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A Case of Primary Histiocytic Sarcoma Arising from Thyroid Gland

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Abstract Histiocytic sarcoma (HS) is an extremely rare true histiocytic malignancy. We report a case of HS arising from thyroid gland in a 69 year-old man. Following subtotal thyroidectomy, a histopathologic, immunohistologic, and genotypic examination revealed HS. This tumor was composed of large spindle or round epithelioid cells with abundant eosinophilic cytoplasm. The neoplastic cells were positive for macrophage-associated antigen CD68, CD163, and lysozymes, as well as CD45, HLA- DR, DP, DQ, and S100, most consistent with a diagnosis of HS. The BIOMED-2 multiplex PCR analysis showed polyclonal B- and T-cell populations. To our knowledge, this is the first report of a rare entity HS involving thyroid gland using a comprehensive immunophenotyping panel including CD163 as well as molecular studies to establish the true histiocytic nature of these lesions.

Keywords Histiocytic sarcoma · Thyroid gland · Differential diagnosis · Gene rearrangements · CD163 · Immunohistochemistry

Abbreviations

ALL	acute lymphocytic leukemia
DAB	3,3′-diaminobenzidine
HS	histiocytic sarcoma
IGH	immunoglobulin heavy chain
IGL	immunoglobulin light chain
LCS	langerhans cell sarcoma
PCR	polymerase chain reaction
TCR	T-Cell receptor

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Introduction

Histiocytic sarcoma (HS) is a rare, extremely aggressive lymphohematopoietic malignant neoplasm composed of tumor cells showing morphologic and immunophenotypic features of mature histiocytes [1]. A few cases of extranodal HS have been described in the head and neck region [2], thyroid gland is rarely involved by this disease. Although a case has been demonstrated in thyroid gland [3], its finding was not confirmed in comprehensive studies.

The diagnosis of HS requires the verification of histiocytic lineage and exclusion of malignancies of other lymphohematopoietic lineages with extensive immunophenotypic workup including histiocytic markers such as CD68, lysozyme, MAC387, α_1-antitrypsin, and α_1-antichymotrypsin. CD68 is the most important antigen that detects macrophages [4]. However, these markers are not always specific for histiocytic differentiation. Recently, several authors have reported that CD163, a hemoglobin scavenger receptor, may be a more specific marker of the monocytic/histiocytic lineage [5, 6]. Many earlier reported cases of HS were positive for CD68 but were not evaluated for CD163. We present one cases of HS involving thyroid gland using a comprehensive immunophenotyping panel including CD163 as well as molecular studies to establish the true histiocytic nature of these lesions.

Clinical History

A 69 year-old man presented with bilateral progressive nodular enlargement of the thyroid. Ultrasound scans of the

thyroid showed multiple irregular hypoechoic solid nodules with characteristic punctate calcification and ill-defined margins. The left lobe was distorted and enlarged to an irregular spheroid by a lobate tumor mass, measuring 6.5× 5.0×4.0 cm in size, although the isthmus was obscured. The consistency was soft to friable, with occasional more firm light gray-tan areas mingled with dark-red hemorrhagic foci. There were no enlarged lymph nodes in the resected specimen. No fresh tissue was available for electron microscopy studies.

Materials and Methods

The specimen was fixed in formalin, embedded in paraffin, sectioned at 5-μm intervals, and stained using H&E, and examined under routine light microscope. An extensive panel of immunohistochemical antibodies was applied to deparaffinized tissue sections according to standard methods. A DAKO EnVision system with a 3,3′-diaminobenzidine (DAB) chromogen was then used to develop the stain. Clonality analysis for immunoglobulin heavy chain (IGH), light chain (IGL) and T-Cell receptor (TCR) genes were performed using a commercially available IgH and TCRγ gene rearrangement assay kit. The DNA was prepared from formalin-fixed, paraffin-embedded tissue sample and purified according to previously published methods [7]. DNA from the immunophenotypically and gentically proved B-cell lymphoma and T-cell lymphoma was used as a positive control. DNA from reactive lymphomatic proliferation specimens was used as negative control. Additional negative and empty PCR were also included for internal controls. All tests were run in duplicate.

