



Liver Metastatic Melanoma: a Unique Case with Normal Alkaline Phosphatase and Melanuria

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Introduction

Over the last decade, the incidence of melanoma has rapidly increased in the USA [1]. Liver involvement occurs frequently in metastatic melanoma, in approximately 10–20% of cases [2]. However, fulminant liver failure from metastatic malignant melanoma is rare, as only 11 cases are reported in the literature [3–13]. In the cases which liver function tests were reported, all patients had elevated alkaline phosphatase (ALP). Furthermore, none of previous cases reported melanuria. We report a unique case of fulminant liver failure secondary to metastatic melanoma with normal ALP level and melanuria.

Case Presentation

A 41-year-old male presented to the internal medicine service for evaluation of malaise for 2 weeks, associated with 1 week of subjective fever and dark urine. His past medical history was significant for primary hypogonadism, for which he received weekly testosterone injections. Family history was positive for an unknown leukemia and bipolar disease in his father. Social history was negative for any smoking, positive for occasional alcohol use (unquantified), and positive for marijuana and cocaine use more than 20 years ago.

On admission, physical exam was significant for mild tachycardia, right upper quadrant (RUQ) abdominal tenderness, hepatomegaly, and black urine. Patient's initial laboratories were notable for an aspartate aminotransferase (AST) of 897 U/L and alanine aminotransferase (ALT) of 831 U/L, with

a normal alkaline phosphatase (ALP) of 108 U/L. Urinalysis was negative for bilirubin. An extensive work-up for infectious, toxin, obstructive, ischemic, autoimmune, and hereditary causes was all negative. RUQ ultrasound showed an enlarged liver at 19.2 cm, with reduced echogenicity and prominent biliary ducts in a starry sky appearance, which was suggestive of acute hepatitis (Fig. 1a) [14, 15]. Portal vein flow was normal and common bile duct size was 8 mm. Magnetic resonance cholangiopancreatography was unrevealing, without gallstones or choledocholithiasis. The liver was enlarged and edematous, consistent with acute hepatitis; an indeterminate hypodense lesion was found in segment 2, measured 1.1 cm (Fig. 1b). Patient was treated with broad spectrum antibiotics, antivirals, and intravenous steroids; however, he decompensated 3 days after admission and was transferred to the Medical Intensive Care Unit. A liver biopsy was unable to be performed due to his hemodynamic instability. Despite an aggressive resuscitation effort, he developed fulminant liver failure and passed away on hospital day seven, without a diagnosis. On autopsy, the liver had black appearance from extensive infiltration by confluent black nodules. Histology studies revealed more than 80% of liver parenchyma was replaced by metastatic melanoma with HMB-45 positive tumor cells (Fig. 2). The spleen was the second most heavily involved organ by metastatic melanoma. Showers of tiny metastases were seen grossly in the omentum, mesentery, epicardial fat, myocardium, adrenal glands, lungs, and vertebral bone marrow. The primary lesion, a compound nevus containing invasive malignant melanoma, was found behind patient's left ear, hidden by hair (Fig. 3). The diagnosis was established postmortem as fulminant liver failure secondary to metastatic malignant melanoma.

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Discussion

Liver metastasis commonly occurs in melanoma; however, fulminant liver failure secondary to metastatic malignant

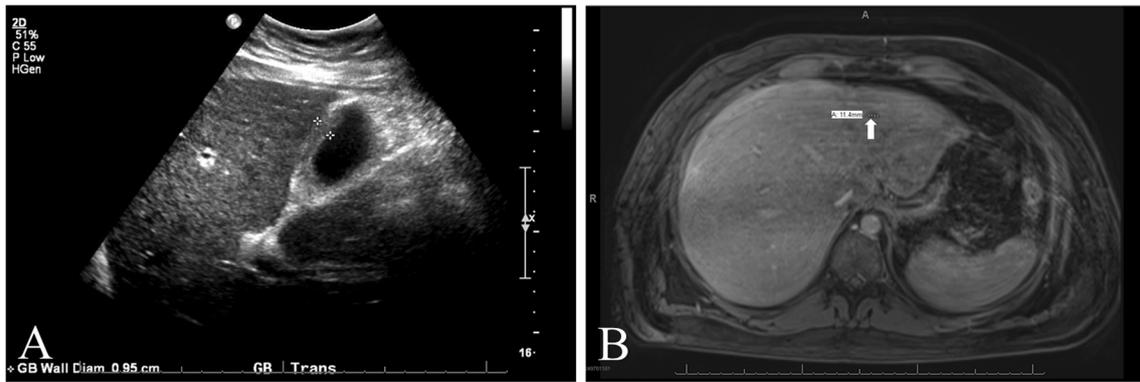


Fig. 1 Ultrasound (US) and magnetic resonance cholangiopancreatography (MRCP) of liver. **a** US of the liver showed reduced echogenicity with increased prominence of the biliary ductal system, created a

