



Case Report

Mast cell leukemia: An extremely rare disease

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Abstract

Systemic mastocytosis is characterized by pathologic proliferation and accumulation of mast cells in at least one extracutaneous organ such as liver, spleen, bone marrow, or lymph nodes. The clinical features are highly variable depending on impairment of the involved organ systems. It often raises diagnostic challenges. Here we report a case of a 78-year-old patient with mast cell leukemia. The literature is reviewed regarding the diagnosis and updated management of this rare disease.

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1. Introduction

Systemic mastocytosis (SM) is a heterogeneous clonal disorder, characterized by abnormal mast cell infiltration in extracutaneous organs. It is classified into a subcategory under myeloproliferative neoplasm in the 2008 revision of the World Health Organization classification.¹ The clinical presentation varies, depending on impaired organ function resulting from accumulation of these clonally derived mast cells in different tissues including bone marrow, skin, gastrointestinal tract, liver, spleen, and lymph nodes. In Taiwan, SM is an extremely rare disease with limited clinical experiences shared by local hematologists. Here we report a

patient of mast cell leukemia (MCL). The literature is reviewed regarding the diagnosis and updated management of this rare disease.

2. Case report

A 78-year-old male patient presented with a 3-month history of fever and thrombocytopenia. He had a past history of coronary artery disease, chronic obstructive pulmonary disease, and duodenal ulcer. On admission, physical examination revealed jaundice, splenomegaly, marked edema and multiple petechiae over lower limbs, and no skin rashes. Laboratory examinations showed a leukocyte count of $12.2 \times 10^9/L$ with 75% segmented neutrophil and 9% lymphocytes in differential; hemoglobin level of 9.4 g/dL and platelet count of $15.0 \times 10^9/L$. Total bilirubin level was 2.48 mg/dL (normal range 0.2–1.6 mg/dL). Serum albumin level was 2.7 g/dL (normal range 3.7–5.3 g/dL). The LDH level was 389 U/L (normal range 130–250 U/L). Infiltration in bilateral lower

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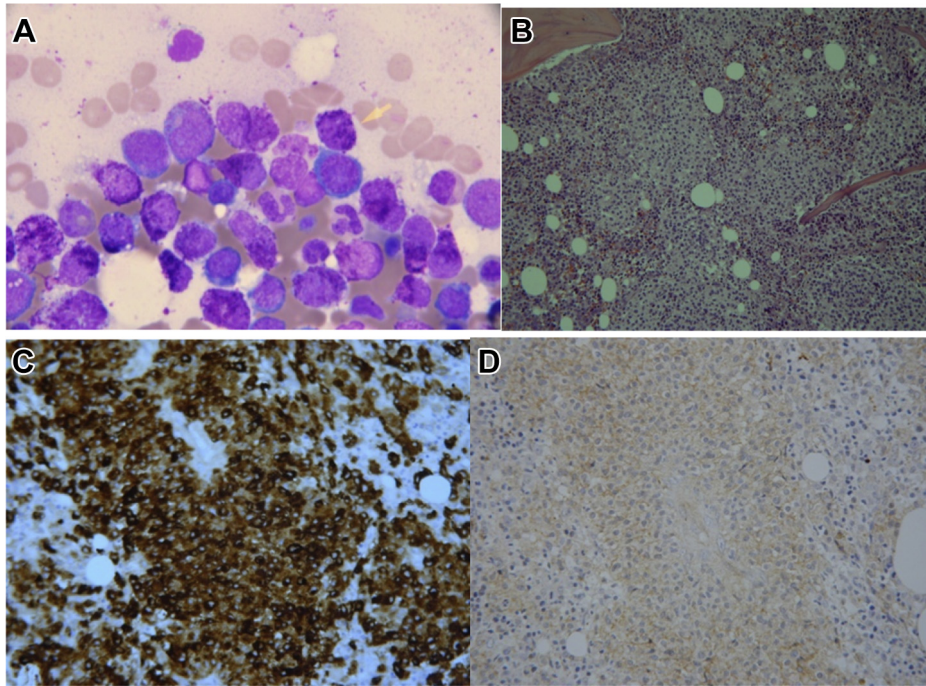