Results

Histologic Findings

The tumor composed of discohesive sheets of large mononuclear epithelioid cells infiltrating surrounding tissues with mild to moderate cytologic atypia (Fig. 1a), with some areas showing spindle cell (Fig. 1b) and clear cell components (Fig. 1c), occasional anaplastic cells and numerous bizarre mitotic figures. The tumor usually showed in a diffuse growth pattern with extensive geographic-like necrosis, in some areas, formed granuloma-like structures, which contained central areas of tumor necrosis surrounded by palisading epithelioid histiocytes, and multinucleate giant cells, capsuled by fibrosis (Fig. 1d and e). The neoplastic cells showed marked anisokaryosis and macrokaryosis, with moderate to abundant eosinophilic vacuolar cytoplasm, round to irregular eccentric, and pleomorphic nuclei (Fig. 1b and c). Occasionally, both cell types were present within one lesion. Neoplastic multinucleated giant cells were common and presented as either large round cells or as bizarre stellate cells with long cytoplasmic processes (Fig. 1f). Areas of thyroid affected by the disease show intrafollicular neoplastic infiltration, with partial or complete disruption thyroid follicles. These changes tend eventually to lead to replacement of the damaged follicles by tumor cells and fibrosis.

Immunophenotypic Findings

The neoplastic cells showed immunoreactivity for CD45 (Fig. 2a), although expression was diffusely weaks, and consistently intense immunoreactivity for macrophage/histiocytic marker CD68 (Fig. 2b), CD163 (Fig. 2c), HLA- DR (Fig. 2d), and HLA-DP, DQ, DR, weak to moderate immunostaining for Lysozyme (Fig. 2e), α-1-antitrypsin, S100 (Fig. 2f), CD15 (granulocyte marker), myeloperoxidase (myeloid cell marker), and focal staining for CD43 (myeloid cells and macrophages) and ALK (anaplastic large-cell lymphoma marker). All remaining makers, including CD3, CD4, CD8, CD45RO (T-cell marker), CD20, CD79a (B-cell markers), CD23 (B-cell chronic lymphocytic leukemia/lymphoproliferative disease marker), CD1a, CD21, CD23, CD35 (accessory/dendritic cell markers), Fascin (mature B-cell and follicular dendritic cell marker), and CD30 (anaplastic large-cell lymphoma and Reed-Sternberg cell marker), were uniformly negative. The neoplastic cells were also negative for HMB-45, Melan-A, Keratin, Cytokeratin, high molecular cytokeration, EMA, E-Cadherin, CD31, CD34, von Willebrand Factor, actin, α-SMA, desmin, NSE, SYN, chromogranin, PGP9.5, and GFAP. These immunohistochemical features are typical of HS [8]. Ki-67 immunoreactivity was variable, staining 31% of malignant nuclei.

Molecular Genetic Findings

The polymerase chain reaction (PCR) amplification with primers IGH-A, IGH-B, IGH-C, IGH-D, IGH-E, IGK-A, IGK-B, and IGL to framework region III and the joining region of the IGH gene showed no identical clonal bands in sample. PCR amplification with two primer-sets TCRB-A, TCRB-B, TCRB-C, TCRG-A, TCRG-B and TCRD for detection of TCRB, TCRG and TCRD gene rearrangements also did not show identical bands in sample. These results indicate polyclonal features in IGH, IGK, IGL, TCRB, TCRG and TCRD genes of its origin. It should be noted that TCRγ gene rearrangements are common in precursor B-cell acute lymphocytic leukemia (ALL).

