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CASE REPORT

Asymptomatic malignant melanoma of the gallbladder with multiple brain metastases diagnosed with endoscopic ultrasound-guided fine-needle aspiration cytology

Koji Tamura[1,3] · Yoshiro Umemura[2] · Susumu Hijioka[4] · Kenjiro Date[1] · Naoki Maehara[1]

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Abstract
Malignant melanoma of the gallbladder (MMG) is extremely rare and its early stage diagnosis is difficult. Most reports of MMG describe metastatic tumors. We herein report a rare case of presumed primary MMG diagnosed by endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) cytology without surgical resection. A 72-year-old Japanese male was diagnosed with multiple brain metastases. Fluorodeoxyglucose (FDG) positron emission tomography showed an abnormal uptake of FDG at the gallbladder; enhanced CT and MRI also showed an enhanced gallbladder lesion, which indicated a malignancy. We performed endoscopic naso-gallbladder drainage. However, cytological examination of the drained bile showed no evidence of malignancy. Finally, EUS-FNA was performed to confirm the histological diagnosis; cytopathological assessment, including immunohistochemical analysis, showed a cluster of small to large-sized cells with nuclear pleomorphism and melanin pigment, which was compatible with malignant melanoma. The patient subsequently underwent chemotherapy; however, he died 2 months after diagnosis. In patients with gallbladder tumors, MMG should be suspected even in patients with no history of malignant melanoma or any cutaneous lesions. EUS-FNA is safe and useful to confirm histological diagnoses and to determine optimal treatment strategies.

Keywords Malignant melanoma · Gallbladder · EUS · FNA · Brain metastasis

Abbreviations
EUS Endoscopic ultrasound
FNA Fine-needle aspiration

Introduction

Malignant melanoma of gallbladder (MMG) is uncommon, and as it does not have any specific symptoms nor imaging features, it may be incorrectly diagnosed and/or treated [1, 2]. Because some patients with MMG have no medical histories of malignant melanoma nor cutaneous lesions, they are often diagnosed with conventional gallbladder cancer unless they undergo surgical resection. Malignant melanoma is very aggressive and a gallbladder lesion is usually one of multiple widespread metastases; the efficacy of resection for asymptomatic patients is, therefore, controversial [3–5].

Endoscopic ultrasonography (EUS) has been suggested to be superior to transabdominal US for diagnosing gallbladder tumors [6]. Moreover, EUS-guided fine-needle aspiration (EUS-FNA) is recognized as a sensitive and a safe diagnostic modality for tumors of the gastrointestinal tract, biliary tract and gallbladder [7].

We herein report a histologically confirmed presumed primary MMG diagnosed by EUS-FNA without surgical resection and discuss the role of EUS-FNA in determining appropriate therapeutic strategies.

✉ Koji Tamura
k-tam@surg1.med.kyushu-u.ac.jp

1 Department of Surgery, Fujimoto General Hospital, 17-1, Hayasuzu, Miyakonojo, Miyazaki 885-0055, Japan

2 Department of Radiology, Fujimoto General Hospital, Miyakonojo 885-0055, Japan

3 Department of Surgery, Hamanomachi Hospital, Fukuoka 810-8539, Japan

4 Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo 104-0045, Japan

Case report

A 72-year-old Japanese man was admitted to our hospital for detailed examination of a right-side visual field defect. He had no medical history, or family history, of malignancy. Physical examination showed no abnormality, including any skin lesion, except for the visual problem. Laboratory examination revealed elevated serum level of prostate-specific antigen (114.67 ng/ml; normal limit 4.0 ng/ml), while serum levels of carcinoembryonic antigen and carbohydrate antigen 19-9 were within normal limits. An enhanced head MRI showed multiple enhanced lesions that were consistent with multiple metastatic tumors (Fig. 1a). Gamma knife radiosurgery was performed for the multiple brain metastases and the patient's vision improved. Systemic fluorodeoxyglucose (FDG) positron emission tomography screening showed an abnormal uptake of FDG at the gallbladder, prostate, sacrum and coccyx, with maximum standardized uptake values (SUVmax) of 7.80, 5.36, 7.83 and 7.83, respectively (Fig. 1b). Abdominal contrast-enhanced CT showed an enhanced elevated lesion and wall thickness at the body and neck of the gallbladder (Fig. 1c, d) and enlarged prostate. The prostate biopsy specimen was diagnosed as a moderately differentiated adenocarcinoma.

