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Case Study

Eosinophilia and Bone Lesion as Clinical Manifestations of Aggressive Systemic Mastocytosis

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We report a patient with aggressive systemic mastocytosis (SM), who exhibited eosinophilia and unusual destructive bone lesions. A 43-year-old female was referred to our hospital because of a vertebral compression fracture, multiple lytic bone lesions, and eosinophilia in February 2011. A diagnosis of aggressive SM was made on the basis of abnormal mast cells in the bone marrow, high serum tryptase levels, and multiple lytic bone lesions including vertebral compression fractures. Polymerase chain reaction and subsequent sequencing of its products to identify mutations of *c-kit* yielded negative results and imatinib mesylate failed to improve the SM of the patient. She was then treated with interferon-α, with considerable improvement of the disease, although severe myelosuppression prevented the continued administration of a sufficient dose of this agent. In August 2011, the patient suddenly developed paraplegia of the lower extremities. Magnetic resonance imaging demonstrated epidural mass lesions at the levels from Th9 to Th11, compressing the spinal cord. Emergent laminectomy and subsequent irradiation of the tumors were performed without improvement of the paraplegia. Histopathologic examination of the epidural tumors, from samples obtained intraoperatively, confirmed the diagnosis of SM. She was further treated with dasatinib and then cladribine without obvious improvement, although the latter reduced the eosinophilia to some extent ; however, she died of sepsis in September 2011. 〔*J Clin Exp Hematop 53(3) : 207-213, 2013*〕

Keywords: aggressive systemic mastocytosis, eosinophilia, bone lesion, interferon-α, epidural tumor

INTRODUCTION

Mastocytosis is one of eight subcategories of myeloproliferative neoplasms proposed by the World Health Organization (WHO) classification in 2008.[1] Mastocytosis is a clonal disorder of mast cells that proliferate and accumulate in one or more organs. Mastocytosis consists of a number of subtypes, which are determined using the distribution of the disease and its clinical manifestations. In cutaneous mastocytosis, mast cell infiltration is restricted to the skin, whereas systemic mastocytosis (SM) is characterized by the disease involvement of at least one extracutaneous organ irrespective of the presence of skin lesions.[1,2] The WHO classification has defined the following subcategories of SM : indolent SM, smoldering SM, bone marrow mastocytosis, SM with an associated hematologic non-mast cell-lineage disease, aggressive SM, and mast cell leukemia. Aggressive SM involves systemic organs and is refractory to conventional chemotherapies, having a very poor prognosis.[1-4]

A small group of patients with SM present with eosinophilia, which has been reported to be of clinical and prognostic significance.[4-6] Similarly, a small number of patients with aggressive SM develop destructive bone lesions, although osteoporosis is relatively common.[7] Here, we report an aggressive SM case with eosinophilia and unusual lytic bone lesions at presentation, which later presented with epidural mass lesions, an exceptionally rare complication in SM.

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CASE REPORT

A 43-year-old female was referred to the Departments of Hematology and Orthopedics, Shinko Hospital, because of a vertebral compression fracture, multiple lytic bone lesions, eosinophilia, and weight loss of more than 10 kg in February 2011. Three months before visiting our hospital, she had

developed back pain when she was cleaning the floor, which gradually worsened. An abdominal computed tomography (CT) scan in a hospital demonstrated a pathologic fracture of the fourth lumbar spine (L4) and lytic bone lesions in the right sciatic bone and the left femoral neck. However, osteoporosis was not observed as evaluated by dual-energy X-ray absorptiometry. She had also been aware of intermittent itching and flushing, especially after taking a bath, which involved her face, neck, trunk, and proximal extremities and continued for about six hours, with a 10-year history. Her past history including allergic disease or drug allergy was unremarkable.

