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CASE REPORT

Acute myeloid leukemia with infiltration of thyroid gland complicating Hashimoto's thyroiditis

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Abstract We describe a case of acute myeloid leukemia with infiltration of thyroid gland complicating Hashimoto's thyroiditis. In Hashimoto's thyroiditis, the leukocyte function-associated antigen-1 (LFA-1)/intercellular vascular cell adhesion molecule-1 (ICAM-1) and very late antigen-4 (VLA-4)/vascular cell adhesion molecule-1 (VCAM-1) pathways in T lymphocytes and the vascular endothelium both play a role in the initiation and enhancement of lymphocyte recruitment to the thyroid glands during an autoimmune attack. The leukemic blast cells were positive for VLA-4 and negative for LFA-1 by immunohistochemistry. The presence of VLA-4 in blast cells might play a key role in the migration of blast cells to the thyroid glands.

Keywords Acute myeloid leukemia · Hashimoto's thyroiditis · Infiltration · VLA-4 · VCAM-1

Introduction

Metastasis of cancer to the thyroid gland is much more frequent than primary cancer of this organ. Several studies have reported that metastases to the thyroid gland are relatively common; the incidence reported in autopsy studies varies from 2 to 17% among patients afflicted with cancer. Based on cytomorphological evaluation, secondary thyroid infiltration was diagnosed in 10–12% of the leukemia cases in these studies. It is likely that in most cases, massive replacement of the thyroid gland by metastatic tumor tissue does not occur soon enough to produce easily recognizable signs of hypothyroidism before death. Metastatic thyroid neoplasms do not present with important clinical issues despite being ten times as numerous as primary thyroid cancers [1]. Thus, most of these metastatic lesions are occult [1]. Although previous autopsy studies have reported that leukemia commonly involves the thyroid gland, there is only one case report of acute myeloid leukemia (AML) with infiltration of the thyroid gland diagnosed in live persons based on cytomorphological evidence [2]. However, these studies do not mention the mechanism involved in blast cell migration. To the best of our knowledge, this is the first case report of AML with infiltration of the thyroid gland complicating Hashimoto's thyroiditis, indicating that the migration of leukemic blast cells to the thyroid gland might be regulated by activated endothelial cells (ECs) through the very late antigen-4 (VLA-4)/vascular cell adhesion molecule-1 (VCAM-1) adhesion pathway.

Case report

A 72-year-old woman was admitted to the clinic because of general fatigue, including anorexia, tiredness, and weight loss. Her symptoms had started 2 weeks previously and gradually worsened. She had been relatively well until then and had no history of any other disorders or bleeding

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episodes. Laboratory findings demonstrated an increased white blood cell count ($12.3 \times 10^9\ l^{-1}$) with 35.0% blast cells, and elevated serum lactate dehydrogenase (638 U ml^{-1}). Hemoglobin (Hb) levels indicated anemia ($93\ g\ l^{-1}$) and thrombocytopenia ($32 \times 10^9\ l^{-1}$). Coagulation levels were altered in several fibrinolytic factors [prothrombin time, (PT), 14.2 s; activated partial thromboplastin time (APTT), 33.6%; antithrombin III, 107%; fibrinogen, 216 mg dl^{-1}; fibrin/fibrinogen degradation product (FDP), 27.6 mg l^{-1}; and D-dimer 28.0 mg l^{-1}]. Bone marrow biopsy showed hypercellularity and bone marrow aspiration showed 69.1% infiltration of leukemic cells, including well-differentiated monocytic cells. These cells comprised monoblasts with abundant cytoplasm, round nuclei with delicate, lacy chromatin, and prominent nucleoli, and promonocytes showing marked nuclear lobulation with an irregular and delicately convoluted nuclear configuration. The blast cells were positive for VLA-4 (9F10; BioLegend, San Diego, CA, USA; Fig. 1) and negative for leukocyte function-associated antigen-1 (LFA-1) (EP1285Y; Epitomics, Inc., Burlingame, CA, USA) (data not shown) by immunohistochemical staining (Fig. 2).

