Acute Liver Failure Associated with Diffuse Hepatic Infiltration of Malignant Melanoma of Unknown Primary Origin

Kaori Tanaka¹,², Hiroyuki Tomita¹, Kenji Hisamatsu¹, Yuichiro Hatano¹, Kazuhiro Yoshida² and Akira Hara¹

Abstract

An 83-year-old man admitted for left hand pain due to a large necrotic ulcer presented with many sites of erythema on his trunk. Computed tomography revealed multiple poorly marginated masses in the liver; however, no malignant cells were detected on a biopsy of several skin lesions. He died on the 47th hospital day, and autopsy was subsequently performed, showing multiple nodules in the liver. The histological findings revealed clusters of malignant melanoma cells that had diffusely infiltrated the liver parenchyma. No tumor cells were detected in the skin lesions or lymph nodes. Immunohistochemically, the patient was diagnosed to have metastasis from malignant melanoma of unknown origin.

Key words: malignant melanoma, unknown primary origin, acute liver failure, diffuse liver infiltration


Introduction

Malignant melanoma usually originates from the skin (90%), and as many as 20% of patients develop metastasis. Cutaneous or subcutaneous nodules and lymph nodes are the most frequently affected sites, with the abdominal viscera being the least common site, of metastasis of malignant melanoma (1). In particular, liver metastases are diagnosed in 10-20% of patients with melanoma (2).

Both metastasis of malignant melanoma of unknown primary origin to the liver and acute liver failure caused by histological diffuse hepatic infiltration of malignant melanoma are rare. We herein present the case of a patient with diffuse hepatic infiltration involving malignant melanoma of unknown primary origin and acute liver failure.

Case Report

An 83-year-old man was referred for pain and itching in his left hand that had been present for the previous few months. His past history included diabetes mellitus and hypertension, and he had taken steroids (5 mg/day) for systemic atopic dermatitis for approximately 10 years. A physical examination showed a temperature of 38.8°C, a large (10×10 cm) ulcer with necrosis on the dorsal aspect of the left hand and many sites of erythema with crusting on the trunk that had been present for many years. No superficial nodules were observed.

The patient was subsequently hospitalized with a diagnosis of phlegmon of the left hand, which was treated with antibiotics and debridement. The laboratory data revealed abnormal liver function parameters, and a complete workup was initiated. The serum biochemical findings were as follows: aspartate aminotransferase (AST), 40 IU/L (normal <37); alanine aminotransferase (ALT), 55 IU/L (normal <45); alkaline phosphatase (ALP), 1,743 IU/L (normal <335); total bilirubin (TBIL), 0.47 mg/dL; γ-glutamyl transferase (γ-GTP), 581 IU/L (normal <49); lactate dehydrogenase (LDH), 895 IU/L (normal <228); white blood cell count, 20,800/μL; and C-reactive protein, 2.17 mg/dL. Serum tumor markers were slightly elevated, including carcinoembry-
mass lesions in the liver (Fig. 1a), with no ascites or lymphadenopathy. Ultrasonography and abdominal computed tomography (CT) scans showed multiple poorly marginated nodules. The serum biochemical values obtained on the 25th day of hospitalization were elevated, as follows: AST, 1174 IU/L; and LDH, 4118 IU/L. The patient's clinical course continued to worsen, and he died of hepatic failure on the 47th hospital day.

At autopsy, the patient's liver weighed 1,750 g and was occupied by multiple green- and black-colored nodules (Fig. 1b). Neither ascites nor lymphadenopathy were detected, and the histological findings demonstrated clusters of malignant melanoma cells that had infiltrated diffusely into the liver parenchyma and intrasinoidally (Fig. 2a). No malignant cells were detected in the skin lesions or lymph nodes, although no other remarkable findings were observed in the viscera macroscopically, the histological findings revealed diffuse infiltration of tumor cells into the spleen and stomach with vertebral bodies. Immunohistochemically, the tumor cells were positive for human melanin black (HMB)-45 and S100 proteins and negative for the AE1/AE3 epithelial marker (Fig. 2b-d). These results are consistent with metastasis of malignant melanoma. We carefully investigated the patient's entire body; however, no primary lesions were detected.

