CASE REPORT

Amelanotic Malignant Melanoma of Unknown Primary Origin Metastasizing to the Bone Marrow: A Case Report and Review of the Literature

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Abstract

We herein describe the case of a 77-year-old Japanese man who presented with progressive thrombocytopenia. No lymphadenopathies, bone lesions, hepatosplenomegaly or masses within any internal organs were detectable. Bone marrow smears revealed diffuse infiltration of large atypical cells morphologically resembling mature lymphoid neoplasms. A flow cytometric analysis showed that the tumor cells strongly expressed CD56 without myeloid or lymphoid antigens, suggesting that they were non-hematologic in origin. Ultimately, amelanotic malignant melanoma of unknown primary origin was diagnosed based on positive immunostaining for S100 proteins, HMB-45 and Melan-A. This case illustrates the usefulness of flow cytometric analyses for making such diagnoses. We also review the available literature on similar cases.

Key words: malignant melanoma, unknown primary origin, bone marrow, amelanotic, CD56

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Introduction

Although more than 90% of malignant melanomas have a cutaneous origin, melanomas may present metastatically in the absence of an identified primary lesion (1); such tumors are designated “melanomas of unknown primary origin” (MUP). Furthermore, some malignant melanomas are “amelanotic,” meaning that they do not contain histopathologically detectable melanin pigment, which often makes diagnosing MUP difficult (2, 3). We herein report a case of bone marrow metastasis of amelanotic MUP and describe the usefulness of flow cytometric analyses for diagnosing this disease, with a review of the literature.

Case Report

A 77-year-old Japanese man was referred to our hospital due to progressive thrombocytopenia that had developed over the previous two months. His medical history included myocardial infarction, diabetes mellitus and early gastric cancer that was completely resected via endoscopy. On a physical examination, the patient exhibited general weakness and significant emaciation (body mass index: 17 kg/m\(^2\)) without other significant findings, including superficial lymphadenopathy or skin lesions. He also had no fever or night sweats.

Peripheral blood tests showed thrombocytopenia (platelet count: 2.6×10^4/μL), normocytic anemia (a hemoglobin level of 10.3 g/dL with an absolute reticulocyte count of 4.5×10^4/μL) and mild leukocytosis (1.1×10^4/μL with 10% myelocytes, 4% metamyelocytes, 74% neutrophils, 9% lymphocytes, 2% monocytes, 1% eosinocytes and 4% erythroblasts). Additional laboratory tests showed an elevated FDP level of 153 μg/dL, suggesting the presence of coexisting disseminated intravascular coagulation (DIC). No lymphadenopathies, bone sclerotic or lytic lesions, hepatomegaly, splenomegaly or masses within any internal organs were detectable on contrast-enhanced computed tomography. Bone marrow aspiration indicated hypercellular marrow with diffuse involvement of tumor cells and strongly suppressed hemopoiesis, as revealed on May-Giemsa staining.

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The tumor cells were non-cohesive and large with abundant vacuoles in basophilic cytoplasm. More than two nuclei were evident in 5% to 10% of infiltrating cells. The tumor cells were negative for myeloperoxidase staining and, based on their morphology, were suspected of being derived from mature lymphoid neoplasms (Fig. 1a, b).

However, an immunophenotypic analysis of bone marrow aspiration using flow cytometry (FCM) showed a strong CD56 expression in the tumor cells; however, myeloid and lymphoid antigens, including CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11c, CD16, CD19, CD20, CD23, CD25, CD30, CD33, CD34, CD43 and CD45, were absent.

The bone marrow biopsy specimen showed diffuse infiltration of large, rounded neoplastic cells with clear nucleoli without evidence of melanin pigmentation (Fig. 2a). An immunohistochemical examination demonstrated tumor cells positive for CD56 (Fig. 2b), S100 proteins, HMB-45 (Fig. 2c) and Melan-A (Fig. 2d) and negative for CD3, granzyme, keratin, synaptophysin and chromogranin A. These results confirmed that the patient had metastasis of
malignant melanoma to the bone marrow.

We carefully reexamined the patient after making the diagnosis, although no evidence of concomitant cutaneous or mucosal primary lesions was identified and no previous history of skin lesions or surgery was reported. Although the patient had been periodically examined by an ophthalmologist due to his diabetic retinopathy, uveal melanoma had not been detected. He experienced continuous nasal and gastrointestinal bleeding as a result of rapidly aggravating DIC and died approximately one week after the diagnosis on palliative treatment.

### Discussion

The incidence of MUP varies from 4% to 8% of patients with malignant melanoma (4-7). Standard criteria for diagnosing MUP have been described by Das Gupta (8); the present patient met these diagnostic criteria. Baab et al. reported the metastatic site at diagnosis in 98 cases of MUP to be as follows: lymph node metastases only (55%), subcutaneous metastases with or without lymph node involvement (13%) and visceral metastases with or without lymph node involvement (32%). Among the visceral cases, metastasis to the bone was observed in only two patients (2% of the cases) (3). Interestingly, amelanotic melanoma has been reported to be associated with an even more aggressive clinical course and a high incidence of metastasis (13-15), similar to the fulminant course observed in the present case.

