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Case Study

Secondary Malignant Fibrous Histiocytoma Following Refractory Langerhans Cell Histiocytosis

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We describe a rare case of secondary malignant fibrous histiocytoma (MFH) following Langerhans cell histiocytosis (LCH). A 23-year-old Japanese male exhibited systemic lymphadenopathy, multiple lung tumors, and osteolytic changes in bilateral iliac bones in 1989. A biopsy specimen from the left iliac bone revealed an infiltration of S-100 protein-positive histiocyte-like cells intermingled with eosinophils, which confirmed the diagnosis of eosinophilic granuloma, a type of LCH. Although the patient was treated with prednisolone initially, the disease did not respond well and progressed gradually over time. The patient subsequently received multiple courses of chemotherapy and immunosuppressive therapy with many kinds of anticancer agents for 6 years. He also received radiotherapy totaling 136.8 Gy for lung tumors and osteolytic lesions of the pelvis. In 1997, because of the LCH refractoriness, biopsy was performed again from the right inguinal lymph node. Microscopic examinations demonstrated a mixture of spindle-shaped cells and histiocyte-like cells, which appeared to be in a storiform pattern. The tumor cells were immunohistologically positive for CD68 and vimentin, but negative for CD1a and S-100 protein. Therefore, the patient was diagnosed with MFH. Although chemotherapy was continued, the patient died of pneumonia during the neutropenic period following chemotherapy. Autopsy revealed systemic invasion of MFH and dissemination of mucormycosis. LCH was not detected histologically in any tissues. 〔*J Clin Exp Hematopathol 49(1) : 33-37, 2009*〕

Keywords: Langerhans cell histiocytosis, malignant fibrous histiocytoma, radiation-induced sarcoma

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disease characterized by the accumulation and proliferation of abnormal Langerhans cells. These dendritic cells, together with lymphocytes and eosinophils, form infiltrates typical of the disease, which may be found in various organs to different extents.[1-6] The disease includes diseases previously defined as Letterer-Siwe disease, Hand-Schüller-Christian syndrome, and eosinophilic granuloma, which primarily affects bone and lung in children and young adults. The pulmonary involvement is often symptomatic with dyspnea, cough, and pleural effusions. The osseous changes present as lytic, destructive lesions in the skull, mandible, ribs, pelvis, femur, and tibia. General symptoms including fever, malaise, and lymphadenopathy are also seen. Patients with a mild case of the disease have an excellent prognosis even without systemic therapy ; however, cases with multifocal skeletal involvement and disseminated or recurrent disease are usually refractory to corticosteroids and require aggressive therapy. Moreover, the likelihood of development of a malignant neoplasm is increased, especially after administration of anticancer agents and radiotherapy. These malignancies become problems because they worsen the prognosis of LCH. Here, we report a case of secondary malignant fibrous histiocytoma (MFH) that developed after repetitive chemo- and radio-therapy for refractory systemic eosinophilic granuloma.

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CASE REPORT

A non-smoking Japanese male was first admitted to St.

Marianna Medical University Hospital in 1989 when he was 23 years old. His chief complaints were fever and lumbago. Radiographic analyses revealed systemic lymphadenopathy, multiple lung tumors, and osteolytic changes in bilateral iliac bones. A biopsy specimen from the left iliac bone demonstrated an infiltration of histiocyte-like cells intermingled with eosinophils.[7] These histiocyte-like cells were immunohistologically positive for S-100 protein. CD1a positivity was not assessed. Eosinophilic granuloma was therefore diagnosed.[7] Although treatment with 60 mg of prednisolone was initiated, the disease was refractory to the therapy, and the symptoms including fever, lymphadenopathy, lung tumors, and osteolytic lesions progressed gradually over time. In 1991, upon moving back to his birthplace Fukui, the patient was admitted to University of Fukui Hospital. Thereafter, he received multiple courses of chemotherapy and immunosuppressive therapy with many kinds of anticancer agents for 6 years (Fig. 1, Table 1). Moreover, radiation totaling 136.8 Gy was administered to various lesion sites in the lungs and pelvis (Fig. 1). Nevertheless, the disease progressed, with the regrowth of systemic lymph nodes, fever, and pelvic pain, and the patient was admitted again in July, 1997.