Endoscopic retrograde cholangiography (ERC) demonstrated a defective lesion in the gallbladder and of a part of common bile duct. There was no evidence of a pancreatobiliary maljunction. We performed endoscopic nasogallbladder drainage (ENGBD), using a guidewire inserted through the cystic duct, after which a 5-Fr drainage catheter was placed into the gallbladder and the drained bile was submitted to cytology total 3 times within 48 h. The result of cytology showed no evidence of malignancy.

While the patient was systemically evaluated over the next few weeks, he started to complain of nausea, headache and mild hearing loss. A head MRI showed multiple brain tumors at the other sites. Because an upper gastrointestinal endoscopy and a colonoscopy showed no evidence of malignancy, and brain metastases from prostate cancer and conventional gallbladder cancer are rare, one of the brain tumors was resected to obtain the histological diagnosis, using gamma knife radiosurgery. In addition, EUS-FNA was performed to confirm the histological diagnosis of the gallbladder tumor. EUS showed an irregular mass rising from the gallbladder wall and extending into the gallbladder lumen with increased power doppler flow (Fig. 2a, b). Sonazoid-enhanced EUS also showed hypervascularity (Fig. 2c). We saw no evidence of extra-gallbladder invasion or lymph node metastasis. Transduodenal EUS-FNA for the gallbladder tumor, using a 25-gauge cobalt-chromium construction, standard type FNA needle (Expect™; Boston Scientific), was subsequently performed with no complications (Fig. 2d). The cytopathologic assessment included immunohistochemical analyses for S-100 protein (S-100, Leica

