MALT Lymphoma

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Abstract

Primary thyroid lymphomas are uncommon neoplasm and estimated up to 5% of all thyroid malignant neoplasms. They tend to occur in middle- to older-aged women and are usually associated with Hashimoto's thyroiditis. Almost all of them are B-cell origin. The most common subtype is diffuse large B-cell lymphoma (DLBCL), followed by mucosa-associated lymphoid tissue (MALT lymphoma). DLBCL exhibits an aggressive clinical course, and multimodal treatment should be considered. In contrast, MALT lymphoma exhibits an indolent course, and its management is more conservative. The diagnostic accuracy of aspiration cytology for primary thyroid lymphoma is not high enough to rely solely on it. Several series have reported that in 50–90% of patients with primary thyroid lymphoma, the diagnoses have been made by aspiration cytology. This is mainly because of the morphological similarities between Hashimoto's thyroiditis and primary thyroid lymphoma, especially MALT lymphoma. Herein, we show a case of MALT lymphoma and discuss the differential diagnoses between MALT lymphoma and Hashimoto's thyroiditis.

37.1 Introduction

Primary thyroid lymphoma is defined as lymphoma that arises within the thyroid gland. This excludes the lymphoma invaded by metastasis or direct extension. Primary thyroid lymphomas are uncommon neoplasm and estimated up to 5% of all thyroid malignant neoplasms [1]. They tend to occur in middle- to older-aged women and are usually associated with Hashimoto's thyroiditis. Almost all of them are B-cell origin, including diffuse large B-cell lymphoma (DLBCL), mucosa-associated lymphoid tissue (MALT) lymphoma, and follicular lymphoma [2–4]. The most common subtype of primary thyroid lymphoma is DLBCL, followed by MALT lymphoma [1–4]. DLBCL exhibits an aggressive clinical course, and multimodal treatment should be considered. In contrast, MALT lymphoma exhibits an indolent course, and its management is more conservative [1–4]. The diagnostic accuracy of aspiration cytology for primary thyroid lymphoma is not high enough to rely solely on it. Several series have reported that in 50–90% of patients with primary thyroid lymphoma, the diagnoses have been made by aspiration cytology [3, 5, 6]. This is mainly because of the morphological similarities between Hashimoto's thyroiditis and primary thyroid lymphoma, especially MALT lymphoma. Herein, we show a case of MALT lymphoma and discuss the differential diagnoses between MALT lymphoma and Hashimoto's thyroiditis (see Chaps. 35 and 37).

37.2 Case

The case was a 68-year-old woman. She had noticed anterior neck swelling 1 year ago. She visited a hospital for medical checkup, and the ultrasound revealed multiple nodules in her thyroid. Serum TSH was elevated (8.14 μIU/mL). She was referred to our hospital for close inspection. Serum TSH, thyroglobulin, and thyroglobulin antibody were 5.155 μIU/mL, 880.00 ng/mL, and 40.6 IU/mL, respectively. Serum thyroperoxidase antibody was negative. The ultrasound revealed multiple nodules in both lobes of the thyroid (Fig. 37.1). The largest nodule measured 28 × 10 × 22 mm. The nodules were hypoechoic and heterogeneous. The borders were irregular and indistinct. Both the ultrasound and aspiration cytology were suspicious of lymphoma. Flow cytometry CD45 gating test using aspirated

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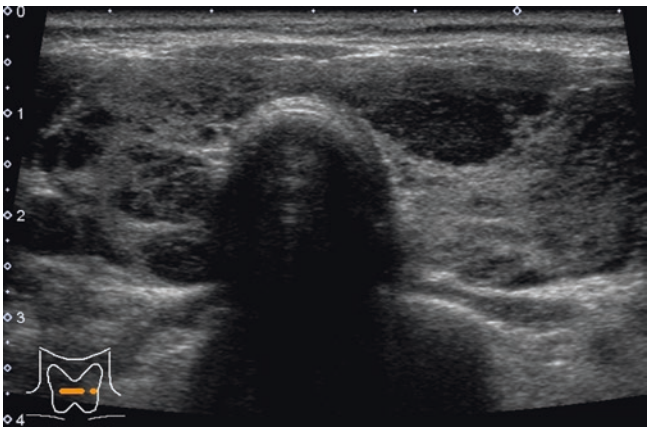

