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【 CASE REPORT 】

Disseminated Bone Marrow Carcinomatosis Due to Malignant Melanoma of Unknown Primary Origin

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Abstract:
An 80-year-old woman was admitted to our hospital due to appetite loss and vomiting. A blood examination showed liver disorder with disseminated intravascular coagulation. All tumor markers and hepatitis virus markers were negative. Contrast-enhanced computed tomography did not show tumor lesions, bone lesions, lymphadenopathies, or thrombosis. A bone marrow biopsy revealed large, atypical cells with brown pigmentation and positive immunostaining for HMB-45, S100 proteins, and CD79a without myeloid or lymphoid markers. We experienced a case of disseminated carcinomatosis of the bone marrow due to malignant melanoma of unknown primary origin.

Key words: malignant melanoma, disseminated carcinomatosis of the bone marrow, unknown primary origin, CD79a

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Introduction

Disseminated carcinomatosis of the bone marrow (DCBM) is caused by bone marrow metastasis of solid tumors and can lead to hematological abnormalities, including disseminated intravascular coagulation (DIC) and microangiopathic hemolytic anemia (MHA) (1, 2). The prognosis of patients with DCBM is very poor. Gastric cancer accounts for 90% of the primary tumors causing DCBM (2); however, there are also a few reports indicating malignant melanoma (MM) as the primary contributory tumor. Furthermore, MM of unknown primary origin (MUP) with DCBM is even rarer, with three such cases reported thus far (3-5).

We herein report a case of DCBM due to MUP diagnosed by a bone marrow biopsy that followed a rapid course. This case report also includes a review of the relevant literature.

Case Report

An 80-year-old woman had been suffering from appetite loss lasting a few days in August 2020. She subsequently visited an emergency outpatient facility due to increased general malaise and vomiting. A series of tests revealed liver injury, elevated hepatobiliary enzyme levels, and significant coagulation disorders. Therefore, the patient was admitted to our department of gastrointestinal medicine for a further examination and treatment. The patient had a history of rheumatoid arthritis and Sjogren's syndrome, which had been treated with prednisolone and methotrexate. She was a nonsmoker; had no history of blood transfusions, hereditary diseases, or allergies; and did not consume significant amounts of alcohol.

Upon admission, a physical examination revealed epigastric and left lumbar pain. Swelling of the lymph nodes was not observed in the neck or axilla. Skin lesions were not observed in the body surface. The laboratory test results are shown in the Table. The total white blood cell count was within the normal range. The platelet count was $5.3\times10^4/\mu L$. The serum aspartate aminotransferase (AST) level was elevated to 123 U/L, the alanine aminotransferase (ALT) level was 44 U/L, and the serum lactate dehydrogenase (LDH) level was 5,084 U/L. The alkaline phosphatase (ALP) level was elevated to 388 U/L, and the γ-glutamyltransferase (γ-

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Table. Laboratory Data on Admission.

Peripheral blood		Blood chemistry			
WBC	6,300 /μL	TP	6.4 g/dL	HbA1c	6.4 %
Neutro	87.3 %	Alb	3.7 g/dL	CRP	4.68 mg/dL
Eos	0.6 %	T-Bil	1.0 mg/dL		
Baso	0.3 %	AST	123 U/L	Blood coagulation factors	
Mono	3.0 %	ALT	44 U/L	PT	81.4 %
Lymph	8.8 %	LDH	5,084 U/L	APTT	29.8 s
RBC	403×10^4 /μL	LDH1	9 %	Fib	105 mg/dL
Hb	11.8 g/dL	LDH2	39 %	FDP	≥110 μg/mL
Ht	33.8 %	LDH3	36 %	D-dimer	≥50 μg/mL
Plt	5.3×10^4 /μL	LDH4	14 %		
		LDH5	2 %	Serological tests	
		ALP	388 U/L	Procalcitonin	0.24 ng/mL
		γ-GTP	46 U/L	ANA	×1,280
Virus markers		Amyl	38 U/L		(CENTROMERE)
HA-IgM	(-)	CK	19 U/L	Ferritin	767.1 ng/mL
HBs-Ag	(-)	UN	6.8 mg/dL	sIL-2R	880 U/mL
HBc-Ab	(-)	Cr	0.43 mg/dL		
HCV-RNA	(-)	Na	124 mEq/L	Tumor markers	
VCA-IgM	(-)	K	4.1 mEq/L	AFP	2.3 ng/mL
HSV-IgM	(-)	Ca	8.5 mg/dL	CEA	1.5 ng/mL
CMV-IgM	(-)	Glu	76 mg/dL	CA19-9	4.9 U/mL