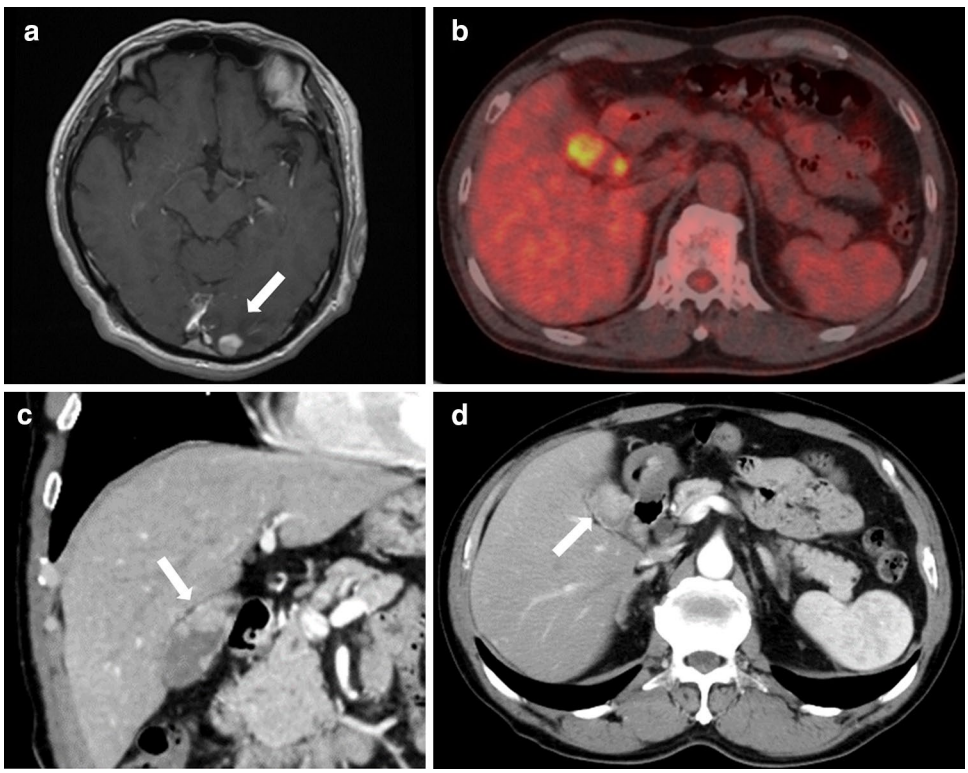

Fig. 1 **a** Head MRI shows multiple enhanced lesions. Arrow: a metastatic tumor in the left occipital lobe (T1W1). **b** PET-CT reveals an abnormal uptake of FDG at the gallbladder (SUV max: 7.83). **c, d** Contrast-enhanced CT shows an early enhanced mass in the gallbladder (arrow). We saw no findings of extra-gallbladder invasion

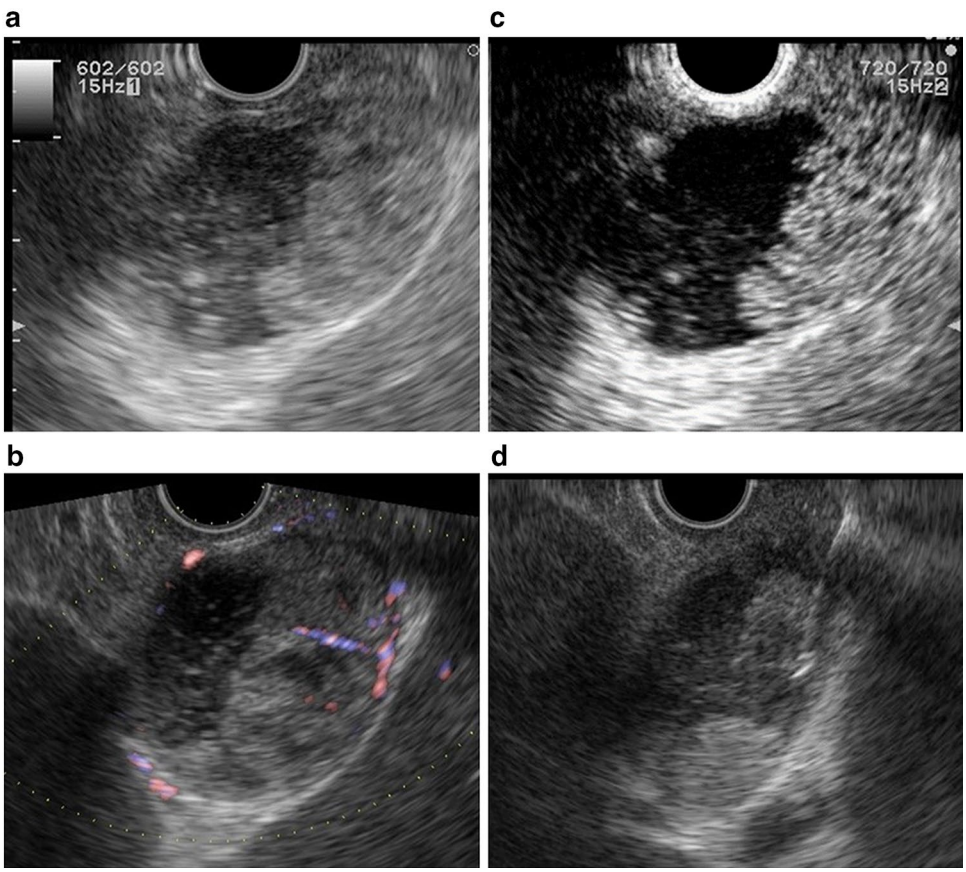

Fig. 2 Endoscopic ultrasonography (EUS) findings. **a** Well-defined isoechoic heterogeneous mass arising from the gallbladder wall. **b** Power Doppler EUS reveals increased flow inside the tumor. **c** Sonazoid-enhanced EUS also showed hypervascularity of the gallbladder tumor. **d** Transduodenal EUS-FNA of the gallbladder mass, using a 25-gauge FNA needle

Biosystems, PA0900), for HMB-45 (Melanoma Marker, HMB45, Leica Biosystems, PA0027) and for Melan-A (Melan-A/MART-1, Novus Biologicals, M2-7C10), using returned cell-block method [8] and showed a cluster of small- to large-sized cells with nuclear pleomorphism and melanin pigment, and positive staining for S100 protein, HMB-45 and Melan-A, which are compatible with malignant melanoma (Fig. 3a–d). Pathological findings for the brain tumor also indicated malignant melanoma, with positive stains for S100 protein and HMB-45, which are consistent with metastatic melanoma.