On admission, the patient was alert and conscious. His body temperature was 37.1°C, blood pressure was 110/60 mm Hg, and his pulse rate was 72/min. Neck, bilateral axillary, and right inguinal lymph nodes were felt (diameters of 1 to 2 cm, elastic hard, and nontender). There were no apparent abnormal findings in the chest on auscultation. The patient's abdomen was soft, and liver edge was palpable 2 FB below the costal margin, but spleen was not felt. Eruptions and peripheral edema were not found. Laboratory tests revealed decreases in peripheral lymphocyte count and γ-globulin levels, suggesting an immunocompromised state due to repetitive chemo- and radio-therapy (Table 2). The increased lactate dehydrogenase (LDH) level might reflect the disease progression (Table 2). Radiographic examinations demonstrated systemic lymphadenopathy, multiple lung tumors, an osteolytic pelvic bone, and a tumor in retroperitoneal soft tissue. Electrocardiogram showed a normal sinus rhythm.

Because the disease had been refractory to the therapy for years, biopsy from the right inguinal lymph node was again performed to detect any histological changes. Hematoxylin-Eosin staining showed marked proliferation of both spindle-

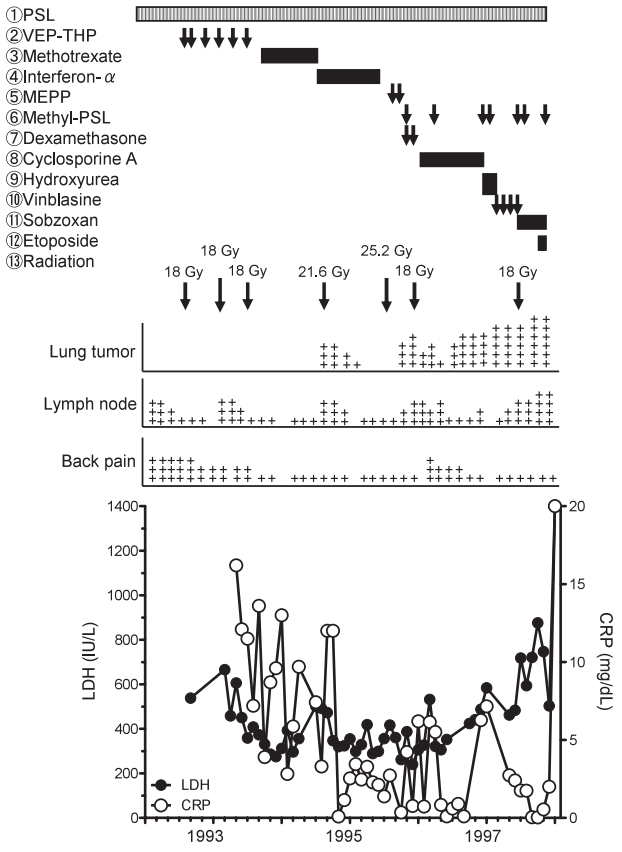

Fig. 1. Clinical course of the patient. Lactate dehydrogenase (LDH) and C-reactive protein (CRP) were plotted, which might reflect the disease progression. Each treatment was detailed in Table 1.

Table 1. Treatment protocol

	Regimen	dose	duration
①	PSL	30-60 mg	9 years
②	VEP-THP		6 courses
	CPA	800 mg/body, day 1	
	VDS	1.5 mg/body, day 1	
	THP	30 mg/body, days 1, 2	
	PSL	60 mg/body, days 1-4	
③	MTX	10 mg/body/week	8 months
④	Interferon-α	3M-10M IU/body	1 year
⑤	MEPP		2 courses
	MIT	8 mg/body, day 1	
	Etoposide	200 mg/body, days 1-3	
	PSL	60 mg/body, days 1-5	
	CBDCA	150 mg/body, days 1-3	
⑥	Methyl-prednisolone	1,000 mg/body, days 1-3	7 courses
⑦	Dexamethasone	40 mg/body, days 1-3	2 courses
⑧	Cyclosporine A	400 mg/body	2 years
⑨	Hydroxyurea	500-3,000 mg/body	2 months
⑩	Vinblastine	5 mg/body/week	4 courses
⑪	Sobzoxan	1,200-2,000 mg/body/week	4 months
⑫	Etoposide	25 mg/body	2 weeks