On a visit to the Department of Hematology, facial flushing and tenderness of the lower back and right chest were noted. She had neither superficial lymphadenopathy nor hepatosplenomegaly. The results of neurologic examination were unremarkable. Laboratory tests (Table 1) showed a white blood cell count of 19×10^9/L with 40.5% eosinophils, a hemoglobin concentration of 13.5 g/dL, and a platelet count of 427×10^9/L. Serum concentrations of alkaline phosphatase and lactate dehydrogenase (LDH) were elevated to 1,051 IU/L (normally 115-360) and 352 IU/L (normally 120-230), respectively. The serum concentration of C-reactive protein was 0.39 mg/dL (normally below 0.3 mg/dL). Other results of serum biochemical tests were unremarkable. Fluorine-18 fluorodeoxyglucose-enhanced positron emission tomography (FDG-PET) combined with CT scanning demonstrated abnormal accumulation of FDG in the right mandible, vertebrae, right rib bones, pelvic bones, right humerus, and left femoral neck (Fig. 1). The FDG-PET also showed a lytic change in the third cervical vertebra (C3), and pathologic fracture of the ninth thoracic vertebra (Th9), Th11, and L4. The findings of gastrointestinal- and colon-endoscopic and breast ultrasound examinations were unremarkable. Histologic examination of the skin flushing lesion was also unremarkable. A bone marrow aspirate showed hypercellular marrow with eosinophilia and a few cell aggregates forming a lumen-like configuration (Fig. 2a). Cytogenetic analysis of the marrow cells showed a normal karyotype of 46, XX. On the basis of the lytic and infiltrative bone lesions and the cell aggregates of undetermined origin in the bone marrow, a tentative diagnosis of metastatic adenocarcinoma of unknown origin was made. The subsequent clinical course is shown in Fig. 3.

The patient was subsequently admitted and received four courses of chemotherapy, which consisted of paclitaxel, carboplatin, and dexamethasone, in the Department of Oncology. However, the diagnosis of metastatic cancer was reassessed because bone pain, skin flushing, and eosinophilia were unchanged. Furthermore, no detectable epithelial cells were observed in the bone marrow on immunohistochemical studies of clot preparation of the marrow aspirate. Reexamination of the bone marrow smear preparation revealed the cell aggregates (Fig. 2a) to be granulocyte clusters and the presence of abnormally large atypical mast cells. The marrow nucleated cell count was 339×10^9/L, and huge atypical mast cells (Fig. 2b), large atypical mast cells (Fig. 2c), mast cells/basophils of normal size, and eosinophils comprised 0.6%, 6.2%, 2.4%, and 22.8% of the nucleated cells, respectively. The blast cells comprised 0.2% and there was no morphological evi-

Table 1. Laboratory findings on admission (February 2011)

White blood cell	19×10^9/L	Total protein	6.9 g/dL	sIL-2R	678 U/mL
Red blood cell	$4{,}010 \times 10^9$/L	Albumin	4.3 g/dL	CEA	1.2 ng/mL
Hemoglobin	13.5 g/dL	AST	15 IU/L	CA19-9	4 U/mL
Hematocrit	39.60%	ALT	23 IU/L	CA15-3	12.3 U/mL
Platelet	427×10^9/L	ALP	1,051 IU/L	NCC-ST-439	2.4 U/mL
Band	0.30%	Total bilirubin	0.5 mg/dL	SLX	34.6 U/mL
Segmented	46.70%	LDH	352 IU/L	CA125	15.7 U/mL
Eosinophil	41.00%	γ-GTP	18 IU/L	PT-INR	1.26
Basophil	0.00%	Blood urea nitrogen	9.2 mg/dL	APTT	32.6 sec
Monocyte	2.70%	Creatinine	0.62 mg/dL	Fibrinogen	358 mg/dL
Lymphocyte	9.00%	Uric acid	3.3 mg/dL	Interleukin-3	< 31 pg/mL
		Na	140 mEq/L	Interleukin-5	14.3 pg/mL
		K	4.0 mEq/L	GM-CSF	< 8 pg/mL
		Cl	101 mEq/L	tryptase	182 μg/L
		Ca	9.7 mg/dL	histamine	31.4 ng/mL
		C-reactive protein	0.39 mg/dL		

AST, aspartate aminotransferase ; ALT, alanine aminotransferase ; ALP, alkaline phosphatase ; LDH, lactate dehydrogenase ; γ-GTP, γ-glutamyl transpeptidase ; sIL-2R, soluble interleulkin-2 receptor (normal range 124-466) ; CEA, carcinoembryonic antigen (< 5.0) ; CA19-9, carcinoma 19-9 (< 37), CA15-3 (< 25), NCC-ST-439 (< 7.0) ; SLX, sialyl lewis X-I (< 8.0) ; CA125 (< 35) ; PT-INR, prothrombin time-international normalized ratio ; APTT, activated partial thromboplastin time ; IL-5 (< 3.9 pg/mL), GM-CSF, granulocyte macrophage colony stimulating factor ; histamine (0.15-1.23). The values of IL-3 and GM-CSF were below the detection limits.