starry sky appearance. **b** MRCP of the liver showed enlarged and edematous liver, an indeterminate hypodense area measured 1.1 cm was found in segment 2 (arrow)

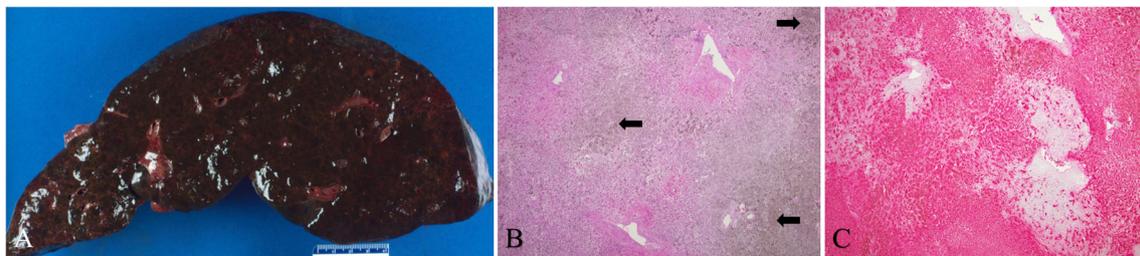


Fig. 2 Liver histology of metastatic melanoma. **a** Gross picture of the liver, appears to be black due to diffuse replacement of liver parenchyma by metastatic melanoma. **b** H&E stain of liver tissue, with infiltration by

pigmented melanoma cells (arrows). **c** HMB-45 melanoma marker of liver tissue (red stained areas represent melanoma involvement)

melanoma is rare [3–13]. In previous reported cases, common presentation included non-specific symptoms such as fatigue, weight loss, and abdominal pain for several weeks. Physical exam revealed various degree of jaundice, tender hepatomegaly, and altered mental status. Typically, these patients present with elevated liver enzymes in an infiltrative pattern [16]. In this pattern, ALP level is elevated due to intra-and/or extrahepatic obstruction. Previous case reports of fulminant liver failure from melanoma metastasis with ALP level ranged from

134 to 1080 U/L on presentation (normal 34–122 U/L) [3–13]. However, our patient ALP level remained normal up until the last day (Table 1). At autopsy, there was no extrahepatic obstruction present, but histologic evaluation revealed intrahepatic obstruction with extensive replacement of liver parenchyma, including biliary structures (Fig. 4). Most of the biliary epithelial cells which secrete ALP had been replaced, resulting in a normal ALP despite an obstructive picture. This case demonstrates that a normal ALP should not

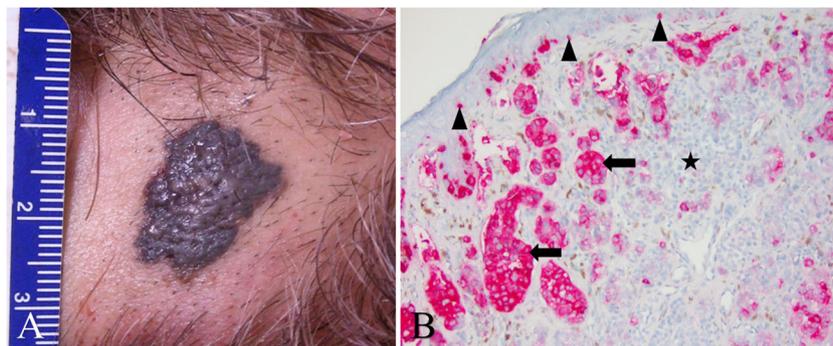


Fig. 3 Primary lesion, compound nevus containing invasive malignant melanoma. **a** Gross appearance. **b** HMB-45 stain of primary lesion, showing nests of malignant melanoma cells (staining red, large arrows)