Fig. 37.1 Multiple hypoechoic and heterogeneous nodules are seen in both lobes of the thyroid (ultrasound B-mode image)

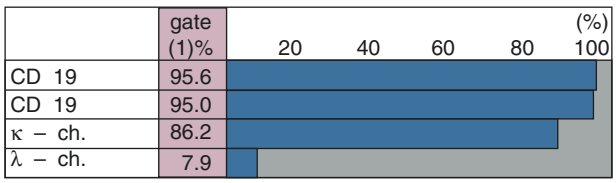

Fig. 37.2 CD45 gating test shows light chain restriction

material revealed light chain restriction (κ/λ ratio; 10.9) (Fig. 37.2). To confirm the diagnosis of lymphoma, a total thyroidectomy was performed.

37.3 Cytological Findings

Aspirated materials were highly cellular and composed of lymphoid cells (Fig. 37.3). A few follicular cells with oncocytic features were seen (Fig. 37.4). Most of lymphoid cells were small- to moderate-sized, but a small number of large-sized lymphoid cells were intermingled. The chromatin pattern of lymphoid cells was similar regardless of the difference in size (Fig. 37.5). Micronucleoli were observed, even in small-sized lymphoid cells. Lymphoglandular bodies were not apparent.

37.4 Pathological Findings

Resected thyroid was enlarged due to multiple nodular lesions (Fig. 37.6). The nodules were tan to whitish yellow in color. The borders were indistinct and tended to merge each other. The nodules were composed of various-sized lymphoid cells (Fig. 37.7). Most of them were small- to medium-sized. Nests that proliferative follicular cells and lymphoid cells were intimately intermingled (lymphoepithelial lesions) (Fig. 37.8) and an aggregation of lymphoid cells within thy-

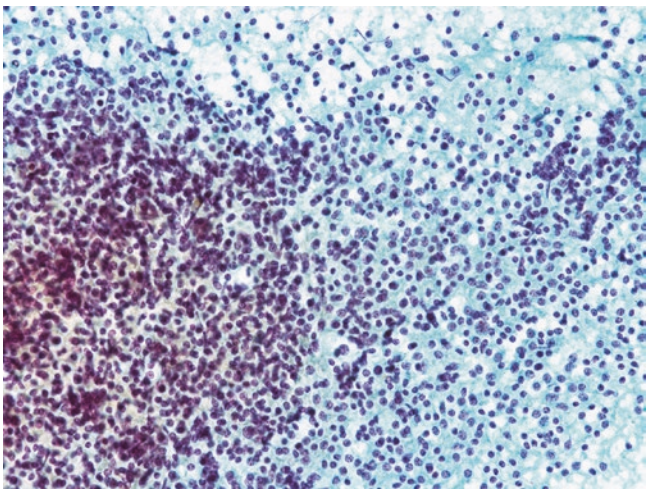

Fig. 37.3 A large number of lymphoid cells are smeared (Pap, 20×)

