Malignant Lymphoma of the Bone Associated with Systemic Sarcoidosis

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Abstract

A 57-year-old woman was hospitalized with malignant lymphoma of the right talus. After treatment, complete remission was obtained. Gallium-67 scintigraphy to confirm the remission demonstrated increased uptake in the whole body skeletal muscle, especially in her thighs. Biopsy of right gastrocnemius muscle showed epithelioid granuloma. Serum angiotensin-converting enzyme activity (ACE) and lysozyme had increased to several times the normal range. We diagnosed her disease as bone-associated sarcoidosis-lymphoma syndrome. Human herpes virus 8 (HHV-8) genome was examined in the bone marrow specimen, and the relationship between sarcoidosis-lymphoma syndrome and HHV-8 was discussed.

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Key words: sarcoidosis-lymphoma syndrome, Ga-67 scintigraphy, HHV-8

Introduction

Sarcoidosis is in rare cases complicated by malignant lymphoma called sarcoidosis-lymphoma syndrome. This concept was proposed by Brincker who reported 46 cases in 1986 (1). In Japan, only 11 cases of sarcoidosis-lymphoma syndrome have been reported, and 4 of them were associated with lymphoma in stomach (2). We report a case of sarcoidosis-lymphoma syndrome in which lymphoma arose from the bone.

Case Report

A 57-year-old woman was admitted because of a few months history of right foot pain and swelling. An appendectomy had been performed in her childhood. The radiograph of the right

ankle showed a compression fracture of the talus (Fig. 1), and gallium (Ga)-67 scintigraphy demonstrated increased uptake in the same lesion (Fig. 2). Biopsy of the right talus demonstrated malignant lymphoma of bone which was diffuse large-B cell type (Fig. 3). Bone marrow aspiration examination including chromosomal analysis of sternum was normal. HHV-8 virus genome was not detected in her sternum bone marrow specimen by nested PCR method (3). Laboratory findings showed a white blood cell count of 6,800/mm³ with normal differentiation, platelet count 244,000/mm³, red blood cell count 5.14×10⁶/mm³, lactic dehydrogenase (LDH) 473 U/l, creatinine phosphokinase (CPK) 71 U/l, and creatinine 0.67 mg/l. Serum electrolyte levels were sodium 144 mEq/l, potassium 4.0 mEq/l and calcium 10.4 mg/dl. β 2-microglobulin was 3.1 mg/l. Soluble IL2 receptor was 1,790 U/ml, IgG 1,600 mg/dl, IgA 328 mg/dl and IgM 225 mg/dl. The skin reaction to PPD was negative. Chest X-rays revealed moderate bilateral hilar lymphadenopathy. The ECG and echocardiogram were normal. Eye examination revealed no lesion.

The patient was given 6 courses of bi-weekly CHOP therapy (990 mg of cyclophosphamide, 66 mg of adriamycin, 1.8 mg/day of vincristine day 1, and 65 mg/day of prednisolone days 1–5) (4) followed by 40 Gy irradiation of the right foot. The foot lesion improved, and the joint pain and swelling disappeared. However, a chest X-ray still showed moderate bilateral hilar lymphadenopathy, and the serum soluble interleukin-2 receptor level was not decreased. Ga-67 scintigraphy for confirmation of the remission revealed intense uptake in the whole body skeletal muscle, especially her thighs (Fig. 4). Biopsy of right gastrocnemius muscle showed epithelioid granuloma (Fig. 5). A diagnosis of sarcoidosis was made. Serum angiotensin-converting enzyme activity (ACE) (57.4 U/l) and lysozyme (43.8 μ g/ml) were increased to several times the normal range. Serum aldolase was 6.2 U/l. To date, a year after the onset of foot symptoms, sarcoidosis is asymptomatic without treatment.

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Discussion

In the present case, we assumed that sarcoidosis subsisted when the patient showed the symptom of malignant lymphoma because her bilateral hilar lymphadenopathy remained after induction of complete remission of her lymphoma. Furthermore, intense uptake on Ga-67 scintigraphy in the skeletal muscle immediately after chemotherapy suggested that chemotherapy for her malignant lymphoma had advanced her sarcoidosis. Keohane et al reported a similar case in which sarcoi-

Figure 1. X-ray film of the right foot reveals compression fracture of the talus.

Figure 2. Gallium-67 scintigraphy on admission reveals intense uptake in the right foot.

Figure 3. Microscopic findings of the right talus. Malignant cells show extensive infiltration in the bone marrow (HE stain, $\times 1,000$).

Figure 4. Gallium-67 scintigraphy after of 6 courses of biweekly CHOP treatment. The intense uptake is shown in the skeletal muscles.

Figure 5. Sarcoid granuloma with giant cells seen in the biopsy specimen of the right gastrocnemius muscle (HE stain, ×400).

dosis was accelerated during chemotherapy of the lymphoma (5).

Only 11 cases of sarcoidosis-lymphoma syndrome have been reported in Japan in the past 12 years. Moreover, the type and site of lymphoma in this syndrome may differ with race. Brincker reported the association of Hodgkin's lymphoma in 18 of 46 cases (6). On the contrary, all of the cases were complicated with non-Hodgkin's lymphoma in Japan, and one-third of them were associated with gastric lymphoma. These findings may suggest the etiology is different with race in sarcoidosis-lymphoma syndrome. However, the incidence of Hodgkin's lymphoma is rare in Japan.

There are some hypothetical reasons for the association of malignant lymphoma with sarcoidosis (7). Sarcoidosis is characterized by the formation of generalized granulomas. According to the study by Lawrence et al, alveolar macrophage, T lymphocyte, and various cytokines such as interleukin-2 (IL-2) are involved in granuloma formation of the lung (8). Lymphocytes in sarcoidosis are activated by several cytokines, and the proliferation potency is up-regulated (9). Disorganization and proliferation of lymphocytes under the continuous stimulation by antigens may induce malignant properties in the lymphatic system. Some investigators propose that propionibacterium is the antigen which stimulates the immune system and causes sarcoidosis (10).

Furthermore, a high incidence of infection of HHV-8 in the lymph nodes of sarcoidosis patients has recently been reported (11). HHV-8 is known to be associated with Kaposi's sarcoma and body cavity space lymphoma (BCSL) (12). This virus possesses genes resembling human IL-6, MIP, cyclin D and bcl-2 gene, and the products translated from these genes have biological activities in human cells (13). This suggests the possibility that the interaction of HHV-8 and other agents such as the propionibacterium for sarcoidosis might be involved in the pathogenesis of the sarcoidosis-lymphoma syndrome. It is known that about five percent of the entire Japanese population is positive for the HHV-8 antibody (14).

HHV-8 infection is an attractive hypothesis to explain the development of sarcoidosis-lymphoma syndrome, but two studies (15, 16) failed to confirm its involvement in sarcoidosis not associated with lymphoma. In the present patient, HHV-8 was not detected in the bone marrow, and the precise manner of HHV-8 infection in the human body remains to be elucidated. Further study of HHV-8 is needed to elucidate the possible association between the occurrence of malignant lymphoma and sarcoidosis involvement.

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