γ-GTP: γ-glutamyltransferase, AFP: α-fetoprotein, Alb: albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, Amyl: amylase, ANA: antinuclear antibody, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, Baso: basophils, Ca: calcium, CA19-9: carbohydrate antigen 19-9, CEA: carcinoembryonic antigen, CK: creatine kinase, CMV-IgM: cytomegalovirus-IgM, Cr: creatinine, CRP: C-reactive protein, Eos: eosinophils, FDP: fibrin/fibrinogen degradation products, Fib: fibrinogen, Glu: glucose, HA-IgM: hepatitis A virus antibody-IgM, Hb: hemoglobin, HBc-Ab: hepatitis B core antibody, HBs-Ag: hepatitis B surface antigen, HCV-RNA: hepatitis C virus RNA, HSV-IgM: herpes simplex virus-IgM, Ht: hematocrit, K: potassium, Lymph: lymphocytes, LDH: lactate dehydrogenase, Mono: monocytes, Na: sodium, Neutro: neutrophils, Plt: platelet count, PT: prothrombin time, RBC: red blood cell count, sIL-2R: soluble interleukin-2 receptor, T-Bil: total bilirubin, TP: total protein, UN: urea nitrogen, VCA-IgM: viral capsid antigen-IgM, WBC: white blood cell count

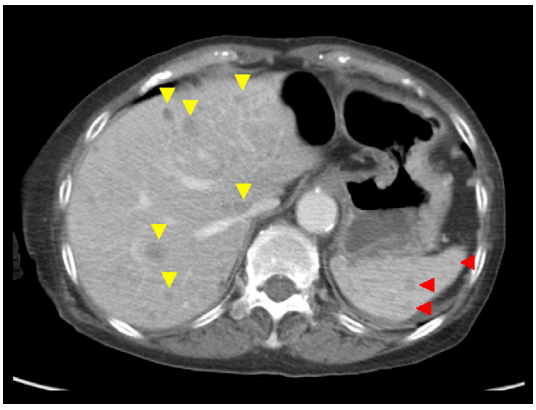

Figure 1. Contrast-enhanced computed tomography shows multiple small low-density nodules in the liver and spleen.

GTP) level was 46 U/L. The total bilirubin level was not elevated. The prothrombin time (PT) was within the normal range. The fibrinogen level was decreased to 105 mg/dL. The levels of fibrinogen degradation products (FDP) and D-dimers were higher than the measured values.

Tests for IgM-type antibodies against hepatitis A virus (anti-HA-IgM), hepatitis B virus core antibody (anti-HBc-Ab), and hepatitis B virus surface antigen (anti-HBs-Ag) were all negative. Serum HCV RNA was undetectable with polymerase chain reaction. Serology for Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex virus (HSV) also showed negative results. The anti-nuclear antibody (ANA) titer was 1:1,280 with a centromere pattern. The ferritin level was elevated to 767.1 ng/mL, and the level of soluble interleukin-2 receptor (sIL-2R) was 880 U/mL. The levels of tumor markers, alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and cancer antigen 19-9 (CA 19-9) were within the standard values.

Contrast-enhanced computed tomography (CECT) did not show any tumor lesions, bone lesions, lymphadenopathy, or thrombosis; however, it did indicate multiple small, low-density nodules in the liver and spleen (Fig. 1).

The laboratory findings, along with an assessment of the diagnostic criteria, indicated DIC; therefore, at the time of admission, we started anticoagulation therapy with heparin and antithrombin III, and changed it from heparin to thrombomodulin alfa on the 4th day of illness. However, the subsequent general condition worsened, as shown by the elevated levels of LDH and ALP. Considering the appearance of granulocytic immature cells, myelocytes, and metamyelo-

cytes, as well as the isozyme pattern (in which LDH2 and LDH3 were dominantly elevated during the clinical course), we performed a bone marrow biopsy on the seventh day of illness to test for hematological malignancies, such as leukemia and malignant lymphoma. The patient experienced no complications after the examination; however, she displayed a worsening respiratory condition and disruption of consciousness on the eighth day of illness, which was followed by death on the ninth day of illness.