The patient was finally diagnosed with MMG with multiple brain metastases. He subsequently underwent chemotherapy using nivolumab; however, he died 2 months after the diagnosis of malignant melanoma.

Discussion

Malignant melanoma of gallbladder is extremely rare. Most published reports and reviews of MMG describe metastatic tumors in patients with histories of cutaneous malignant melanoma or spontaneous cutaneous lesions [9, 10]. Although diagnosing gallbladder cancer is difficult, melanoma is the most common malignancy that can metastasize to the gallbladder [11, 12]. To our knowledge, this is the first report of a case of presumed primary MMG diagnosed using EUS-FNA cytology.

Until the EUS-FNA was performed, we had not been able to detect the origin of the multiple brain metastases. Although laparoscopic cholecystectomy was another option to determine the histological diagnosis, this patient was asymptomatic and had already been diagnosed with multiple brain metastases. Finally, EUS-FNA cytology showed malignant melanoma cells in the gallbladder, which led us to the correct diagnosis and best treatment strategy without unnecessary surgery.

Malignant melanoma is a very aggressive disease. The median survival term of patients with metastatic melanoma is reportedly 6–9 months [13]. Retrospectively, it took time to diagnose, using brain surgery, ENGBD and EUS-FNA. Laparoscopic cholecystectomy might be the fastest option for earlier diagnosis and treatment. However, the patient was asymptomatic and did not want to have an operation because cholecystectomy alone would not be a curative operation. Katz et al. reviewed 13 patients treated for MMG and indicated that resection remains the optimal treatment for patients with isolated metastases, even in cases in which simple cholecystectomy is less invasive [5]. Because cholecystectomy remains controversial, even for patients with