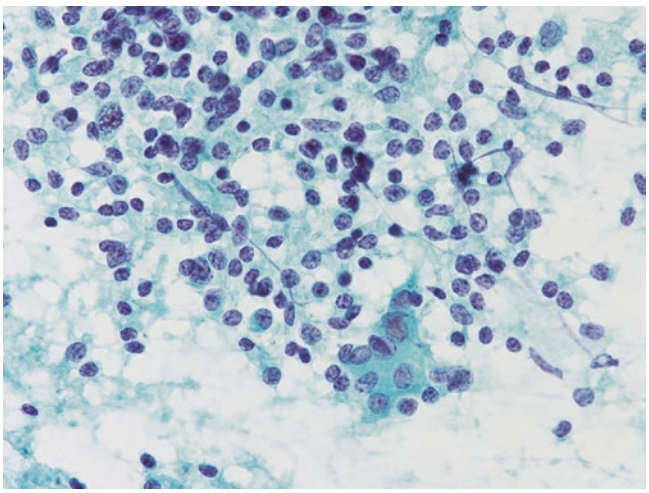

Fig. 37.4 A small cluster of the follicular cells with oncocytic features is seen (Pap, 40×)

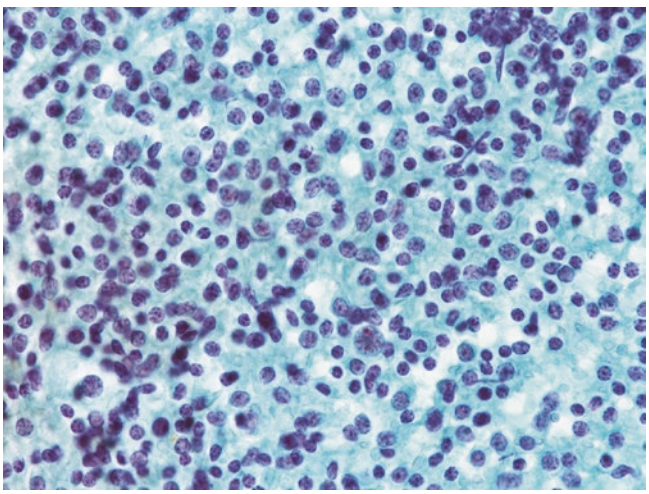

Fig. 37.5 Lymphoid cells have similar chromatin pattern regardless of the difference in size (Pap, 40×)

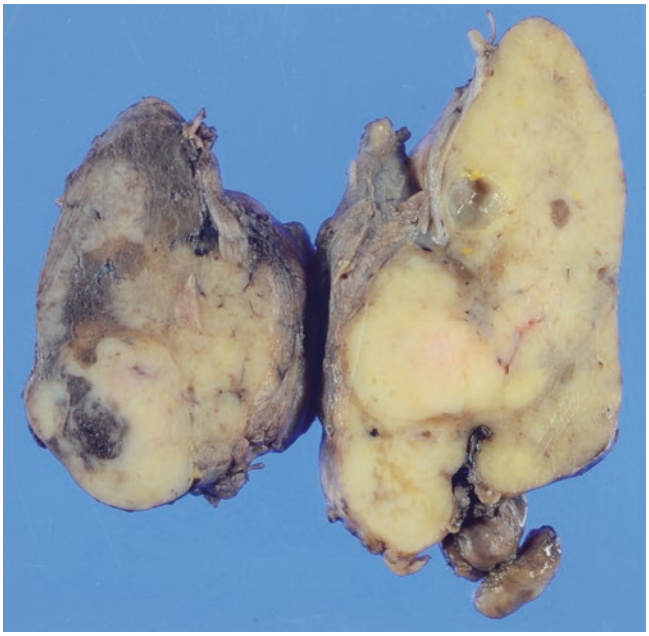

Fig. 37.6 The thyroid is enlarged due to multiple nodules

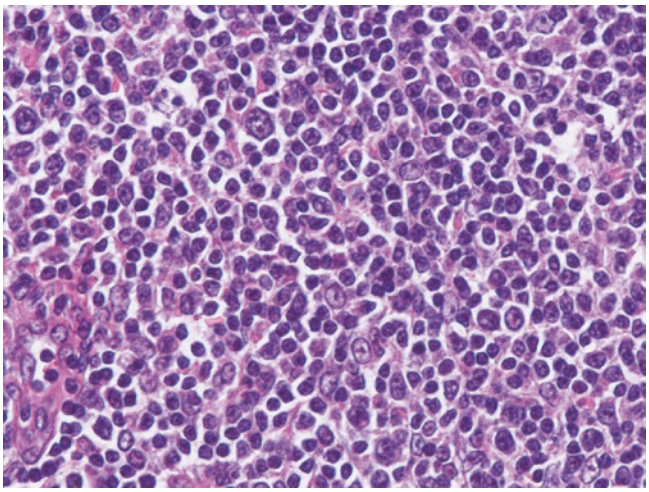

Fig. 37.7 The nodules are composed of mainly small- to medium-sized lymphoid cells (HE, 40×)