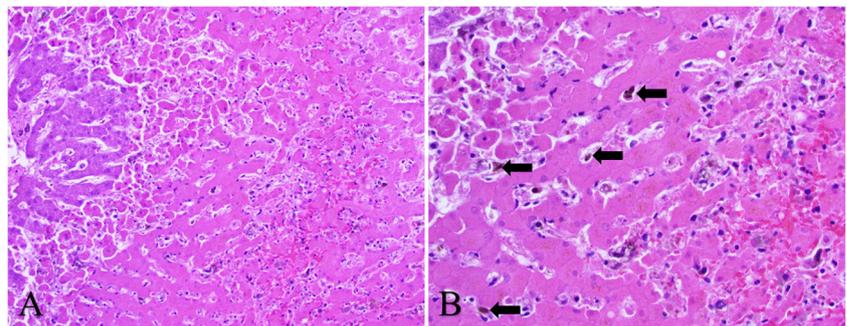
adjacent to benign nevus cells (star, non-staining). Note that normal junctional melanocytes in the basal epidermis are also immunopositive with this marker (arrowheads)

Table 1 Previous reported cases with elevated alkaline phosphatase (ALP), this case ALP level was normal up until the last day [3–13]

ALP level (normal 34–122 U/L)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Bouloux et al. [3]	166	182	288	448	418	455	–
Fusasaki et al. [4]	845	–	–	–	–	–	–
Kaplan et al. [5]	–	–	–	–	–	–	–
Mashayekhi et al. [6]	605	–	–	–	–	–	–
Montero et al. [7]	503	–	–	–	–	–	–
Rubio et al. [8]	287	–	–	–	–	–	–
Schlevogt et al. [9]	–	–	–	–	–	–	–
Shan et al. [10]	134	–	–	–	–	–	–
Tanaka K et al. [11]	1743	–	–	–	–	–	–
Tanaka M et al. [12]	204	–	–	–	–	–	–
Te et al. [13]	206	–	180	–	315	–	421
This case	108	94	106	104	102	ND	152

– not reported, *ND* not drawn

Fig. 4 Liver histology. **a** H&E stain showed extensive areas of coagulative necrosis of liver parenchyma. **b** Circulating pigmented melanoma cells are seen in sinusoids (arrows)

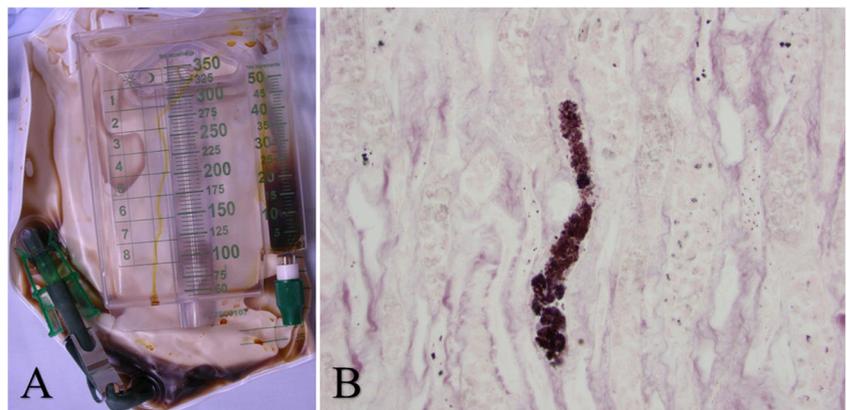


lower our suspicion for an infiltrative process, including malignancy.

Furthermore, a unique and important clue for our patient’s diagnosis presented in the form of black urine (Fig. 5a). His urinalysis showed proteinuria with no myoglobin or bilirubin. Urine microscopy showed few red blood cells with granular casts. Renal histology study

demonstrated melanin inside the renal tubules (Fig. 5b). This illustrates the cause for our patient’s black urine was melanuria. Melanuria is not uncommon in metastatic melanoma and occurs in 15% of the cases [17]. In the appropriate setting, metastatic melanoma should be considered as part of the differential diagnosis in patients with black urine.

Fig. 5 . Patient’s urine. **a** Gross urine appearance with black color. **b** Fontana-Masson melanin stain of renal tubule demonstrated melanin pigment in tubular lumens



Conclusion

This is the first case of fulminant liver failure secondary to metastatic melanoma with normal ALP and melanuria. These two unique findings were correlated by histology images. This case demonstrates that a normal ALP level should not lower our suspicion for an infiltrative process; and in the appropriate setting, metastatic melanoma should be considered in the differential diagnosis of black urine.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from patient's medical power of attorney.

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