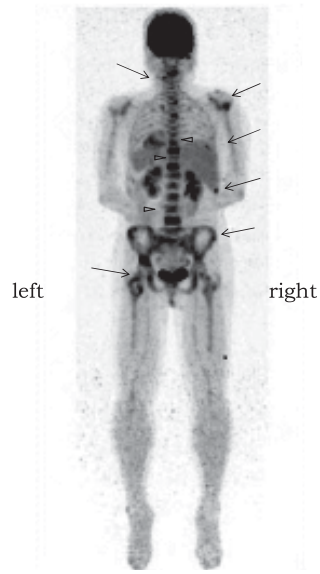

Fig. 1. Fluorine-18 fluorodeoxyglucose-enhanced positron emission tomography (FDG-PET) combined with computed tomography scanning demonstrates abnormal accumulation of FDG in the right mandible, vertebrae, right rib bones, pelvic bones, right humerus, and left femoral neck (*arrows*). The FDG-PET also shows pathologic fractures of the ninth thoracic vertebra (Th9), Th11, and L4 (*arrowheads*).

dence of myelodysplastic syndrome or acute myeloid leukemia. Therefore, she was again referred to the Department of Hematology for further examinations in the beginning of April 2011.

Physically, the patient was afebrile and flushing was intermittently noted. Hepatosplenomegaly and superficial lymphadenopathy were not observed. At this time, she was on oral prednisolone therapy (20 mg/day) as part of the chemotherapy. Hematologic tests revealed the white cell count to be 11.8×10^9/L with 50.8% neutrophils, 26.4% eosinophils, 1.2% basophils, 3.2% monocytes, and 17.6% lymphocytes, a hemoglobin concentration of 9.7 g/dL, and a platelet count of 93×10^9/L. Regarding the differential count of white cells, no immature or abnormal cells were observed.

Serum biochemical and serological tests showed that the concentrations of alkaline phosphatase, LDH, and C-reactive protein were elevated to 840 IU/L, 582 IU/L, and 0.5 mg/dL, respectively. Other biochemical tests including aspartate aminotransferase, alanine aminotransferase, and total bilirubin were unremarkable. The second bone marrow aspiration was difficult, and a sufficient number of cells were not obtained. However, large atypical mast cells were observed on the smear preparation. These cells showed metachromasia to toluidine blue staining (Fig. 2d). These findings prompted us to measure the serum concentrations of tryptase and histamine, which were clearly elevated to 182 ng/mL (normally 5.5-13.5) and 31.4 ng/mL (normally 1.25-1.23), respectively. A bone marrow biopsy specimen stained with hematoxylin-eosin showed clusters of pale eosinophilic cells and isolated giant cells with lobulated nucleus. On immunohistochemistry, these cells were positive for CD117 (c-kit). A diagnosis of aggressive SM was made on the basis of the significant infiltration of mast cells into the bone marrow (one major criterion by the WHO 2008 classification), serum tryptase levels greater than 20 ng/mL (one minor criterion), and "C" findings by the WHO classification, that is, skeletal involvement with large osteolytic lesions and pathologic fractures.

To confirm the diagnosis of aggressive SM, further examinations were performed using cryopreserved bone marrow cells taken at the first occasion. Reverse transcriptase-polymerase chain reaction (RT-PCR) to examine the major and minor *bcr-abl* fusion genes gave negative results. PCR and subsequent sequencing of its products, to identify possible mutations of *c-kit* in exons 8, 10, 11, and 17, also yielded negative results (performed by SRL, Hachioji, Tokyo, Japan). Regarding the eosinophilia, the patient did not have bronchial asthma or allergic dermatitis, such as eczema or urticaria. She also did not regularly take drugs during the eosinophilia.

After the diagnostic procedure, H1- and H2-histamine receptor antagonists and prednisolone at 30 mg/day were orally administered to control constitutional symptoms such as flushing, skin itching, nausea, vomiting, and diarrhea with some improvement. Before the diagnosis was made, the patient was given opiate analgesics once for severe pain, which caused nausea and severe vomiting, presumably by direct or indirect activation of mast cell mediator production.[8] To control the severe lower back/hip joint pain, transdermal fentanyl citrate and tramadol hydrochloride were employed, which were useful for pain relief.