Fig. 1. (A) Bone marrow cytology (Wright stain, 1000 \times), profuse infiltration of blast-form cells with more than half of the blasts containing metachromic granules or vacuoles in the cytoplasm. (B) Bone marrow biopsy (hematoxylin and eosin stain, 100 \times), profuse infiltration of monotonous malignant cells. (C) Bone marrow biopsy (tryptase stain, 200 \times). (D) Bone marrow biopsy (CD 25 stain, 200 \times).

lung fields was observed on chest X-ray. Computed tomography (CT) of the abdomen revealed splenomegaly, pleural thickness, and increased infiltration and consolidation over bilateral lower lung fields. Immature blast-like cells with cytoplasmic vacuoles were observed in peripheral blood smear. Bone marrow aspirate showed diffuse infiltration of blast-like cells around 75%, with more than half of blasts containing metachromatic granules (appearing a different color after staining by basic dye methylene blue of Wright's stain) or vacuoles in the cytoplasm (Fig. 1A and B). The granules occupied nearly the whole cytoplasm suggestive for mast cell lineage. Surface marker study in bone marrow biopsy showed positive staining for tryptase, CD117, and CD25 in the majority of the cells, while negative staining for lysozyme (Fig. 1C and D). The whole picture is compatible with

systemic mastocytosis and MCL was diagnosed based on >20% blasts in the marrow aspirate. Chromosome analysis of bone marrow cells noted the presence of trisomy 8. Molecular analysis of the marrow cells confirmed the presence of KITD816V mutation (Fig. 2), whereas a study of the JAK2V617F mutation showed negative results.

During hospitalization, the patient had been weak and confined to bed all day. With the use of antibiotics, his fever subsided in the 3rd week of hospitalization. However, generalized edema deteriorated owing to malnutrition and hypoalbuminemia status and respiratory distress persisted.

Treatment with imatinib mesylate was tried initially without clinical improvement in thrombocytopenia and jaundice. Abdominal pain and vomiting developed later with elevated levels of amylase (322 U/L; normal range, <180 U/L)

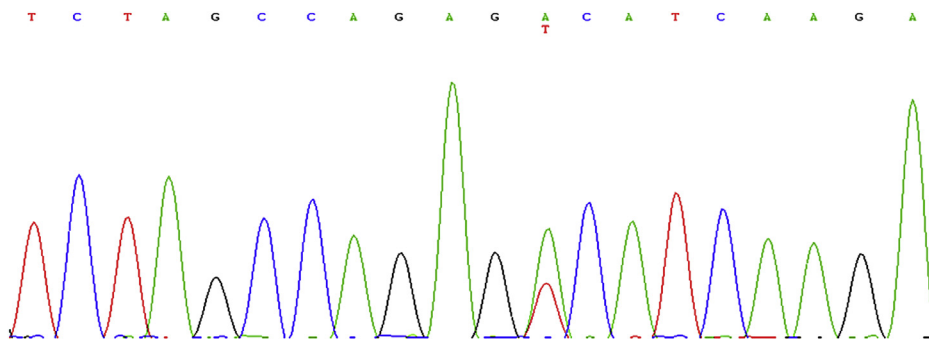


Fig. 2. Sequencing results of the PCR product for c-Kit shows 2447 A > T pathogenic variation at codon 816 of exon 17 (D816V).

and lipase (837 U/L; normal range, <180 U/L). Acute pancreatitis was diagnosed. With the detection of the KITD816V mutation, compassionate use of another multi-target protein kinase inhibitor, midostaurin (PKC412), had been tried for 1 week. Fever relapsed again and persisted, and the patient's clinical condition gradually deteriorated. He finally died of sepsis and disseminated intravascular coagulation 3 weeks after the diagnosis of the malignancy.

