Coexistent B-cell Lymphoma and Cutaneous T-cell Lymphoma

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Abstract

A 78-year-old man with a history of mycosis fungoides was referred for evaluation of a right adrenal mass. A physical examination showed the left cervical lymph node to be palpable, which was later shown to be caused by a diffuse large B-cell lymphoma. The patient was diagnosed with concurrent mycosis fungoides and a diffuse large B-cell lymphoma. Three courses of chemotherapy were performed, however, the patient died of advanced disease. Autopsy findings showed that the right adrenal and soft tissue masses had an identical B-cell origin. Although the exact mechanism remains unclear, the pathogenesis of this rare association is discussed.

Key words: T-cell lymphoma, B-cell lymphoma, mycosis fungoides, coexistence

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Introduction

Mycosis fungoides, also known as cutaneous T-cell lymphoma, belongs to non-Hodgkin’s lymphoma, though it has a lower malignancy potential. Development of second malignancies in patients with a lymphoma is well recognized and the incidence rate with cutaneous T-cell lymphoma is greater than coincidental (1), however, coexistence of mycosis fungoides and B-cell malignancy in the same patient is rare. Herein, we describe a rare association between a cutaneous T-cell lymphoma and diffuse large B-cell non-Hodgkin’s lymphoma in a patient, along with a review of pertinent literature and speculation on the mechanisms of the association.

Case Report

A 78-year-old man was referred to our department for hormonal evaluation after a mass in the right adrenal region was found incidentally during a urological prostate examination. He was diagnosed with pulmonary tuberculosis at the age of 20, and had a 12-year history of prostatic hypertrophy and 9-year history of mycosis fungoides, for which he had been receiving psoralen-ultraviolet A (PUVA) therapy at the Department of Dermatology at our hospital since 1996, with a good response. There were no other complications, and his family history did not include lymphoproliferative diseases or malignancies among the first degree relatives. Height and weight were 163 cm and 67 kg, respectively, while blood pressure was 108/62 mmHg, pulse rate was 87/minute, and BT was 36.7°C. A clinical examination revealed multiple pigmented patches and infiltrated plaques without tumor formation on the trunk (Fig. 1) or limbs, and swelling in the right buttock of the patient. A thumb-sized, non-tender, palpable lymph node in the area of the left neck was also present, however, there was no evidence of hepatosplenomegaly. The other physical examination findings were unremarkable. Computed tomography (CT) and MR-CT scans of the abdomen revealed a well circumscribed, smooth margined mass, 6x7 cm in size, in the region of the right adrenal gland, which was compressing the inferior vena cava, right lobe of the liver, and right kidney. The tumor was homogeneous and showed a low intensity with gradual enhancement in a dynamic study (Fig. 2a, b). Ultrasonography of the neck demonstrated a hypoechoic mass...
Figure 1. Photograph of mycosis fungoides. Multiple pigmented patches and infiltrated plaques without tumor formation were seen on the trunk and limbs.

Figure 2. Computed tomography (CT) scanning of the abdomen. (a) CT scan image of the abdomen showing a well circumscribed, smooth margined mass, about 6 × 7 cm in size, in the region of the right adrenal, compressing the inferior vena cava, right lobe of the liver, and right kidney. (b) Dynamic image showing the tumor to be homogeneous with a low intensity and gradual enhancement. (c) Pelvic CT scan demonstrating marked soft tissue swelling around the right iliac bone (arrow).

measuring 2×5 cm with mural thickening. During the course of the examinations, the patient developed a fever and complained of right hip pain, and a subsequent pelvic CT scan showed marked soft tissue swelling around the right iliac bone (Fig. 2c). In addition, gallium scintigraphy demonstrated an intense uptake of gallium 67 in the regions of the right adrenal, left neck, and right hip (Fig. 3).
Figure 3. Gallium scintigraphy. A gallium scintigram shows marked uptake of gallium 67 in the regions of the right adrenal, left neck, and right hip.