The *c-kit* mutation at D816V is detectable in more than 80% of adult SM patients[4]; however, this mutation was not detected in this case. Nonetheless, some SM patients have other *c-kit* mutations, and these mutants sometimes make this disease susceptible to imatinib mesylate.[3] With this rationale, treatment with imatinib mesylate (400 mg/day) and oral prednisolone (30 mg/day) was started in the middle of April 2011. Soon after the initiation of the treatment, the serum level of LDH increased to 1,749 IU/L, and the liver enlarged, being palpable 3.0 cm below the costal margin with the development of ascites. On day 5, the patient developed severe myalgia in bilateral buttocks and thighs. Because the pain was not relieved by any medications, and the agent seemed to be ineffective for hepatomegaly, eosinophilia, and skin flushing, imatinib mesylate was discontinued on day six. The myalgia gradually decreased and disappeared on day nine.

At the end of April 2011, treatment with interferon-α (IFN-α) (three million units, 5 times/week) and oral dexamethasone (8 mg/day) was started to induce remission of the aggressive SM. Two weeks after the initiation of therapy, hepatomegaly, ascites, and skin flushing were markedly im-

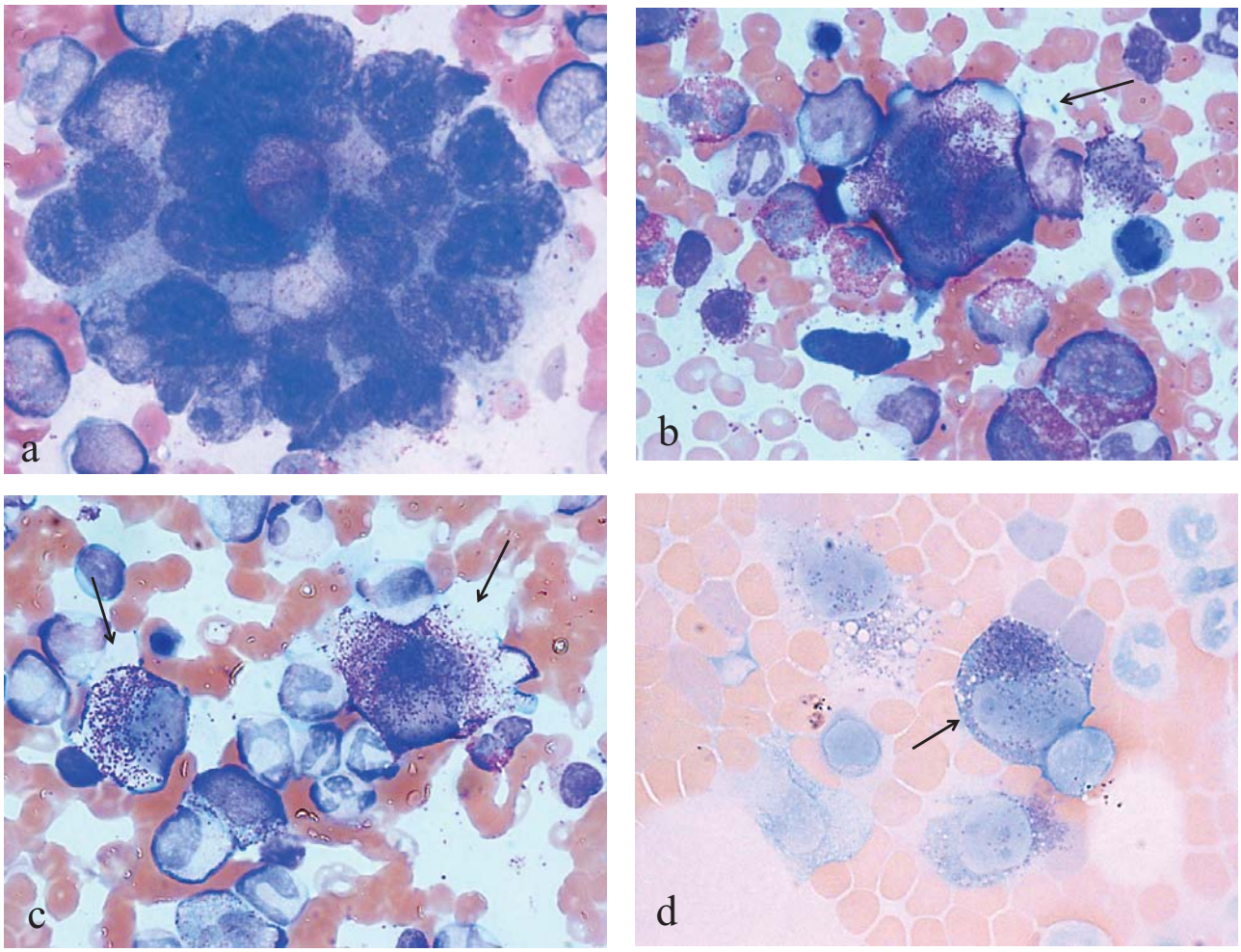

Fig. 2. Smear preparations of bone marrow aspirate (February 2010). A cell aggregate forms a lumen-like configuration (*2a*), which was later revealed to be a granulocyte cluster on reexamination of the smear (Wright-Giemsa staining, × 1, 000). Some mast cell-like cells are huge (*2b*) (*arrow*), and some are large (*2c*) (*arrows*) (Wright-Giemsa staining, × 1,000). The granules of these cells (*arrow*) show metachromasia to toluidine blue staining (×1,000).