roid follicles (packing) (Fig. 37.9) were observed. Lymphoid cells did not invade extrathyroidal tissue. Nonneoplastic thyroid tissue was consistent with Hashimoto's thyroiditis.

Immunohistochemically, most of lymphoid cells were positive for CD20. Monoclonality (light chain restriction) was not confirmed. CD23 immunostaining manifested disrupted follicular dendritic cell meshwork (follicular colonization) within huge and irregular-shaped germinal center (Fig. 37.10). Cytokeratin AE1/AE3 immunostaining highlighted lymphoepithelial lesions and packing (Fig. 37.11). In flow cytometry CD45 gating test, κ/λ ratio of the lymphoid cells was 15.3. G-banding chromosomal examination revealed chromosomal abnormality, 46, XX, der (2) add (2)

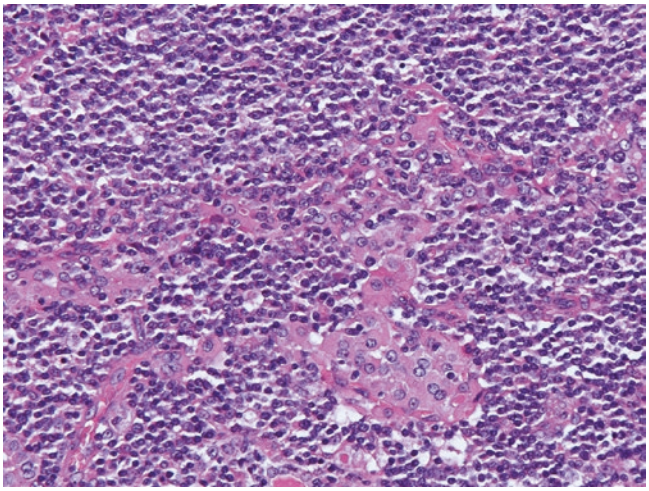

Fig. 37.8 Lymphoepithelial lesion composed of proliferative follicular cells and lymphoid cells is seen (HE, 20×)

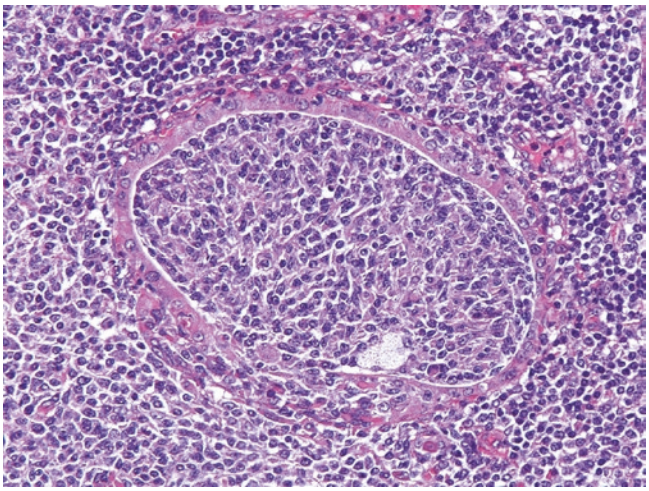

Fig. 37.9 An aggregation of lymphoid cells within thyroid follicles (packing) is seen (HE, 20×)