FCM is an essential tool for diagnosing hematological malignancies in order to confirm the immunophenotype of leukemia and lymphoma (16). However, there is little evidence regarding the clinical significance of FCM for diagnosing non-hematological malignancies. In the presented case, the tumor cells were strongly positive for CD56 but expressed no T-cell, B-cell or myeloid antigens, suggesting that they were more likely non-hematological in origin. CD56 is a cell adhesion protein called NCAM1 (neural cell adhesion molecule 1) that is known to be expressed in hematological malignancies, such as NK/T cell neoplasms, malignant myeloma and some cases of acute leukemia. However, CD56 is also expressed in some non-hematological malignancies, such as melanoma (17), small cell carcinoma (18), rhabdomyosarcoma (19), Merkel cell carcinoma (20), neuroblastoma (21) and neuroendocrine tumors/carcinoma (22).

Farionla et al. evaluated the CD56 expression in neuroendocrine tumors obtained from fine-needle aspiration biopsy specimens and reported the utility of the CD56 expression in the absence of lymphoid antigens for specifically diag-

### Table. Three Case Reports of Malignant Melanoma of Unknown Primary Origin with Metastasis to the Bone Marrow

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Reference No.9</th>
<th>Reference No.2</th>
<th>Current case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chief complaint</td>
<td>34/male</td>
<td>22/male</td>
<td>77/male</td>
</tr>
<tr>
<td>Blood examination</td>
<td>axillary mass</td>
<td>weakness, weight loss</td>
<td>thrombocytopenia</td>
</tr>
<tr>
<td>WBC (µL)</td>
<td>2,900</td>
<td>7,800</td>
<td>11,400</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>7.1</td>
<td>5.5</td>
<td>10.2</td>
</tr>
<tr>
<td>Plt (µL)</td>
<td>20,000</td>
<td>65,000</td>
<td>20,000</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Other metastasis sites</td>
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<td>lymph node</td>
<td>none</td>
</tr>
<tr>
<td>Amelanotic/melanotic</td>
<td>melanotic</td>
<td>melanotic</td>
<td>amelanotic</td>
</tr>
<tr>
<td>Flow cytometric analysis</td>
<td>CD56 was not described</td>
<td>not performed</td>
<td>performed</td>
</tr>
<tr>
<td>Positive immunostains</td>
<td>S 100 proteins, HMB-45</td>
<td>S 100 proteins, HMB-45, Melan-A</td>
<td></td>
</tr>
<tr>
<td>Prognosis</td>
<td>died 3 weeks after diagnosis</td>
<td>not available</td>
<td>died 1 week after diagnosis</td>
</tr>
</tbody>
</table>

The histopathological findings of MUP suggest that the tumor cells are comprised of polygonal or spindle cells with prominent nucleoli (2). On the other hand, they may also exhibit varying cellular morphology with high-grade anaplastic cellular features (10). Because making the morphological diagnosis of MUP is often difficult, approximately 10% of MUP lymph node biopsies may be misdiagnosed as anaplastic carcinoma instead of MUP (5). Importantly, most melanoma cells have melanin pigment in their cytoplasm, which is a major clue to suspect MUP; however, the diagnosis of MUP is established based on immunostaining for markers such as HMB-45, Melan-A and S-100 proteins (11, 12).

However, if the MUP cells are amelanotic, the tumor cells will lack melanin pigment, as observed in the present case, and it becomes difficult to identify malignant melanoma based on histopathology (10). Because there are multiple differential diagnoses to be considered in such cases, the diagnostic process is complicated. Giuliano et al. reported that 50 of 2,881 melanoma patients (1.7%) had amelanotic malignant melanoma, including 29 amelanotic primary sites and 21 amelanotic metastases from a melanotic primary site. Only three patients presented with an absence of pigment in both the primary and metastatic sites (3). Interestingly, amelanotic melanoma has been reported to be associated with an even more aggressive clinical course and a high incidence of metastasis (13-15), similar to the fulminant course observed in the present case.

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nosing neuroendocrine tumors (22). On the other hand, few reports regarding the usefulness of FCM in diagnosing malignant melanoma have been published. Bhagwati et al. performed FCM on samples of bone marrow metastasis obtained from a patient with MUP. However, the authors did not test for CD56 positivity and obtained little information for diagnosing malignant melanoma using FCM (9).

We herein reported a case of amelanotic MUP with metastasis exclusively to the bone marrow and demonstrated the usefulness of FCM for diagnosing malignant melanoma, especially when the tumor cells at the biopsy site are amelanotic.

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

References