Most blast cells expressed CD4, CD11c, CD33, and HLA-DR as assessed by flow cytometric immunophenotyping with CD45 gating, while the lymphoid markers CD3, CD4, CD7, and CD20 were negative. Karyotype analysis with Giemsa band staining showed 46, XX. The above clinical findings led to the diagnosis of acute monocytic leukemia according to the WHO classification [3], of the M5b subtype according to the French–American–British classification [4]. Although the patient exhibited no clinical signs of hypothyroidism and had no relevant family history, her thyroid gland was diffusely enlarged; thyroid function testing demonstrated a free thyroxine concentration of 1.30 ng dl^{-1} (normal range, 0.90–1.70 ng dl^{-1}), total

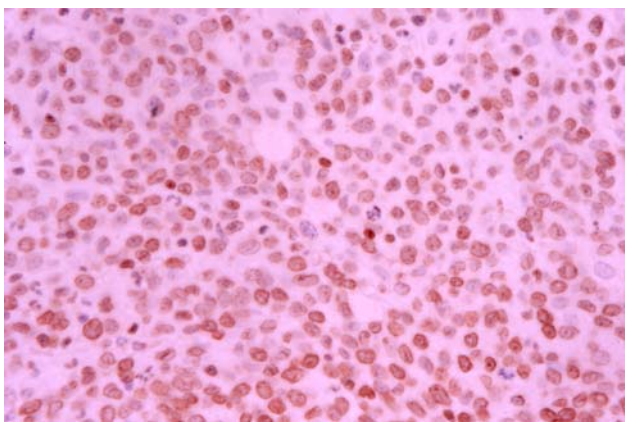

Fig. 1 Immunohistochemical staining of bone marrow showing blast cells positive for VLA-4 (9F10, ×20)

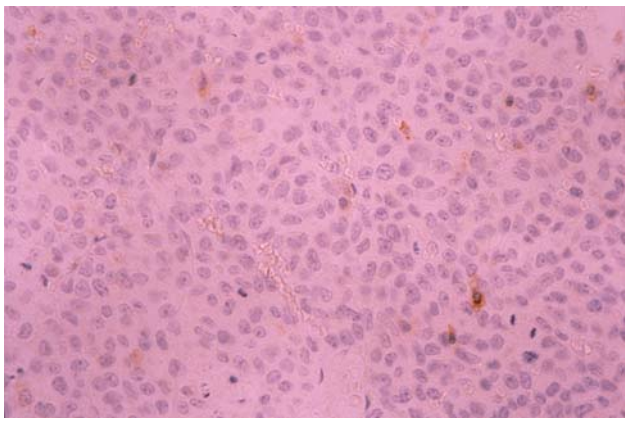

Fig. 2 Immunohistochemical staining of bone marrow showing blast cells negative for LFA-1 (9F10, ×20)

triiodothyronine 2.08 ng dl^{-1} (2.30–4.30 ng dl^{-1}), thyrotropin 3.960 μg ml^{-1} (4.34–5.00 μg dl^{-1}), and thyroglobulin 146.3 ng ml^{-1} (1.4–78.0 ng ml^{-1}). Thyroid-stimulating hormone receptor and antithyroglobulin antibodies were negative. The antithyroid peroxidase antibody concentration was 0.6 U ml^{-1} (normal range, <0.3 U ml^{-1}). These clinical findings led to the diagnosis of subclinical Hashimoto's thyroiditis and nonthyroidal illness syndrome [5]. Computed tomography of the neck revealed bilateral diffuse enlargement of thyroid lobes with multiple low-density areas (Fig. 3).

Ultrasonography showed a finely and diffusely nonhomogeneous structure with hypoechogenic and undefined areas (Fig. 4).

^{67}Gallium scintigraphy performed after 72 h of injection showed an abnormal diffuse, but intense uptake in the thyroid gland (Fig. 5).

Since the ^{67}gallium scan was positive in patients with Hashimoto's thyroiditis, a diagnostic biopsy was performed to rule out malignancy [6]. Fine-needle aspiration biopsy of the thyroid gland revealed infiltration with blast cells (Fig. 6).