PSL ; Prednisolone, CPA ; cycolphosphamide, VDS ; vindesine, THP ; pinorubin, MTX ; methotrexate, MIT ; mitoxantrone, CBDCA ; carboplatin, VEP-THP ; the combination chemotherapy using cyclophosphamide, veindesine, pinorubin, and prednisolone, MEPP ; the combination chemotherapy using mitoxantrone, etoposide, prednisolone, and carboplatin.

Table 2. Laboratory findings on admission

Complete blood count	Value (normal range)
White blood cell	6,400/μL (3,400-9,600)
Neutrophil	85.0% (30-70)
Eosinophil	0.0% (0-8)
Basophil	0.0% (0-3)
Lymphocyte	3.0% (17-55)
Monocyte	12.0% (1-11)
Red blood cell	387 x 10^4/μL (430-570 x 10^4)
Hemoglobin	11.9 g/dL (13-18)
Hematocrit	34.6% (40-52)
Reticulocyte	21‰ (2-23)
Platelet	12.4 x 10^4/μL (13-41 x 10^4)
Serology	**Value (normal range)**
C-reactive protein	0.12 mg/dL (0-0.32)
IgG	378 mg/dL (870-1,700)
IgA	47 mg/dL (110-410)
IgM	30 mg/dL (46-260)
Biochemistry	**Value (normal range)**
Na	142 mEq/L (136-147)
K	3.5 mEq/L (3.4-5.1)
Cl	101 mEq/L (98-108)
Ca	8.8 mg/dL (8.4-10.6)
Blood urea nitrogen	26 mg/dL (8-20)
Creatinine	0.8 mg/dL (0.8-1.2)
Uric acid	7.7 mg/dL (3.5-7.5)
Total protein	5.2 g/dL (6.5-8.3)
Albumin	3.5 g/dL (3.8-5.2)
Aspartate aminotransferase	11 IU/L (5-35)
Alanine aminotransferase	21 IU/L (5-40)
Lactate dehydrogenase	509 IU/L (230-460)
Alkaline phosphatase	97 IU/L (85-270)

shaped cells and histiocyte-like cells mixed with collagen fibers, which appeared to make a storiform pattern (Fig. 2). These abnormal cells were immunohistologically positive for CD68 and vimentin, but negative for CD45, CD45RO, CD34, α-smooth muscle actin, desmin, neuron-specific enolase, CD1a, and S-100 protein (Fig. 2). In addition, Birbeck granules were not found in these cells under electron microscopic examination. MFH of the storiform-pleomorphic type was eventually diagnosed.[8-11]

Although the chemotherapy was continued for treatment of MFH (Fig. 1, Table 1), the disease was also refractory to this treatment. The patient died of pneumonia during the neutropenic period following chemotherapy in December 1997. Autopsy was performed. Under a microscope, MFH was identified in the lungs, pancreas, left kidney, retroperitoneal soft tissue, bilateral iliac bones and lumbar vertebra, and lymph nodes of the neck (diameters of 1-3 cm), parabronchia