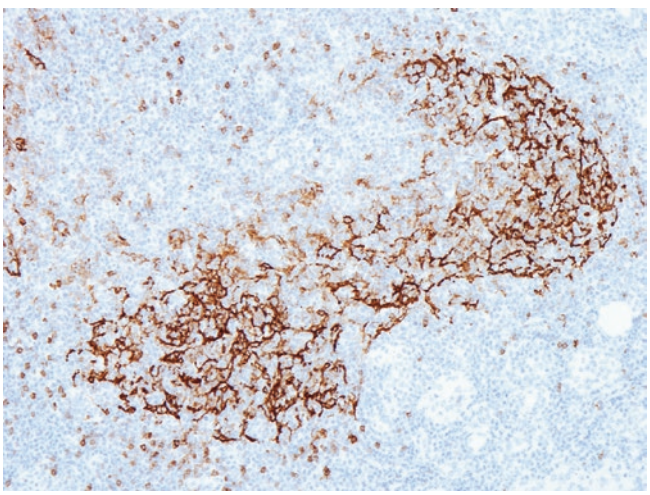

Fig. 37.10 CD23 immunostaining manifests disrupted follicular dendritic cell meshwork within enlarged germinal center (CD23 immunostaining, 10×)

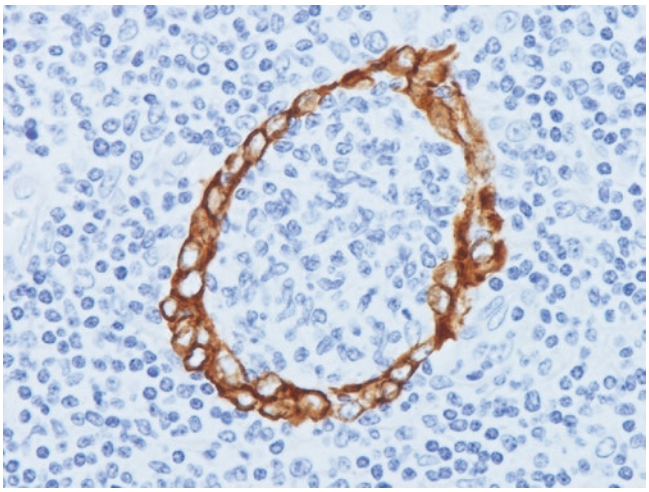

Fig. 37.11 Cytokeratin AE1/AE3 immunostaining highlights packing (cytokeratin AE1/AE3 immunostaining, 40×)

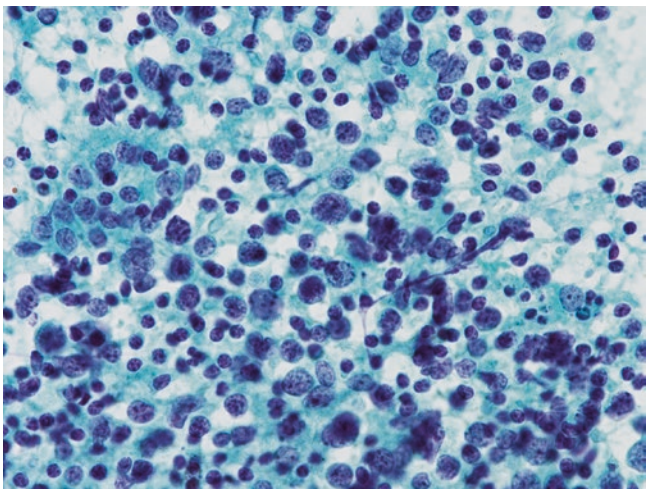

Fig. 37.12 Diffuse large B-cell lymphoma. Two-cell pattern composed of the large-sized atypical lymphoid cells and nonneoplastic small-sized lymphocytes is seen (Pap, 40×)

(p11.2) del (2) (q?). On immunoglobulin heavy chain JH DNA rearrangement analysis, clonal rearrangements of the IGH gene were not identified.