3. Discussion

Mastocytosis is classified into three categories according to the 2008 World Health Organization classification: (1) cutaneous mastocytosis, in which mast cell infiltration is confined to the skin; (2) SM, in which at least one extracutaneous organ is involved; and (3) extracutaneous mast cell neoplasm, either as malignant mast cell sarcoma or as benign extracutaneous mastocytoma.²

SM can be further categorized into four subtypes: (1) indolent SM, with maculopapular skin lesions but no organ dysfunction; (2) aggressive SM (ASM), defined by pathological mast cells infiltrating bone marrow, liver, spleen, gastrointestinal tract and the skeletal system; (3) SM with an associated clonal hematological nonmast cell lineage disease, in which the nature of the associated hematological disorder dictates treatment and prognosis; and (4) MCL, with a high percentage of neoplastic mast cells in bone marrow aspirate (>20%) and peripheral blood, resulting in multiorgan failure and a fatal outcome.²

KITD816V mutation was detected in this patient. SM is frequently associated with the gain-of-function mutation in the gene encoding the tyrosine kinase KIT. The most frequently detected single-point mutation in neoplastic mast cells is KITD816V, which disrupts the hydrogen bond between residues D816 and N819, leading to KIT auto-phosphorylation and uncontrolled proliferation.^{3,4} In a recently reported series including 342 cases of SM, the mutation rate of KITD816V was 78% in indolent SM, 82% in ASM, and 60% in SM with an associated clonal hematological nonmast cell lineage disease.⁵

Although serum tryptase level was not determined, the tissue infiltration of mast cells combined with the aberrant expression of CD25 in mast cells and the presence of D816V mutation fulfilled the diagnostic criteria of mastocytosis. Moreover, profuse infiltration of immature mast cells (>20%) in the bone marrow aspiration smear was observed in this patient, supporting categorization of the diagnosis into MCL. MCL is an extremely rare disorder, accounting for <1% of patients with SM.

The clinical course of SM varies, from slowly progressive to rapidly fatal. Individualized treatment regimen is required. Generally speaking, SM remains incurable, and therapy is primarily palliative. In patients with ASM, cytoreductive therapy is required. Current first-line treatment options include interferon and 2-chlorodeoxyadenosine (2CdA). These agents may temporarily stop disease progression but

do not have long-lasting effects. Owing to the rarity of MCL, treatment of this disease is mainly based on the experience from ASM.

Although the mutant KITD816V kinase can be frequently detected in patients with SM,⁶ clinical response to treatment with tyrosine kinase inhibitor has been disappointing. Imatinib is the first tyrosine kinase inhibitor used to treat SM. It inhibits *in vitro* the growth of cells with wild type KIT protein or with KITV560G mutant, but not the cells with KITD816V mutant.⁶ Using imatinib to treat 24 patients of advanced SM, an Italian study reported that only one patient achieved complete remission and four patients achieved partial remission. None of the responders had the KITD816V mutation.⁷ Imatinib has been approved by the United States Food and Drug Administration for treating adult patients who have ASM without the KITD816V mutation or with unknown KIT mutational status.

The median survival in MCL is relatively short.⁵ Our case died of the disease shortly after diagnosis. First-line therapy with interferon was skipped because the medicine would not be reimbursed by the National Health Insurance and was not available otherwise. Our patient had received treatment with imatinib for 1 week prior to the detection of the KITD816V mutation. Consistent with previous reports, no clinical improvement was observed. The patient had jaundice on admission and developed acute pancreatitis during hospitalization. The pancreatitis was probably related to systemic organ infiltration by mast cells.

Midostaurin (PKC412) is an oral multitargeted kinase inhibitor, capable of inhibiting KIT, FLT-3, and PDGFR.⁸ It can suppress the growth of human mast cells harboring either KITD816V mutant or wild-type KIT. In a Phase 2 trial, Midostaurin demonstrated efficacy in patients with ASM or MCL, with or without the KITD816V mutation. A positive correlation was observed between the presence of KITD816V mutation and major response ($p = 0.0095$).⁹ Midostaurin had been tried in our patient without clinical response, probably related to the far advanced disease status precluding enough time of medication with this novel agent.

In conclusion, we encountered a patient of MCL, who pursued a rapidly fatal clinical course despite the trial of imatinib and midostaurin. Although extremely rare, systemic mastocytosis can challenge hematologists in the aspects of diagnosis and management. Early diagnosis of the disease and prompt initiation of novel active agents probably could improve the prognosis.

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