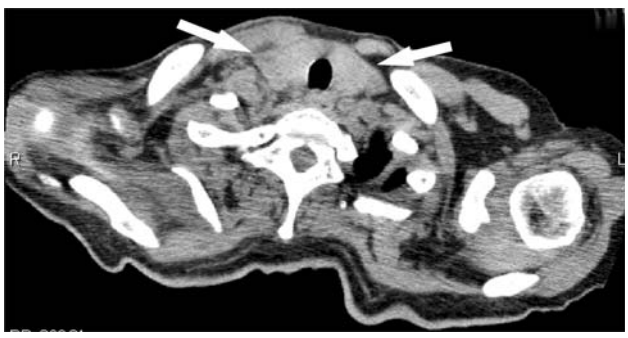

Fig. 3 Computed tomography of the neck on admission showing bilateral diffuse enlargement of thyroid lobes with multiple low-density areas

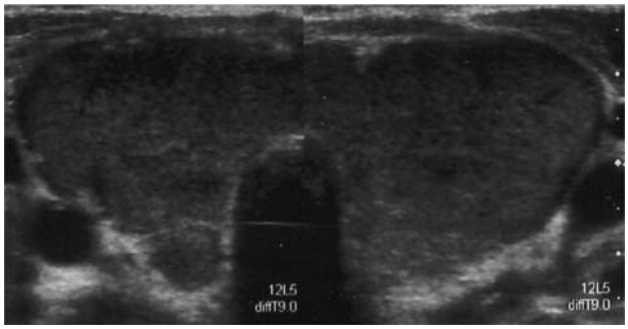

Fig. 4 Ultrasonogram of the thyroid gland showing a finely and diffusely nonhomogenous structure

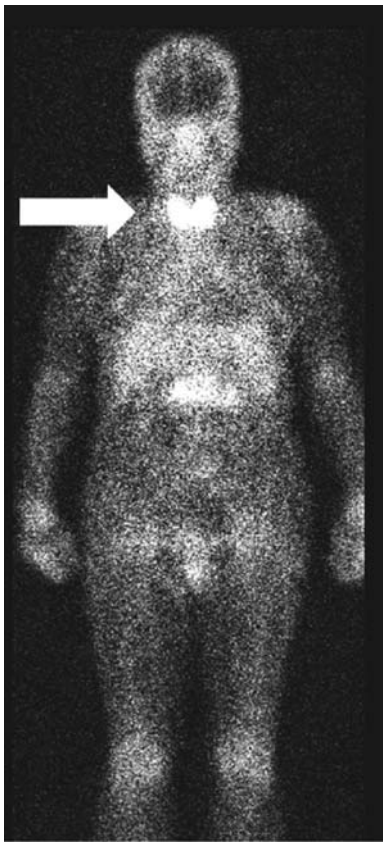

Fig. 5 Whole body ^{67}gallium scan taken 72 h after injection. *Arrow* shows abnormal diffuse uptake in the thyroid gland

Coexistence of Hashimoto's thyroiditis and AML with infiltration of the thyroid gland was diagnosed. The patient underwent chemotherapy with daunorubicin for 4 days and cytarabine for 7 days [7]. We decided against thyroid hormone replacement therapy, because whether thyroid hormone administration in nonthyroidal illness has a positive influence on disease outcome or prognosis remains unresolved and controversial [8]. Bone marrow aspiration was performed 22 days after the beginning of chemotherapy and showed cytogenetic complete remission. However,

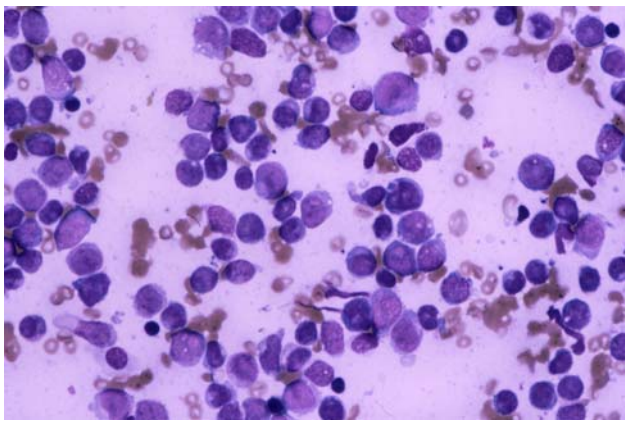

Fig. 6 Fine-needle aspiration biopsy of thyroid gland showing infiltration by leukemic blast cells (May–Giemsa, ×20)

1 day later (23 days after the beginning of chemotherapy), the patient fell and died of epidural hematoma. Laboratory data showed anemia (Hb 94 g l^{-1}), low platelet count (6×10^9 l^{-1}), and altered coagulation levels of the fibrinolytic factors (PT, 14.3 s; APTT, 37.3%; antithrombin III, 78%; fibrinogen, 484 mg dl^{-1}; FDP, 14.2 mg l^{-1}; D-dimer 10.5 mg l^{-1}). Since the thyroid was not assessed by clinical examination, imaging, and biopsy, the occurrence of histological remission in the thyroid could not be confirmed.