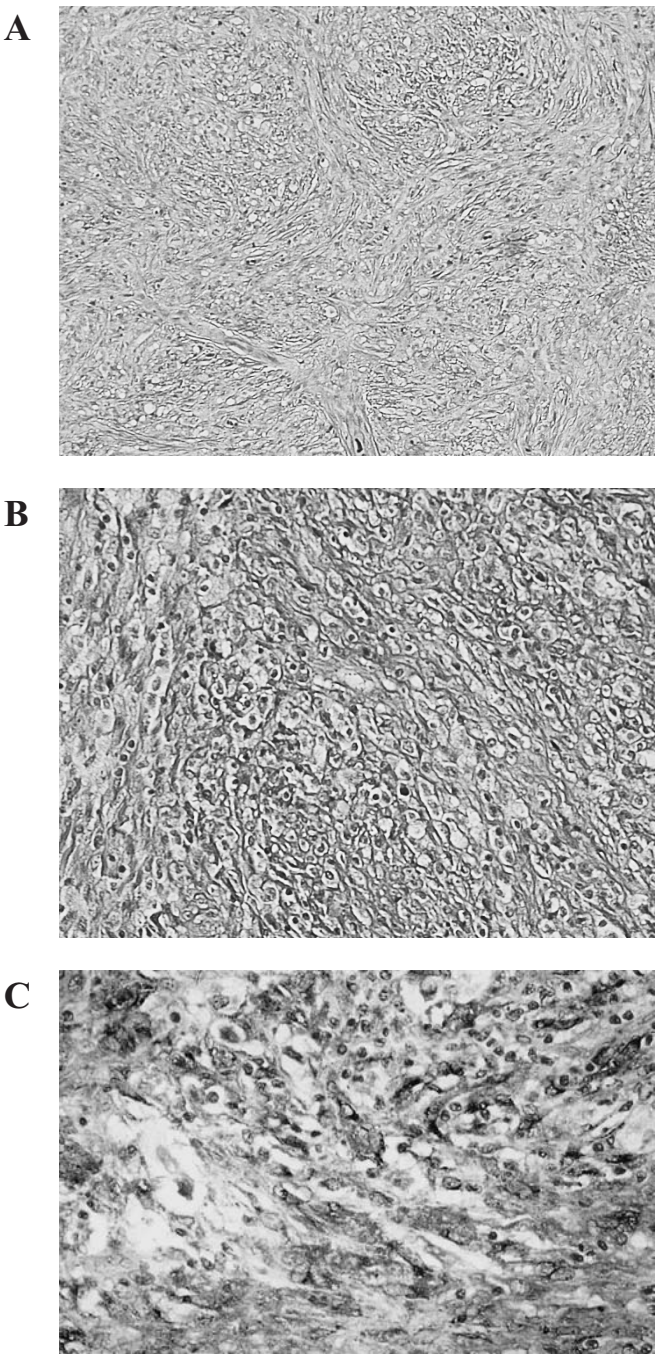

Fig. 2. Histopathological findings of right inguinal lymph node biopsy. (***2A***) In biopsy specimen tumor grew showing a storiform pattern. Hematoxylin-Eosin (HE) stain, x100. (***2B***) Tumor consisted of a mixture of spindle-shaped and histiocyte-like cells and often hyalinized collagen fibers. HE stain, x200. (***2C***) Immunostaining of CD68. A majority of tumor cells were positive. Counterstained with hematoxylin, x200.

(diameters of 0.5 - 3 cm), paraaorta (diameters of 1 - 2 cm), bilateral hilum of lungs (diameters of 0.5 - 1 cm), bilateral axilla, and bilateral inguinal (diameters of 0.5 - 3 cm) regions. The lungs were occupied bilaterally by multiple tumors with diameters of 3 - 5 cm. Bilateral iliac bones and lumbar vertebra were osteolytic and damaged by the invasion of MFH. Dissemination of mucormycosis also was found.[12] The postmortem findings did not suggest the origin of MFH. LCH was not detected in any tissues histopathologically.

DISCUSSION

The diagnosis of LCH is usually established by biopsy of organ lesions, most commonly bone, lungs, and skin.[13-15] Conventional histology shows destructive granulomatous lesions containing mononuclear cells with indented nuclei sharing the morphology of dendritic antigen-presenting Langerhans cells. A concomitant infiltration by lymphocytes and eosinophils is characteristic.[13-16] In these regards, the histopathology of the biopsy specimen obtained from the left iliac bone of this patient in 1989 was compatible with eosinophilic granuloma.