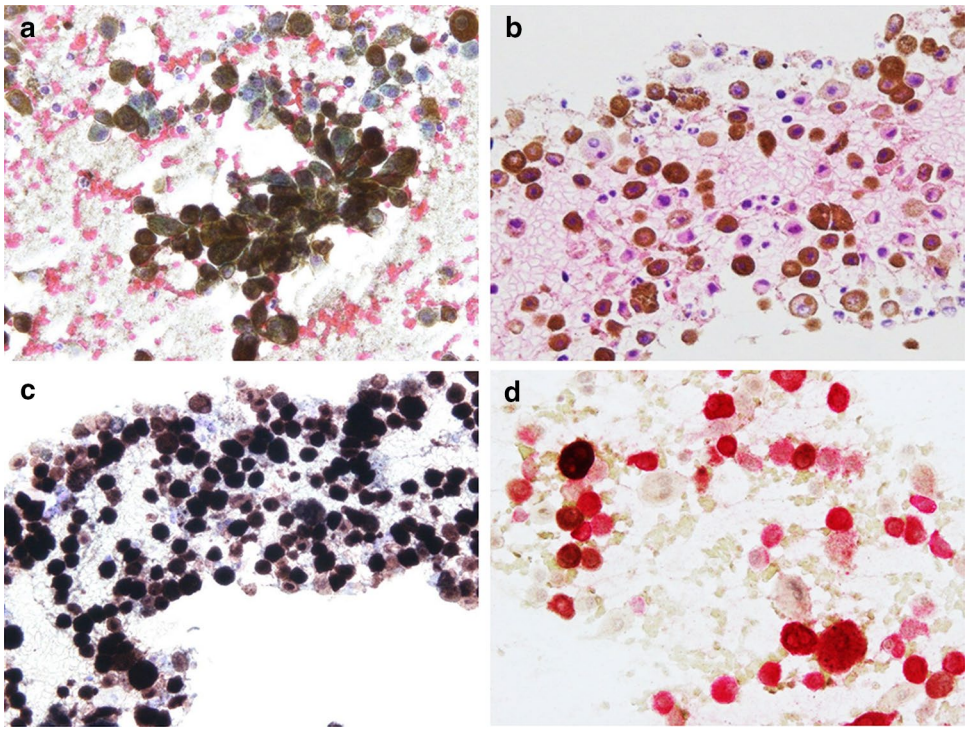

Fig. 3 Cytopathological findings of the EUS-FNA specimen including immunohistochemical analysis. **a, b** Cytological assessment shows a cluster of small- to large-sized cells with nuclear pleomorphism and melanin pigment (**a** Papanicolaou stain; **b** hematoxylin and eosin stain). **c** Immunohistochemical findings. Tumor cells are positive for S-100 protein (DAB-peroxidase substrate). **d** Tumor cells are positive for HMB45 (alkaline phosphatase substrate)

isolated MMG, surgeons should carefully consider the surgical indication.

The existence of MMG as a primary tumor is unclear, despite several published studies [3, 14–16]; and whether this present case is primary MMG is not certain, because of the possibility of undiagnosed or spontaneously regressed cutaneous melanoma lesion. In theory, primary melanoma can occur in the gallbladder, if nonneoplastic melanoblasts migrate from the neural crest to endodermal derivatives during embryologic development [15, 17]. Heath et al. reported that "junctional activity" is necessary for reliable diagnosis of primary MMG [18]. If so, then definite primary MMG cannot be diagnosed from cytology alone. Further investigation is needed to determine if primary MMG really exists.

EUS-FNA is a highly sensitive and specific diagnostic modality for the biliary tract and gallbladder tumors, with sensitivity and specificity close to 100% and 87%, respectively [7, 19, 20]. Only two cases of MMG have been reportedly diagnosed by EUS-FNA, both in patients with medical histories of cutaneous melanoma whose gallbladder melanomas were diagnosed as metastases [21, 22]. This present case is the first report of possible primary MMG histologically confirmed by EUS-FNA in a patient without a history of malignant melanoma at other organs.

Matsubayashi et al. reported a case diagnosed cytologically, in which ENGBD fluid played an important role [21]; however, we did not see any malignant cells in this patient's ENGBD fluid. Malignant melanoma tumors are often located at the intramucosal layer and we could not effectively obtain enough cells derived from the tumor, although we repeated the ENGBD cytology. However, EUS-FNA cytology usually can provide enough cells, which also makes possible to construct cell blocks and to investigate further immunohistochemical analysis, as we did.

We previously reported on the diagnostic yield of ERC and of EUS-FNA sampling in gallbladder carcinomas; post-procedure complications were detected in 6.7% of the ERC-group (4/59; all were mild post-ERC pancreatitis), and none in the EUS-FNA group, including tumor seeding [20]. Severe post-ERC pancreatitis can be a fatal complication. However, the risk of tumor seeding/dissemination should be considered during EUS-FNA. The important point is that we should puncture the wall thickening site without passing through the cavity of the gallbladder to avoid tumor dissemination.

In this case, the patient died 6 months after the first medical examination. His outcome might have been different, if EUS-FNA was performed earlier. When an EUN-FNA route is available to safely aspirate tumor cells in the gallbladder, it may be the best procedure to confirm the histological diagnosis.

In conclusion, this is the first report of a primary MMG diagnosed using EUS-FNA. Although MMG is uncommon, it should be suspected even in patients with no history of malignant melanoma or any cutaneous lesions. EUS-FNA is safe and useful for histological diagnosis of such intraluminal gallbladder tumors.

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Author contributions KT contributed to the management of the patient, acquisition of the data, and drafting of the manuscript. NM assisted during the surgery and supervised the management of the patient. SH and YU contributed to the endoscopic and radiological diagnosis. KD contributed to the acquisition of the data. All authors have read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Human/animal rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from the patient for being included in the study.