37.5 Discussion

MALT lymphomas of the thyroid show a vaguely nodular or follicular pattern, and the boundary between the lymphoma and Hashimoto's thyroiditis is indistinct. The lesions are heterogeneous and composed of small atypical lymphoid cells, centrocyte-like cells, monocytoid B cells, large atypical lymphoid cells, and plasma cells [1–3]. Some cases exhibit excessive plasma cell differentiation [7]. Such cases had been referred to as extramedullary plasmacytoma, but they are currently thought to be one of MALT lymphomas. MALT lymphoma can be associated with amyloid deposition [7]. Follicular colonization (infiltration into germinal center of the lymph follicles), packing (infiltration into the lumen of preserved thyroid follicular structure), and lymphoepithelial lesion (proliferative nests composed of both follicular epithelia and lymphoma cells) are also histological features of MALT lymphomas.

Aspiration cytology is a widely accepted technique for the diagnosis of the thyroid tumors, and it is not difficult cytologically to diagnose DLBCL. The smears from DLBCL are highly cellular and mainly composed of a large number of atypical lymphoid cells (Fig. 37.12) (see Chap. 38). They are large-sized and monotonous. Mitosis, large nucleoli, and nuclear irregularity are frequently observed. There are lymphoglandular bodies in the background. Two-cell pattern may be seen because of an association with nonneoplastic small-sized lymphocytes (see Fig. 1.10 in Chap. 1).

Table 37.1 Differential diagnoses of MALT lymphoma and Hashimoto's thyroiditis

	MALT lymphoma	Hashimoto's thyroiditis with marked lymphoid proliferation
Cellularity	Marked	Moderate to marked
Lymphoid cells	Mainly intermediate-sized Monomorphic or polymorphic	Mainly small-sized Polymorphic
Chromatin pattern	Monotonous	Variable
Micronucleoli in small-sized cells	Present	Absent
Indented nuclear membrane	Present	Absent
Elongated nuclei	Present	Absent
Follicular cells Oncocytic change	Absent or few Absent	Few Present
Connective tissue	Absent	Maybe present
Lymphoglandular bodies	Maybe present	Absent

MALT lymphoma shows a mixture of small- to intermediate-sized atypical lymphocytes (about twice as large as a small mature lymphocyte), monocytoid B cells, immunoblasts, and plasma cells. Thus, it is frequently difficult to distinguish MALT lymphoma from Hashimoto's thyroiditis with marked lymphoid proliferation. Table 37.1 shows differential diagnoses of MALT lymphoma and Hashimoto's thyroiditis with marked lymphoid proliferation. We believe that it is important to pay attention to the chromatin pattern. Chromatin patterns of lymphocytes seen in nonneoplastic lymphoid proliferations vary depending on their sizes. The heterochromatin is rich and coarse granular in small lymphocytes and decreased and fine in large

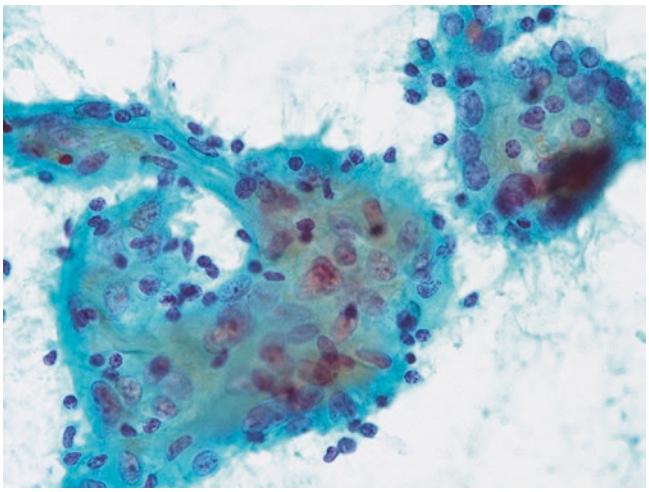

Fig. 37.13 Hashimoto's thyroiditis. Follicular cells show typical oncocytic features (Pap, 40×)