**Discussion**

The frequency of metastatic melanoma of unknown origin has been reported to range from 2.3-4.7% of all cases of melanoma (3, 4). The most commonly observed areas of metastatic melanoma of unknown origin are the regional lymph nodes, subcutaneous areas, abdominal viscera and tissues such as the brain and lungs (3, 4). Several cases of metastatic melanoma of unknown primary origin in the liver have been reported (1, 4-6).

The diagnosis of malignant melanoma of unknown primary origin should be made based on the extensive exclusion criteria developed by Dasgupta et al. (3), as follows: (a) the presence of metastatic melanoma confirmed clinically, histologically and immunohistochemically; (b) the absence of prior excision of suspicious melanocytic or pigmented lesions without a histological examination; (c) the exclusion of patients with no examination findings for ophthalmic and genital areas; and (d) findings for upper airway and lower gastrointestinal examinations, chest CT and/or X-ray, abdominal ultrasonography or CT, lymph node ultrasonography of sites of palpable lymphadenopathy and cranial CT or magnetic resonance imaging prior to diagnosis.

Two main possibilities explaining the development of melanoma metastases of unknown primary origin have been considered (4): (a) complete regression of the primary melanoma after metastasis [Anbari et al. (7) reported that, among 40 patients with melanoma of unknown primary origin, 20% had a history of regressed skin lesions]; and (b) a primary origin of the melanoma in the lymph nodes or other subcutaneous tissues or viscera. Melanoma may also arise from ectopic nevus cells in the lymph nodes and other tissues.

In the present patient, we were unable to diagnose malignant melanoma of unknown primary origin during his lifetime; however, a whole-body autopsy confirmed the diagnosis based on the above criteria. The patient exhibited many skin lesions, including ulcers and sites of erythema, in which no malignant cells were detected on either a biopsy or postmortem examination, and had no history of excision of the lesions. Although it is possible that melanoma cells in the skin lesions disappeared spontaneously, the postmortem examination showed no findings of the primary origin of malignant melanoma.

Liver dysfunction resulting from metastatic malignant melanoma is usually not severe, causing only moderate elevation of liver enzymes. A few cases of acute liver failure secondary to malignant melanoma have been reported (5, 8-11). Each patient presented with rapid progres-
sion of liver dysfunction, subsequently leading to death within days. A significant rise in LDH was also a characteristic in these cases, and this finding has been previously reported to be an ominous sign of acute liver failure (5, 10). Te et al. (10) reported a case in which the patient’s levels of aminotransferases and LDH increased to >100 times the normal values. Although the levels of aminotransferases and LDH in our patient were not as high as those observed in previously reported cases, they were similarly elevated.

The histological findings of hepatic failure due to metastatic malignant melanoma include the following. On gross examinations, macroscopic nodules may be visible on the liver surface. Histologically, the hepatic sinusoids are diffusely infiltrated with tumor cells, and the hepatocyte plates are extensively replaced with tumor cells. Widespread areas of hepatocellular necrosis are also noted (10). Two patterns of tumor infiltration were observed in our patient: areas of infiltration grouped together in nodules and areas of diffuse infiltration in the liver parenchyma and sinusoids. A pattern of diffuse infiltration is usually associated with hepatic failure.

Generally, treatment options for metastatic malignant melanoma in the liver include hepatic resection, hepatic intra-arterial chemotherapy, chemoembolization and systemic chemotherapy (12, 13). Hepatic resection offers the possibility of long-term survival in patients with liver-limited metastasis (14). In patients with unresectable melanoma, empirical systemic chemotherapy is the best treatment option, if their performance status is adequate. In the present case, our patient had multiple unresectable liver metastases and was very elderly with a poor performance status. Therefore, we and his family selected palliative therapy.

In conclusion, we herein reported an unusual case of acute liver failure associated with diffuse infiltration into the liver with malignant melanoma of unknown primary origin. This case demonstrates the difficulty in making the diagnosis of diffuse hepatic infiltration by melanoma of unknown primary origin.

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

References


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