**Laboratory data**

The results of laboratory investigations showed WBC at 4,500/μL (stab. 3.0%, seg. 39.0%, lymph. 21.0%, mono. 31.0%, eos. 6.0%, bas. 0%), with a normal hemoglobin concentration and platelet count. C-reactive protein was 1.1 mg/dL and lactic dehydrogenase was 205 U/L (upper limit of normal), while the remainder of the routine biochemical profile was within normal limits. Serum and urinary concentrations of cortisol, norepinephrine, epinephrine, dopamine, and their metabolites were within normal ranges. DHEA-S and CEA were 17 μg/dL and 1.7 ng/mL, respectively. The serum immunoglobulin concentration was normal and the serum titer of soluble IL-2 receptor was 11,000 U/mL. A purified protein derivative (PPD) test was positive and a serological test for the antibodies against HTLV-1 was negative. Bone marrow aspirate from the sternum disclosed a normal smear pattern.

**Histopathologic findings of skin and lymph node biopsy specimens**

A review of skin biopsy specimens taken 9 and 7 years earlier revealed findings suggestive of mycosis fungoides (Fig. 4). Sections of the left cervical lymph node biopsy specimen showed a proliferation of large cells, the immunophenotypes of which were CD20 (+), CD45RO (-), CD79a (+), and UCHL-1 (-), suggesting a B cell origin for the tumor (Fig. 5). Flow cytometry of the excised lymph node revealed that the surface cell markers CD3, CD20, CD2, CD5, CD7, CD19, and CD56 were positive in 54.6%, 47.6%, 52.8%, 29.8%, 21.5%, 30.0%, and 14.8%, respectively, of the lymphocytes. Although the results of flow cytometric analysis of the lymph node were not conclusive regarding the origin of the lymphoma, the patient was diagnosed with a secondary malignancy, later proven to be a B-cell lymphoma (diffuse large cell type), complicated with a cutaneous T-cell lymphoma.

**Treatment and clinical course**

The patient was treated with systemic combined chemotherapy with cyclophosphamide at 500 mg/m² (day 1), doxorubicin at 35 mg/m² (day 1), vincristine at 1 mg/m² (day 1), and prednisolone at 60 mg/m² (days 1-5). This regimen was repeated every 3 weeks for 2 courses, after which the symptoms, including fever and hip pain, were improved and the superficial lymph nodes had decreased in size. However, right peroneal nerve palsy, considered to be ascribable to an adverse effect of vincristine, and meningoencephalitis developed after the second course of therapy, which delayed the start of the third course. Thereafter, the meningoencephalitis resolved spontaneously, though right peroneal nerve palsy persisted. The lymph node began to grow during the interval period between the second and third chemotherapy courses, when vincristine was not given, and no significant improvement in tumor size around the right pelvis was achieved. After the third chemotherapy course, the patient experienced aspiration pneumonia several times and died of advanced disease 5 months later. An autopsy was performed.

**Autopsy findings**

On autopsy it was revealed that lymphoma cells had diffusely invaded various tissues, including the cervical, para-tracheal, sub-carinal, mesenteric, and para-aortic lymph nodes, as well as the right visceral pleura, right semi-diaphragm, esophagus, spleen, liver, right kidney, right adrenal, urinary bladder, and inferior vena cava, and soft tissues.
Figure 4. Biopsy specimen of the skin. (a, b) Skin biopsy specimen taken 7 years earlier showing a band-like infiltration of lymphocytes in the reticular dermis. A Pautrier microabscess was observed in the epidermis (H-E stain, original magnification ×40, ×200). Immunohistochemical results showed that (c) atypical cells were positive for the T-cell marker (UCHL-1) (original magnification ×200) and (d) negative for the B-cell marker (L26) (original magnification ×100).

Discussion

The two interesting findings in the present case are: 1) unusual extra-nodal involvement (adrenal and peri-iliac soft tissue involvement) with a B-cell lymphoma, and 2) coexistent cutaneous T-cell and B-cell lymphomas. Extra-nodal lymphomas occur in various sites, including the gastrointestinal tract, head and neck region, bone, and soft tissue. However, primary adrenal and soft tissue lymphomas are very rare clinical entities, as a review of English literature revealed 65 cases of primary adrenal non-Hodgkin’s lymphoma (2), and primary soft tissue lymphoma accounted for 0.1% to 1% of new cases of non-Hodgkin’s lymphoma (3). Nevertheless, recognition of these rare forms of extra-nodal malignant lymphoma is helpful for establishing a precise diagnosis and adequate therapy. The largest lesions found in the present case existed in adrenal and peri-iliac soft tissues. However, since the present B-cell lymphoma was not confined to adrenal and soft tissues, those may not have been the primary lesion locations, but rather the results of spreading from the regional lymph nodes as a part of disease progression.