A bone marrow aspiration smear revealed the infiltration of large, atypical cells showing adhesion with vacuoles and black granules in the basophilic cytoplasm (Fig. 2). The atypical cells accounted for about half of the nucleated cells. Flow cytometry of the bone marrow aspiration sample showed that the kappa/lambda ratio was normal. The bone marrow biopsy sample contained atypical cells of different sizes and large cells with brown pigmentation (Fig. 3a). An immunohistochemical examination revealed the presence of tumor cells positive for HMB-45 (Fig. 3b) and S100 proteins (Fig. 3c). Myeloid and lymphoid markers, including CD3, CD5, CD8, CD10, CD20, CD30, and CD56, were almost negative, while CD79a alone was positive (Fig. 3d). The clinical and pathological findings confirmed metastasis of MM to the bone marrow as well as DCBM.

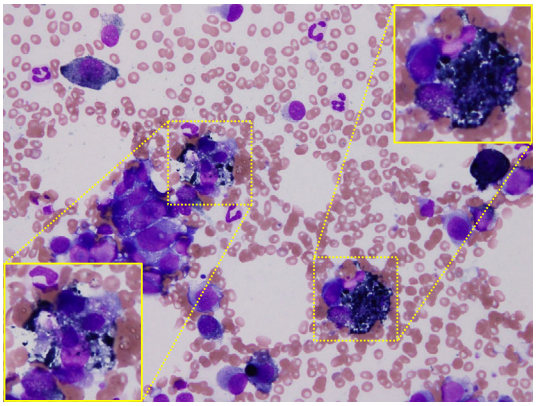

Figure 2. Bone marrow aspiration smear showing infiltration of large, atypical cells. The cells showed adhesion and had vacuoles and black granules in basophilic cytoplasm (original magnification, ×400 with May-Giemsa staining).

Discussion

In 1936, Jarco suggested that diffuse invasive gastric cancer was likely associated with extensive diffuse bone marrow metastasis, anemia, thrombocytopenia, and a bleeding tendency (1). Furthermore, this was the first time these cancers were reported as diffuse infiltrative carcinoma. In 1979, based on this concept, Hayashi et al. defined DCBM as a special metastatic type of cancer by analyzing the accumulation of diffuse bone marrow metastasis cases in solid tumors (2). A rapid increase in LDH and ALP levels is recognized as a characteristic blood finding (2), and in the present case as well, the values tended to increase as the condition