Despite the diagnosis at the onset, MFH was diagnosed without any evidence of LCH in 1997. MFH is the most common malignant tumor of soft tissue. It is one of a variety of pleomorphic soft tissue sarcomas, derived from histiocytes capable of fibroblastic transformation, which were originally characterized as malignant fibrous xanthoma by O'Brien and Stout in 1964.[8] Weiss and Enzinger summarized 200 cases of MFH in 1978[9] and demonstrated that this tumor occurred principally as a mass on an extremity (a lower extremity in 49% of cases and an upper extremity in 19% of cases) or in the abdominal cavity or retroperitoneum (16% of causes) of adults (peak incidence 61 - 70 years of age).[9] Metastasis was most frequently to the lung (82%) and lymph nodes (32%).[9] MFH is classified into five subtypes : storiform-pleomorphic type, myxoid type, giant cell type, inflammatory type, and angiomatoid type. Typically, the tumor is composed of a mixture of pleomorphic spindle-shaped cells and round histiocyte-like cells with a storiform pattern, with infiltration of inflammatory cells and multinucleated giant cells. Differential diagnosis includes pleomorphic liposarcoma, which lacks a storiform pattern, rhabdomyosarcoma, which is positive for desmin, leiomyosarcoma, which is positive for desmin and actin, fibrosarcoma and giant cell tumor, both of which lack pleomorphism.[8-11] Thus, the diagnosis of MFH in 1997 was definitive according to the microscopic findings, which showed typical histopathological and immunohistochemical features.

Sarcomas comprise 1% of adult malignancies, and most sarcomas are sporadic, with no identifiable risk factors.[17] However, several predisposing factors have been recognized, including radiation, chemical exposure, genetic conditions, and infections.[17] Sarcomas have been especially common originating in or near tissues that have received prior radiotherapy ; these post-radiation sarcomas, typically osteosarcoma and MFH, account for 0.5 - 5.5% of all sarcomas.[17,18] Because the present patient had received many courses of chemotherapy using carcinogenic alkylating agents and radiotherapy totaling 136.8 Gy, it is possible that these modalities might have induced secondary MFH. Sheppard and Libshitz reviewed clinical features of 63 cases of post-radiation sarcomas.[18] The median radiation dose delivered was 50.1 Gy, with a mean latency period for the development of the sarcoma of 15.5 years.[18] The latency period appeared to be inversely related to radiation dose, i.e., a shorter latency period was associated with a larger radiation dose.[18] The nine year clinical course of the present patient might be too short to explain the development of secondary MFH after radiotherapy ; however, the high total dose of radiation that had been repeatedly used at the different lesion sites might have shortened the period for the development of MFH in this patient. The origin of MFH could have been the pelvis or lungs where the radiation was administered. The specific time of the emergence of MFH in this patient might be another concern. Until 1996, the disease responded well to immunosuppressants including prednisolone and cyclosporine A, suggesting the presence of refractory LCH. Prednisolone, which had been the mainstay for treatment of LCH, became less effective against the disease after 1996. Moreover, C-reactive protein (CRP) and LDH were two parameters used for determining the aggressiveness of LCH, but CRP, which reflected the inflammation of LCH, became less indicative for the disease progression after 1996, suggesting changes in the nature of the tumor (Fig. 1). Therefore, MFH was suggested to have arisen between 1995 and 1996. An autopsy did not find any lesions for LCH, which might be because MFH took over the place where the LCH had developed.

The frequency of cooccurence of LCH and a malignant neoplasm in the same individual appears to be greater than recognized.[19-21] Developing malignancies may be attributable to the potentially carcinogenic therapies for LCH or to underlying genetic predisposition in LCH patients. Egeler, *et al*. reviewed 91 patients with LCH who developed malignant neoplasms.[20] Of these patients, 39 had malignant lymphomas including 25 with Hodgkin's lymphoma, 22 with leukemia including 16 with acute myeloid leukemia, and 30 with solid tumors including 18 with lung cancer. Among 30 solid tumors, 18 developed malignancies after the onset of LCH, of which 89% (16 of 18) had received prior treatment with anticancer agents or radiotherapy. This report suggested that the development of solid tumors was therapy-related. Vassallo, *et al*. analyzed 102 adult patients with pulmonary LCH.[21] Of these, 16 (16%) developed cancers including 6 hematological malignancies, 5 lung cancers, and 5 other solid tumors. However, most of the patients experienced cigarette

smoking, with the exact incidence not determined.

Secondary MFH in association with LCH has never been reported in the literature. The prognosis of refractory LCH may be worsened by the emergence of a malignant neoplasm. Here we have presented one such uncommon case of secondary malignancy, which developed after repetitive chemo- and radio- therapy for refractory LCH and eventually became the primary cause of death.

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