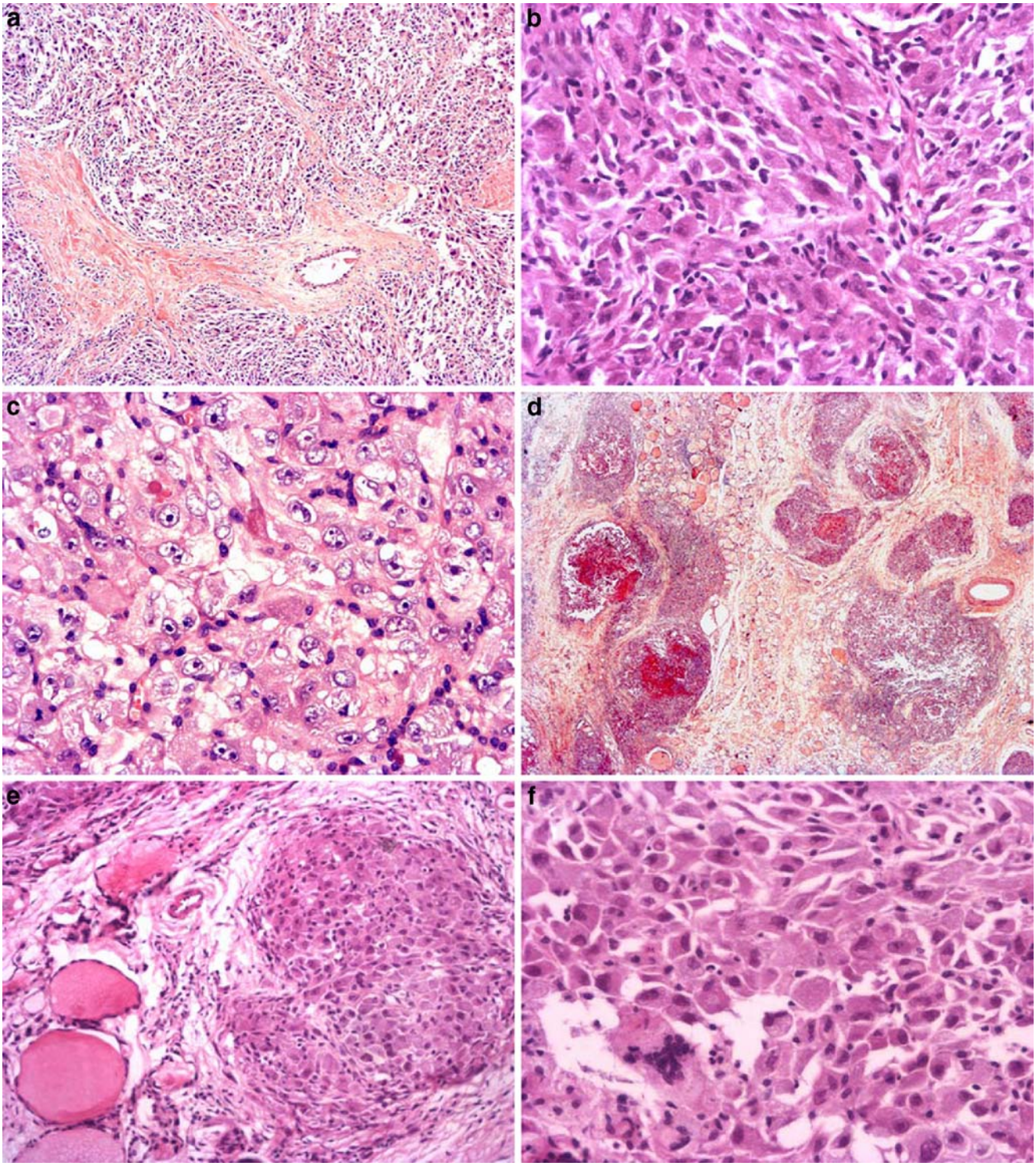

Fig. 1 **a** The tumor is composed of discohesive sheets of cells diffusely infiltrating thyroid gland; **b** The spindle cells have slightly smaller, round or elongate nuclei, characterized by more condensed, coarse chromatin; **c** The clear cells possess large vesicular, round to oval or indented and twisted nuclei with one or more prominent nucleoli and slightly eosinophilic or ample clear cytoplasm; **d** The tumor growth in a granuloma-like pattern varied in shape and size infiltrating thyroid gland; **e** The neoplastic granuloma composed of discohesive sheets of large, polygonal cells; **f** Multinucleated cells admixed with stromal inflammatory infiltrates.a and d: H&E, ×40; b, c and f: H&E, ×200; e: H&E, ×100