proved. Although IFN-α treatment was effective, we tapered its dosage and reduced it to six million units/week (three million units, twice a week) because of severe myelosuppression. With this dosage of IFN-α, serum levels of tryptase and LDH decreased to 171 ng/mL and 506 IU/L, respectively, and the patient was discharged because of a considerably stable disease (Fig. 3). At this time, we planned to undertake allogeneic hematopoietic stem cell transplantation because the patient had an HLA-matched sibling donor if good partial remission was achieved.

In July 2011, the patient was readmitted because of traumatic subarachnoid hemorrhage ; she had fallen from a chair and hit her head on the floor. Her consciousness was clear without any paralysis or sensory disturbance ; therefore, the subarachnoid hemorrhage was conservatively treated and the IFN-α therapy was continued. In the beginning of August 2011, she suddenly developed paraplegia of the lower extremities, which was associated with vesicorectal disturbance. T2-weighted magnetic resonance imaging demonstrated high-intensity epidural mass lesions at the vertebral levels from Th9 to Th11, compressing the spinal cord. Emergent laminectomy was performed to decompress the affected spinal cord ; however, the procedure did not improve the paraplegia. Biopsy specimens taken at the laminectomy were histopathologically examined. The tumor tissue consisted of pale eosinophilic cells with a spindle-like shape and a small number of large multinucleated cells (Fig. 4a). These cells were positive for CD117 (c-kit) (Fig. 4b), tryptase (Fig. 4c-1), and CD68 (weakly), but not for CD25 (Fig. 4d). Regarding exact diagnosis of the present patient, we summarize hematologic, pathologic, and other clinical findings in Table 2. Following the laminectomy, irradiation of the tumors between Th8 and Th12 was performed without improvement of the paraplegia. During the radiotherapy, IFN-α was discontinued because of

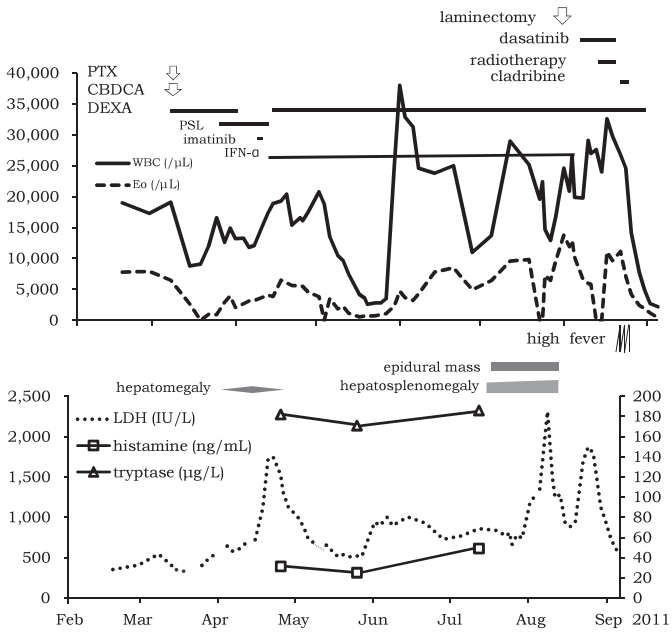

Fig. 3. Clinical course of the present patient. PTX, paclitaxel ; CBDCA, carboplatin ; DEXA, dexamethasone ; PSL, prednisolone ; IFN-*α*, interferon-*α*