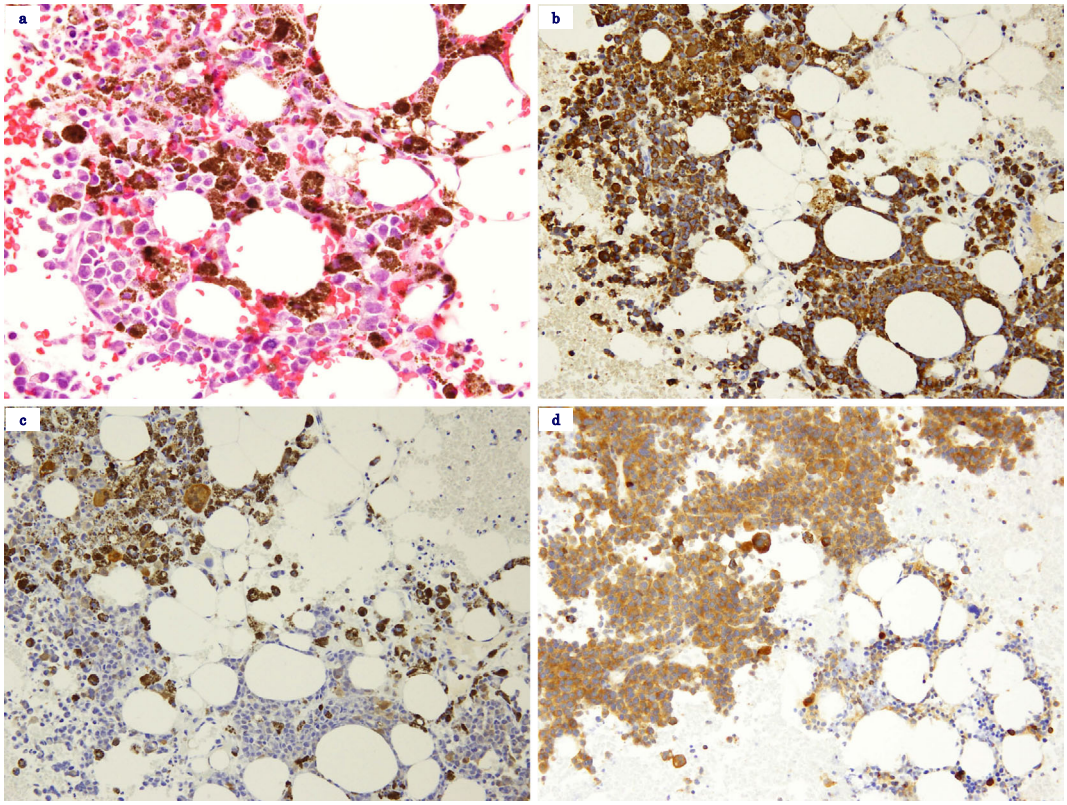

Figure 3. Atypical cells with different sizes, and large cells with brown pigmentation derived from bone marrow biopsy specimens (a: ×400 with Hematoxylin and Eosin staining). Cells positive for HMB-45 (b: ×400), S100 (c: ×400), and CD79a proteins (d: ×400).

progressed. CECT showed multiple low-absorption nodules in the liver; therefore, we suspected metastatic lesions and considered performing a percutaneous liver biopsy. However, given the appearance of granulocytic immature cells in peripheral blood, which might indicate bone marrow metastasis from solid tumors or hematopoietic tumors, we decided to perform a bone marrow biopsy instead. Notably, due to the DIC-related bleeding tendency, a bone marrow biopsy is characterized by a generally lower risk of post-bleeding than a percutaneous liver biopsy.

The characteristics cell morphological feature of MM is melanin pigmentation, and the frequency of occurrence is higher than that of other cell morphologies. Hemosiderin granules have similar pigmentation, but they can be distinguished by specific staining. Therefore, if melanin pigmentation can be proven, MM can be easily diagnosed (6). Although the presence of metastasis was able to be confirmed by a physical examination and laboratory tests during hospitalization in the present patient, primary lesions, including skin lesions, were not recognized. Therefore, we diagnosed the patient with MUP.

The most common metastatic sites of MUP are the lymph nodes and subcutaneous and visceral areas (7). Among visceral metastases, there are few reports of MUP with metastasis to the bone marrow. To our knowledge, there have been three such cases (3-5) reported, and they were characterized by a survival time of one to three weeks. These results suggest a very poor prognosis of DCBM in MUP. Bae et al. reported in a systematic review and meta-analysis that MUP had a better prognosis than melanoma of known primary in stage III and stage IV (8). However, DCBM is a clinical state that deteriorates rapidly, with some patients dying within a few weeks as a result of hemorrhaging or multiple organ dysfunction caused by DIC (9-11). In cases of MUP complicated with DCBM, it is difficult to identify the primary lesion, and the general condition will likely worsen before a definitive diagnosis can be made.

In the present case, the tumor cells were positive for CD 79a but expressed no other B-cell, T-cell, or myeloid markers, suggesting that they were likely of non-hematological origin. CD79a is a membrane protein (also called MB-1) known to be a pan-B-cell marker expressed throughout B-cell development. It is also widely expressed in B-cell neoplasms, including precursor B-acute lymphoblastic lymphoma/lymphoblastic leukemia. Generally, CD79a is not a standard marker for the diagnosis of epithelial tumors. In the present case, a bone marrow biopsy was performed to detect hematological diseases; however, it incidentally confirmed the presence of CD79a-positive MM. While there was a case of MM that tested positive for the hematological marker CD 56 (5), we found no previous confirmed cases of CD79a-positive MM.

We herein report a case of DCBM due to MUP that had a rapid course. The detected tumor was CD79a-positive, but due to a lack of supporting literature, the clinical implications of CD79a expression remain unclear, and further research on this subject is necessary.

The authors state that they have no Conflict of Interest (COI).

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