Discussion

Patients with acute leukemia have a higher prevalence of thyroid disease (including Hashimoto's thyroiditis) as compared with the general population. Thyroid disease was documented in 27 of 870 patients with acute leukemia (3%) indicating a threefold increase in the overall prevalence [9]. However, until date, no causes and associations have been ascertained [10].

Hashimoto's thyroiditis is probably the commonest of the autoimmune thyroid diseases (AITDs). This clinical entity is characterized by organ-specific, autoimmune destruction of the thyroid gland mediated by T lymphocytes, associated with anti-thyroglobulin and anti-microsomal antibody formation, and it frequently results in hypothyroidism [11]. Intrathyroidal T lymphocytes seem to play an important role in the pathogenesis of AITDs through thyroid antigen recognition (as an essential step in B-cell stimulation) and mediation of important inflammatory effects, such as the release of cytokines [12]. The interaction of infiltrating T lymphocytes with thyrocytes plays a central role in the pathogenesis of AITDs [13]. Infiltration of the thyroid gland is a result of the regulation of the expression and function of a set of adhesion receptors on both leukocytes and ECs. Lymphocytic infiltration of the

thyroid gland in autoimmune thyroid disorders requires, as a first step, attachment to ECs and subsequently, interaction with thyrocytes and extracellular matrix proteins [14]. One of the important pathways for lymphocyte adhesion is through the binding of the LFA-1 to intercellular vascular cell adhesion molecule-1 (ICAM-1). Most intrathyroidal lymphocytes are LFA-1-positive. ICAM-1, a known LFA-1 ligand, is also overexpressed by endothelial structures in glands of patients with Hashimoto's thyroiditis [15]. Another important mechanism of T-cell adhesion is through the VLA-4/VCAM-1 adhesion pathway, which plays an important role in the recruitment of lymphocytes and monocytes to the sites of inflammation [16]. Activated thyroid T cells showed increased VLA-4 expression and clear de novo expression of VCAM-1 was observed on the ECs of thyroid glands in patients with Hashimoto's thyroiditis, but not on those in healthy controls [14]. VCAM-1 is not usually present on resting ECs but can be induced in vitro by cytokines such as interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-1 [17]. VCAM-1 expression on thyroid ECs may have been enhanced by the local production of IFN-γ and TNF-α, released by inflammatory infiltrates [18]. Induction of the expression of adhesion molecules within the vascular endothelium of target tissues plays a key role in the recruitment and targeting of autoimmune attacks to certain tissue sites [19]. Therefore, the induction of ICAM-1 and VCAM-1 expression in thyroid gland ECs mediated by cytokines may play an important role in localizing and perpetuating the autoimmune response in AITDs [20].

Moreover, VCAM-1 and ICAM-1 are involved in the migration of leukemic blast cells. Transendothelial leukocyte migration is a prerequisite for firm attachment and extravasation through immunoglobulin-dependent pathways mediated by VCAM-1 and ICAM-1 [20]. There is accumulating evidence regarding the involvement of endothelial adhesion molecules in blast cell migration. If multiple receptor systems act synergistically in promoting blast cell adherence to the endothelium, the increased number of VCAM-1/VLA-4 interactions may add to our understanding of the high incidence of extramedullary disease [21].

To the best of our knowledge, this is the first case report of AML with infiltration of the thyroid gland complicating Hashimoto's thyroiditis, indicating the migration of leukemic blast cells that are immunohistochemically positive for VLA-4. Hashimoto's thyroiditis is more prevalent in older women than in any other age or gender group [5, 22, 23]. Thus, although it may be coincidental that both diseases occurred in this patient, we postulated that one did not affect the other and that the presence of VLA-4 in blast cells plays a key role in the migration of blast cells to the thyroid. Therefore, thyroid infiltration of leukemic blast cells should be suspected in AML patients with blast cells positive for VLA-4 complicating Hashimoto's thyroiditis.

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