severe myelosuppression. Therefore, treatment with dasatinib (100 mg/day) for 14 days was started without the improvement of SM. As the last treatment option for aggressive SM, we intravenously administered cladribine (7.5 mg/day, for 5 consecutive days). This agent reduced the eosinophilia to some extent (Fig. 3) ; however, the patient developed sepsis and died in the beginning of September 2011. Necropsy demonstrated abnormal mast cell infiltration similar to that shown in Fig. 4a in the liver, spleen, and bone marrow (data not shown). The treatments with imatinib mesylate and IFN-*α* were started after written informed consent by the patient, and these treatments were approved by the review board of Shinko Hospital. Dasatinib and cladribine were administered after informed consent by her sister.

DISCUSSION

In the patient described in this report, prominent and persistent eosinophilia was observed from the initial presentation. Previous reports described that a small group of patients with SM present with eosinophilia, and that SM with eosinophilia was of clinical and prognostic significance ; that is, it was associated with significantly reduced overall and event-free survival when compared with patients without eosinophilia.[4,5,9] Our patient did not have obvious allergic diseases or drug allergies. Furthermore, chronic eosinophilic leukemia caused by the fusion of *FIP1-LI* and *PDGFRα* genes was unlikely because imatinib mesylate was ineffective for the eosinophilia in this patient.[10] Indeed, we examined, as a post-mortem analysis, whether or not bone marrow cells carried the fusion of *FIP1-LI* and *PDGFRα* genes by RT-PCR using cryopreserved marrow cells obtained on the first occasion, with a negative result.[11] Future studies should determine whether the eosinophilia is caused by eosinophilopoietic cytokines produced by neoplastic mast cells, such as interleukin-5 (IL-5) or IL-3, or whether the eosinophils themselves belong to a neoplastic clone. In the present patient, however, serum IL-5 but not IL-3 was significantly elevated (Table 1). Therefore, reactive eosinophilia but not a constitutive type is suggested in the present case because IL-5 mediates reactive or allergic eosinophilia.[12]

Several parameters have been described to be associated with an unfavorable prognosis in SM. These include an absence of skin lesions, huge osteolyses, weight loss, malabsorption, enlarged liver with portal hypertension, and splenomegaly with hypersplenism.[2,4,9,13] In the present patient, absence of skin lesions/invasions, multiple bone lesions, weight loss, hepatomegaly, and splenomegaly on CT scanning were observed, although portal hypertension and hypersplenism were unclear. Regarding bone lesions in SM, Barete *et al*. reviewed 75 patients with SM and reported that osteoporosis or osteopenia was commonly observed, that is, in 23 patients (31%), being accompanied by vertebral fracture (13 patients : 17%) or another site fracture (four patients). On the other hand, they described only one patient with focal osteolytic lesion. Bone lesions in the present patient also displayed a focal osteolytic pattern without osteoporosis, which appears to be quite unusual in SM.[7] Furthermore, to our knowledge, epidural mass lesions have been described in only 2 cases of SM.[14,15]

It has been reported that many patients with aggressive SM with slow progression can be successfully treated with IFN-*α* or cladribine with subsequent stable disease for several months or even years.[2-4,9,16] Indeed, the present patient once became ‘stabilized’ with IFN-*α*, although neutropenia was an adverse effect that prevented us from using a higher dose of IFN-*α* to prevent disease progression, that is, tumor formation at the vertebrae. From this point of view, the present case may have been a slow progression type, a subtype of aggressive SM. As the last option, we administered cladribine to control the disease. However, unfortunately, the patient died of sepsis. Therefore, early diagnosis and appropriate treatment appeared to be important in this patient.