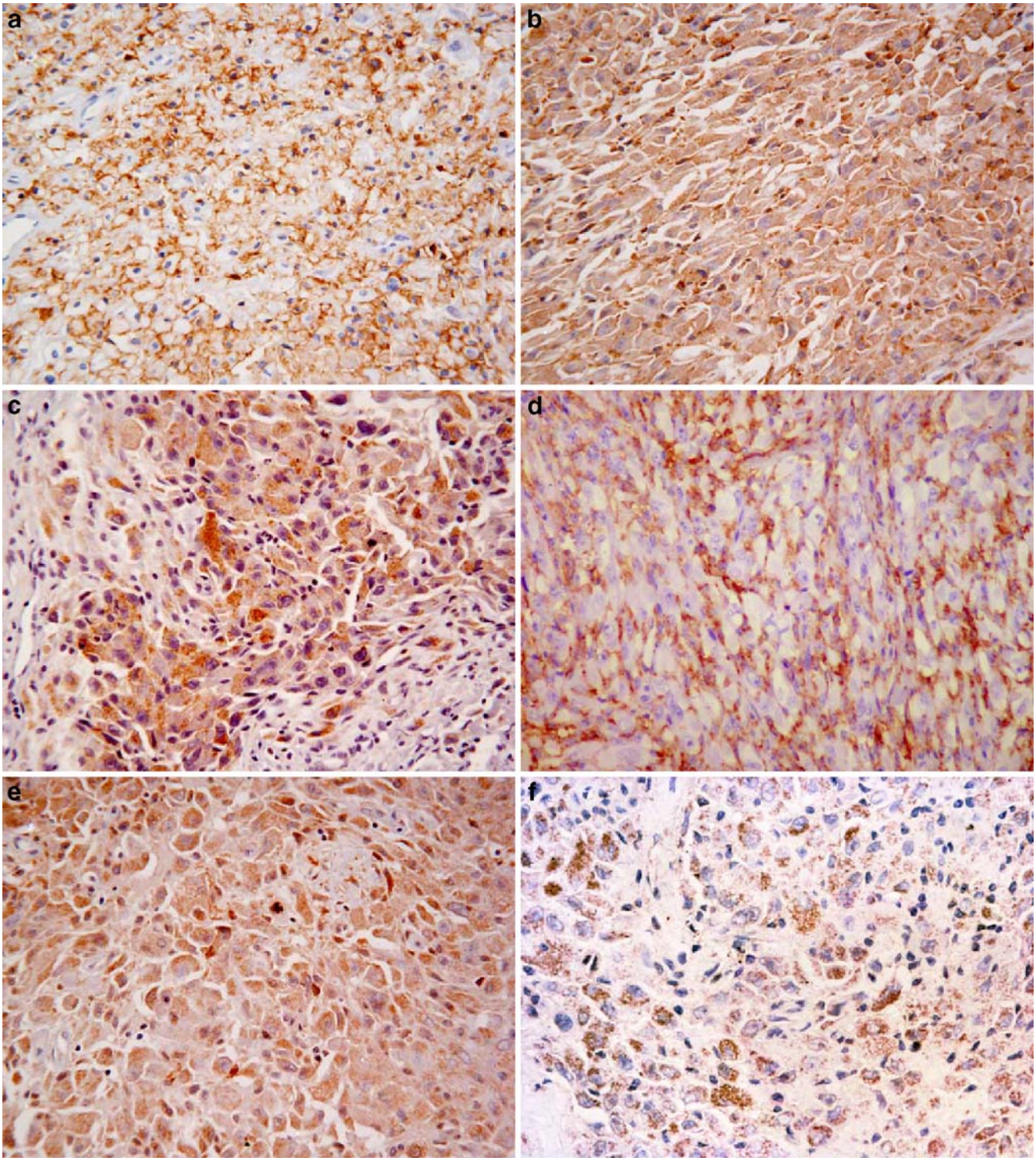

Fig. 2 The tumor cells showed posotivities for **a** CD45; **b** CD68; **c** CD163; d HLA-DR; e Lysozyme; **f** S100. DAKO EnVision system with DAB, ×200

Discussion

HS is a problematic and controversial group of an exceedingly rare malignancy that demonstrates morphologic and immunophenotypic features of macrophage/histiocytic differentiation. The diagnosis of HS is often challenging and relies predominantly on the verification of histiocytic lineage and the exclusion of other, poorly

differentiated, large cell malignancies, usually requires extensive immunophenotypic investigation, and, occasionally, electron microscopic analysis [1, 6, 8].

HS characteristically express histiocytic markers such as CD68 (PG-M1 and KP-1), lysozyme, CD11c, CD14, and the more recently reported histiocytic marker, CD163 [4]. In addition, CD45, CD45-RO, and HLA-DR are usually positive, along with focal to weak S100 expression. In addition, accessory/dendritic cell IHC markers and specific myeloid markers such as myeloperoxidase, CD33, and CD34 give negative results [4]. In our case, the tumor cells are positive staining for CD45, CD68, CD163, HLA-DR, and S100 confirming its histiocytic origin. CD68 staining is also found in cells and tumors of other lineages, including angiosarcoma, melanoma, carcinoma, some lymphomas, schwannoma, Langerhans cell tumor, follicular dendritic cell tumor, interdigitating dendritic cell proliferation, and acute myeloid leukemia without monocytic differentiation [5, 8]. In comparison, CD163, a hemoglobin scavenger receptor, is a new immunohistochemical marker of monocytes and histiocytes. Its expression is limited to neoplasms of monocytic/histiocytic derivation and is more specific than other monocytic and histiocytic markers such as CD68 [5, 6]. Many earlier reported cases of HS were positive for CD68 but were not evaluated for CD163 [3, 8, 9]. Therefore, true histiocytic origin may be questionable in these cases.