Previous studies have shown a rare association between cutaneous T-cell lymphoma and B-cell malignancies, though only sporadic case reports of this association have been published, with only 2 known reports, B-cell lymphoma (4) and multiple myeloma (5), presented in Japanese literature. Grange et al (6), reviewed 13 cases of coexistent cutaneous T-cell lymphoma and B-cell malignancy along with their own 6 cases, and reported the clinical and immunological features. However, cases associated with intermediate grade lymphoma (diffuse large B-cell lymphoma) are very unusual, with only 3 reported to date (6).

The possibility of a fortuitous coexistence of these diseases in the present case could not be fully excluded. However, considering the incidence of cutaneous T-cell lymphoma and B-cell malignancy in the general population, the association is unlikely to be merely coincidental. In addition, previous case reports have suggested a possible rela-
Various explanations regarding the underlying mechanisms of an association between cutaneous T-cell lymphoma and B-cell non-Hodgkin’s lymphoma have been proposed. The mutagenic effects of cytostatic drugs have been considered to be a factor in the development of second malignan-

Figure 5. Biopsy findings for cervical lymph node. (a, b) A biopsy specimen from the neck showing a number of large cells (H-E stain, original magnification ×200, ×400) that were (c) positive for the B-cell marker (L26) (original magnification ×200) and (d) negative for the T-cell marker (UCHL-1) (original magnification ×200).

Figure 6. Autopsy findings. Autopsy findings of the soft tissues around the (a-c) right adrenal (a, H-E stain, ×400; b, L26, ×200; c, CD 45RO, ×200, original magnification), (d-f) right pelvis (d, H-E stain×400; e, L26, ×200; f, CD 45RO, ×200, original magnification), which had identical B-cell origins with neck lymph nodes, as shown by the results of immunoperoxidase staining.
cies (7-10), though there is no known report of a case of chemotherapy-induced cutaneous T-cell lymphoma. About half of those patients had received chemotherapeutic agents for the first malignancy prior to the onset of the second malignancy. However, in the present case, there was no previous history of use of immunosuppressive or cytotoxic agents against cutaneous T-cell lymphoma, only PUVA photosensitization before the onset of the B-cell lymphoma. Therefore, the mutagenic effects of cytotoxic drugs were unlikely to have invoked the development of B-cell lymphoma in the present patient.

An underlying viral infection is assumed to be involved with the pathogenesis of both B-cell and T-cell lymphomas, as cases of concurrent cutaneous T-cell lymphoma and B-cell lymphoma in association with HTLV-I infection (11) and E-B virus infection have been reported (10, 12). Further, E-B virus and HIV infections are considered to be associated with an increased frequency of lymphoma (13-15). Although the HIV antibody was negative in the present case, we did not perform Southern blot analyses or in situ hybridization assays of skin or lymph node samples for those viruses. Therefore, the possibility of a latent E-B virus or HTLV-I infection in the tumor tissues could not be completely excluded.

A genetic predisposition for malignancies or lymphoproliferative disorders may also contribute to the coexistence of these diseases (9, 16, 17). However, that was also considered unlikely in our patient, since malignancies and lymphoproliferative disorders were not apparent in his immediate family or related members.

The contributory effect of monoclonal proliferation of T-lymphocytes in the development of a B-cell lymphoma via cytokines or reactivation of a dormant virus has been postulated (7, 18, 19). In addition, malignant transformation of pluripotent stem cells, which generate both T-cells and B-cells (18), may provide a possible explanation in some cases for a composite T-cell and B-cell lymphoma (19, 20). Although analyses of T-cell receptor (TCR) and IgH gene rearrangement could not be performed, this hypothesis may not be applicable to the present case, since tissues from the B-cell lymphoma did not contain T-cell clones, as shown by the results of immunohistochemical analysis.

Finally, it may be speculated that disturbances in the immune system due to a preceding cutaneous T-cell lymphoma lead to the development of a secondary malignancy, which should be eliminated by the normal immune surveillance system.

In conclusion, there is no clear explanation for the coexistence of cutaneous T-cell and B-cell lymphomas, thus accumulation and analysis of such case reports is needed to clarify the underlying etiology of that association.

References


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