferation of the inflammatory origin. The presence of mixed lymphomas (MALT/DLBCL) suggests that more indolent MALT lymphoma transforms into more aggressive DLBCL. This mechanism explains the occurrence of these neoplasms in elderly patients because the development of these neoplasms lasts many years before they become clinically evident. Other types of lymphoma, such as follicular lymphoma or small B-cell lymphoma, occur less frequently, and T-cell lymphomas, Burkitt lymphoma, and Hodgkin-lymphoma are extremely rare. Thyroid lymphomas are usually diagnosed in stage IE (according to the Ann Arbor staging system), when the disease is limited to the thyroid gland, or stage IIE characterized by the involvement of the lymph nodes on the ipsilateral side of the diaphragm. Stages IIIIE and IVE are reported much less frequently. In these cases, it is impossible to distinguish between a primary thyroid lymphoma with secondary involvement of other organs and a primary disseminated lymphoma with thyroid involvement.

Despite their rarity, primary thyroid lymphomas constitute a difficult diagnostic and therapeutic challenge. Patients are usually referred to a surgeon with the diagnosis of a rapidly growing neck tumor with increasing local symptoms, as well as for rapid histopathological diagnosis. Since a FNAB usually does not allow a definite diagnosis, especially of the type of the lymphoma, an open surgical biopsy still remains the first-line option to collect material for histopathological diagnosis. Extensive surgery is not necessary but feasible in MALT lymphomas. In severe cases of tumor compression, surgical decompression of the trachea may be performed; however, an attempt to introduce corticosteroid therapy instead is worth considering. Prognosis is rather good in MALT lymphomas, although advanced age
of the patient is a poor prognostic factor. There is some strong evidence for lymphoma development from chronic lymphocytic thyroiditis, although this has not been clearly confirmed in our experience. Thus, monitoring of patients with Hashimoto disease with imaging and a comprehensive diagnostic workup in each case of a rapid enlargement of the thyroid gland or regional lymph nodes seem to be justified.

REFERENCES