HS can mimic other spindle cell or round cell sarcomas, evaluation of a battery of antibodies in the context of morphology is essential in the workup of these neoplasms. The differential diagnoses that should be considered in cases of HS are numerous and includes Langerhans cell sarcoma (LCS), diffuse large B-cell lymphoma, peripheral T-cell lymphoma, ALL of T/null-cell type, metastatic undifferentiated carcinoma, and melanoma. Recently, immunostaining of CD68, lysozyme, CD1a, S100 protein, CD21, and CD35 is recommended for the differential diagnosis of histiocytic/dendritic cell neoplasms [8]. Metastatic carcinoma, undifferentiated carcinoma of thyroid in origin and melanoma can be ruled out by the absence of keratin, cytokeratins, EMA, thyroid globulin, TTF-1, Melan-A and HMB-45 expression. HS can also mimic benign histiocytosis, the existence of which has been recently debated since it has often been mistaken in the past for large cell lymphomas [10]. The absence of CD15, CD20, CD79a, PAX-5, CD30, and CD3 expression as well as the lack of clonal IGH and TCRγ rearrangement exclude Hodgkin lymphoma, poorly differentiated large B-cell/T-cell lymphoma, and ALL. Langerhans cell histiocytosis and interdigitating dendritic cell tumors are excluded with negative CD1a and S100 protein. Differentiation from malignant fibrous histiocytoma (MFH) may be extremely difficult. MFH typically demonstrates immunoreactivity to vimentin but fails to show reactivity to immunostains of other lines of differentiation. Histolytic markers (CD68, α1-antitrypsin, α1-antichymotrypsin, and factor XIII) no longer play a useful role in the diagnosis of MFH as immunoreactivity to these markers is found to be nonspecific [4]. These tumors are believed to arise from undifferentiated mesenchymal cells rather than histiocytes, and typically show pleomorphic and storiform growth patterns, negative for histiocytic markers but may contain numerous reactive histiocytes. Histiocyte marker CD163, largely restricted to the monocyte/macrophage lineage [5], may be helpful to differentiate histiocytic sarcoma from malignant fibrous histiocytoma [2, 5, 6, 11]. Comprehensive immunohistochemical study excludes many of these diagnoses and confirms the diagnosis of HS in our case.

As previously noted, true HS demonstrates germ-line configuration for immunoglobulin and TCRs [12]. In present study, we have not deteced IGH, IGK, IGL and TCRB, TCRG and TCRD gene rearrangements, indicating polyclonal B- and T-cell populations in this tumor. TCR and immunoglobulin gene rearrangements have been reported in a few HS cases [13], which usually demonstrate tumor clonality of T-cell and B-cell neoplasms, respectively, however, gene rearrangement is not always lineage specific [14]. To date, the contribution of molecular gene rearrangement studies as a diagnostic tool for HS remains unclear [13], whether the strict definition of HS should include absence of clonal immunoglobulin and TCR gene rearrangements is controversial [15], while gene rearrangement studies may support clonality, they do not always indicate lineage and should be interpreted in the context of morphologic and immunophenotypic data.

HS has been reported to be in association with various other malignant disorders, including ALL [1]. It was interesting to note that both histiocytic tumor and leukemic blasts shared the rearrangements involving IGH and TCRγ chain genes, suggesting lineage infidelity for the recurrent disease [16]. A histiocytic neoplasm with identical IGH gene rearrangement may arise after treatment for T-cell lymphoblastic lymphoma or B-cell ALL [15]. Thus, it is suggested that B-cell ALL cells could act as progenitor cells with the ability to differentiate into other lineages [15]. The subsequent development of ALL followed by HS has been reported [8]. In our case, however, the lack of CD30, but unusual finding of cytoplasmic ALK, MPO staining might reflect residual myeloid, and T-cell marker expression.

In summary, we present one cases of HS involving thyroid gland and used a comprehensive immunophenotyping panel including CD163 as well as molecular studies to establish the true histiocytic nature of these lesions. Additionally, this lesion shows mild to moderate cytologic atypia with extensive necrosis, higher proliferative activity (31%) and mitotic activity. Although we cannot make

accurate conclusions about the relationship of these findings with clinical behavior in our case, future studies are warranted to determine the prognosis of these lesions.

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