References

1. Andreano A, Laeseke P, Lava M, et al. Asymptomatic metastatic melanoma of the gallbladder diagnosed with contrast-enhanced ultrasonography. J Ultrasound Med. 2010;29:1133–7.
2. Samplaski MK, Rosato EL, Witkiewicz AK, et al. Malignant melanoma of the gallbladder: a report of two cases and review of the literature. J Gastrointest Surg. 2008;12:1123–6.
3. Wang JK, Su F, Ma WJ, et al. Primary malignant melanoma of the gallbladder with multiple metastases: a case report. Medicine (Baltimore). 2017;96:e8793.
4. Marone U, Caraco C, Losito S, et al. Laparoscopic cholecystectomy for melanoma metastatic to the gallbladder: is it an adequate surgical procedure? Report of a case and review of the literature. World J Surg Oncol. 2007;5:141.
5. Katz SC, Bowne WB, Wolchok JD, et al. Surgical management of melanoma of the gallbladder: a report of 13 cases and review of the literature. Am J Surg. 2007;193:493–7.
6. Kamata K, Takenaka M, Kitano M, et al. Contrast-enhanced harmonic endoscopic ultrasonography for differential diagnosis of localized gallbladder lesions. Dig Endosc. 2018;30:98–106.
7. Varadarajulu S, Eloubeidi MA. Endoscopic ultrasound-guided fine-needle aspiration in the evaluation of gallbladder masses. Endoscopy. 2005;37:751–4.
8. Azami S, Aoki Y, Ogura K, et al. Application of returned cell block method (cell block from a papanicolaou staining smear on a glass slide) for the evaluation of fine needle aspiration cytology of tumors of the breast. Diagn Cytopathol. 2016;44:505–11.
9. Patel D, Sohrawardy S, Sedhai YR, et al. Metastatic cutaneous melanoma of the gallbladder. Case Rep Gastrointest Med. 2017;2017:8532379.
10. Vernadakis S, Rallis G, Danias N, et al. Metastatic melanoma of the gallbladder: an unusual clinical presentation of acute cholecystitis. World J Gastroenterol. 2009;15:3434.
11. Furumoto K, Miyauchi Y, Ito D, et al. Solitary metastatic gallbladder malignant melanoma originated from the nasal cavity: a case report. Int J Surg Case Rep. 2013;4:965–8.
12. Dong XD, DeMatos P, Prieto VG, et al. Melanoma of the gallbladder: a review of cases seen at Duke University Medical Center. Cancer. 1999;85:32–39.
13. Gogas HJ, Kirkwood JM, Sondak VK. Chemotherapy for metastatic melanoma: time for a change? Cancer. 2007;109:455–64.
14. Haskaraca MF, Ozsoy M, Ozsan I, et al. Primary malignant melanoma of the gallbladder: a case report and review of the literature. Case Rep Surg. 2012;2012:693547.
15. Safioleas M, Agapitos E, Kontzoglou K, et al. Primary melanoma of the gallbladder: does it exist? Report of a case and review of the literature. World J Gastroenterol. 2006;12:4259–61.
16. Virgilio E, Scorsi A, Amodio PM, et al. Primary malignant melanoma of the gallbladder: an outstandingly rare tumor. Clin Exp Med. 2016;16:479–80.
17. Naguib SE, Aterman K. Presumed primary malignant melanoma of the gallbladder. Report of a case and a review of literature. Am J Dermatopathol 1984;6(Suppl):231–43
18. Heath DI, Womack C. Primary malignant melanoma of the gall bladder. J Clin Pathol. 1988;41:1073–7.
19. Wu LM, Jiang XX, Gu HY, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy in the evaluation of bile duct strictures and gallbladder masses: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2011;23:113–20.
20. Hijioka S, Hara K, Mizuno N, et al. Diagnostic yield of endoscopic retrograde cholangiography and of EUS-guided fine needle aspiration sampling in gallbladder carcinomas. J Hepatobiliary Pancreat Sci. 2012;19:650–5.
21. Matsubayashi H, Kiyohara Y, Sasaki K, et al. Metastatic malignant melanoma of the gallbladder diagnosed by cytology of endoscopic naso-gallbladder drainage fluid. J Dig Dis. 2012;13:190–4.
22. Antonini F, Acito L, Sisti S, et al. Metastatic melanoma of the gallbladder diagnosed by EUS-guided FNA. Gastrointest Endosc. 2016;84:1072–3.