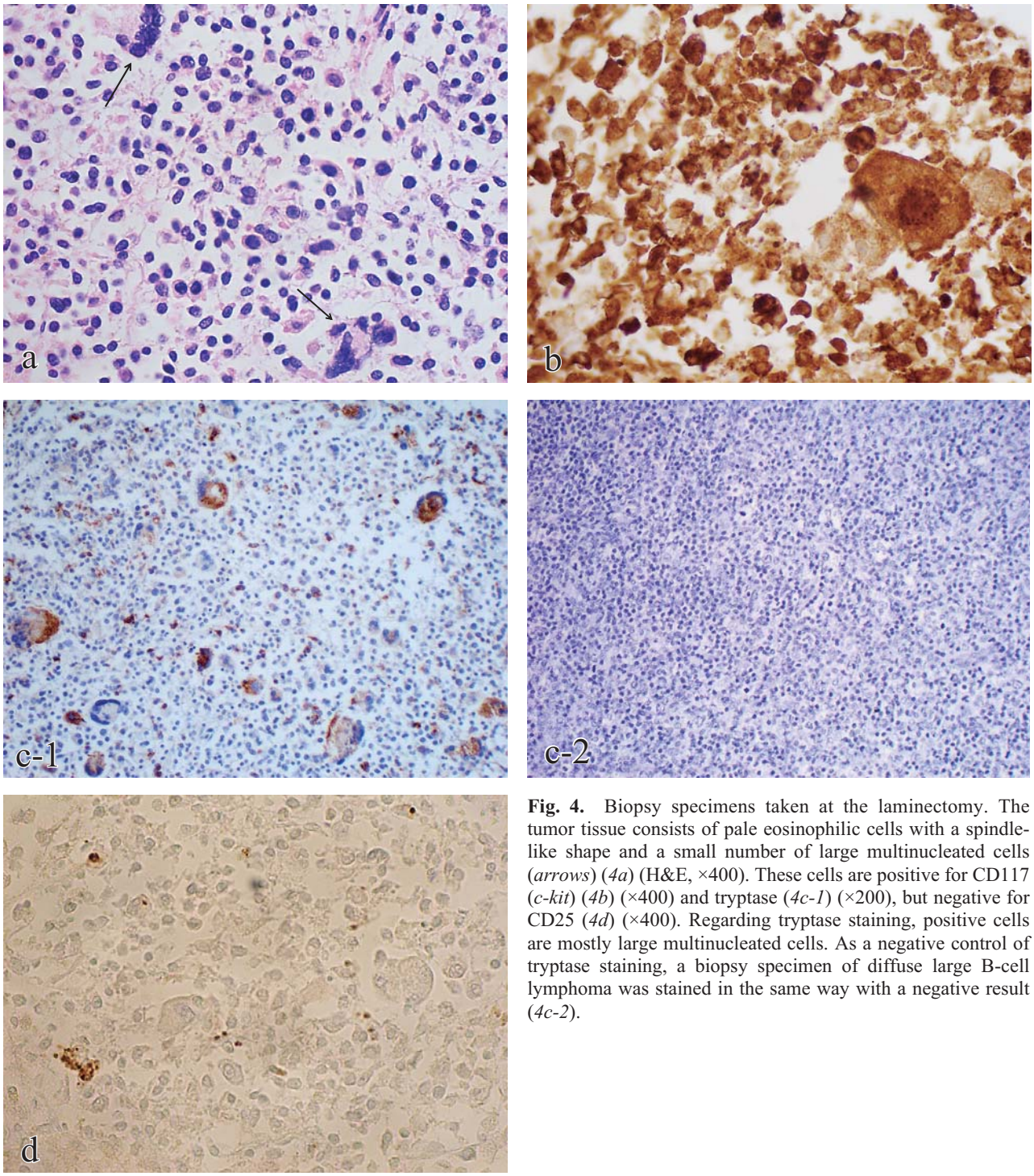

Fig. 4. Biopsy specimens taken at the laminectomy. The tumor tissue consists of pale eosinophilic cells with a spindle-like shape and a small number of large multinucleated cells (*arrows*) (*4a*) (H&E, ×400). These cells are positive for CD117 (*c-kit*) (*4b*) (×400) and tryptase (*4c-1*) (×200), but negative for CD25 (*4d*) (×400). Regarding tryptase staining, positive cells are mostly large multinucleated cells. As a negative control of tryptase staining, a biopsy specimen of diffuse large B-cell lymphoma was stained in the same way with a negative result (*4c-2*).

Table 2. Clinicopathological findings regarding the diagnosis of the present patient

Hematologic findings	Pathologic findings of the tumor	Other findings
Atypical mast cells in the bone marrow	Pale eosinophilic spindle-like picture	Large osteolytic lesions
Metachromasia to toruidine blue	Positive tryptase staining	High serum tryptase level
Negative *bcr-ab*l chimera	Positive c-kit staining	High serum histamine level
Negative *FIP1L1-PDGFRα* chimera		

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