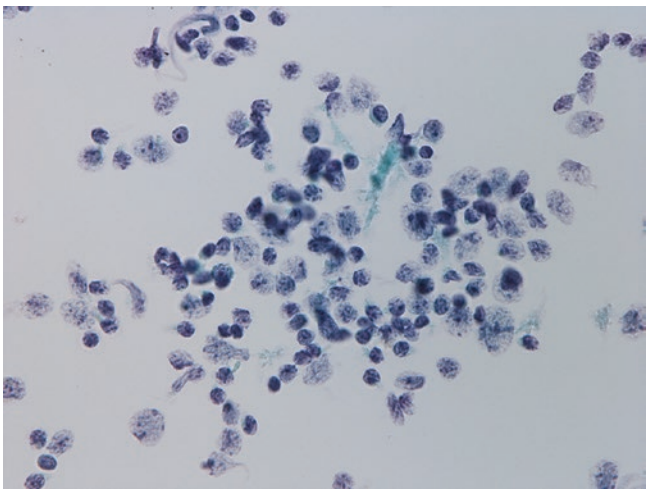

Fig. 37.14 In liquid-based cytology specimen, the nuclei of lymphoma cells were large, swollen and naked, and chromatin is smashed. (Pap, LBC specimen, 100×)

lymphocytes. In contrast, lymphoid cells seen in MALT lymphoma show similar chromatin pattern regardless of the difference in size. An additional clues suspecting MALT lymphoma are the presence of the micronucleoli in small-sized lymphoid cells, indented nuclear membrane, and elongated nuclei. Kaba et al. [8] described that small- to medium-sized cells displaying irregularly shaped nuclei with prominent nucleoli are neoplastic cells, and lymphoepithelial clusters and mountain range-like clusters are clues of MALT lymphoma. The follicular cells seen in lymphoepithelial clusters of MALT lymphoma are not oncocytic, but the follicular cells in Hashimoto's thyroiditis are oncocytic (Fig. 37.13). In liquid-based cytology specimens, the presence of large, swollen naked nuclei with smashed chromatin are useful in distinguishing thyroid lymphoma from nonneoplastic lymphocytes in LBC specimens (Fig. 37.14) [9].

It is difficult to distinguish between MALT lymphoma and Hashimoto's thyroiditis by cytomorphology alone [10, 11] (see Chap. 23). Core needle biopsy, though not considered as a first choice for the diagnosis of lymphomas, has been reported to have a higher diagnostic accuracy [12, 13] (see Chap. 65). It has been demonstrated that ancillary techniques improve the cytological diagnosis of primary thyroid lymphoma [14, 15]. When thyroid lymphoma is ultrasonographically suspected, we examine flow cytometry CD45 gating test using aspirated materials. To identify monoclonal proliferation, we define light chain restriction when the κ/λ ratio of the lymphoid cells counted by gating was greater than 3.0 or less than 0.33 [11]. In the present case, light chain restriction was confirmed in both aspirated materials and resected thyroid.

We established a preoperative diagnostic algorithm for primary thyroid lymphoma by combining the use of these three diagnostic tools, (1) ultrasound, (2) aspiration cytology, and (3) flow cytometry [11]. A scoring system was defined as follows: US, low suspicion 0, intermediate suspicion 1, and high suspicion 2; aspiration cytology, benign 0, undetermined 1, and malignant 2; and flow cytometry, $0.33 < \kappa/\lambda$ ratio < 3 0, κ/λ ratio ≤ 0.33 2, and κ/λ ratio ≥ 3 2. We propose that a score ≥ 4 indicates the need for thyroid resection for diagnosing primary thyroid lymphoma. In such a situation, the case of diffuse large B-cell lymphoma, which was aggressive, was not excluded. Approximately one-fifth of MALT lymphomas may be overlooked, but the patients could be followed up with because of an indolent course.

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