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Case Report

A Case of Gallbladder Metastasis of Malignant Melanoma

Hitoshi Minagi*, Hideki Aoki, Susumu Doita, Eiki Miyake, Toshihiro Ogawa, Fumitaka Taniguchi, Megumi Watanabe, Takashi Arata, Koh Katsuda, and Kohji Tanakaya

Department of Surgery, National Hospital Organization, Iwakuni Clinical Center, Iwakuni, Yamaguchi 740-8510, Japan

In the clinical course of malignant melanoma, which can metastasize to multiple organs, gallbladder metastases are rarely detected. A 69-year-old man who underwent resection of a primary malignant melanoma was subsequently treated with nivolumab for lung metastases and achieved complete response. Seven years after surgery, multiple nodules were found in the gallbladder, and he underwent laparoscopic cholecystectomy. The postoperative diagnosis was metastases of malignant melanoma. He has been recurrence-free 8 months after surgery. If radical resection is possible, such surgery should be performed for gallbladder metastases found in patients with other controlled lesions of malignant melanoma.

Key words: malignant melanoma, gallbladder metastasis, laparoscopic cholecystectomy

Malignant melanoma is a tumor with the ability to metastasize to all organs, but gallbladder metastasis is very rarely detected during the clinical course. We report a case of gallbladder metastasis 7 years after resection of a primary cutaneous malignant melanoma.

Case Report

A 69-year-old man with malignant melanoma of the left gluteal region underwent resection of the primary tumor and dissection of the left inguinal lymph nodes 7 years ago. The pathological stage was T3bN2aM0, stage IIIC (AJCC 8th edition). He was treated with 6 courses of D-feron after surgery and followed with regular visits. Five years after surgery, lung metastases were detected and treatment with nivolumab was initiated. A total of 46 courses of nivolumab were administered, and a complete response of pulmonary metastases was achieved. However, two years later (7 years after resection of the primary tumor), a computed tomography (CT) scan showed multiple nodules in the gallbladder, and endoscopic ultrasonography (EUS) and bile cytology from the gallbladder suggested metastasis of malignant melanoma. No other recurrent lesions, including skin lesions, were observed at this time.

Blood tests showed no elevation of hepatobiliary enzymes or tumor markers, and CT and magnetic resonance imaging (MRI) scans revealed multiple nodules with contrast effect up to 15 mm in size in the gallbladder (Fig. 1). EUS revealed multiple semi-pedunculated tumors in the gallbladder. The outermost layer of the gallbladder was preserved, and the lesions were judged to extend from the mucosa to the muscularis propria (Fig. 2). Biliary cytology showed mild cellular atypia with some brown granules and some intranuclear inclusion bodies, indicative of metastases of malignant melanoma.

Laparoscopic whole-layer cholecystectomy was performed as planned. Laparoscopic observation revealed no change in the serosal surface of the gallbladder.

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*Corresponding author. Phone: +81-86-235-7257; Fax: +81-86-221-8775
E-mail: super.hitoshi.kun.1005@gmail.com (H. Minagi)

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Intraoperative ultrasonography using a laparoscopic ultrasound probe revealed multiple semi-pedunculated tumors in the gallbladder, similar to the preoperative EUS findings. There was no hepatic extension, and the depth of the tumors was considered equivalent to that shown on preoperative imaging.

Multiple dark brown semi-pedunculated tumors were observed on the mucosal surface of the removed gallbladder (Fig. 3). The lesions were clusters of tumor cells with irregular nuclei and weakly acidic spores and were accompanied by brown pigmentation. The lesions were confined to the mucosa. The histopathological findings confirmed the diagnosis of malignant melanoma metastasis (immunohistochemistry positive for S-100 and HMB-45, Fig. 4).

The postoperative course was uneventful. Gene sequencing analysis of the metastasis revealed mutations in *BRAF V600E*, and the patient was started on a combination of a BRAF inhibitor and an MEK inhibitor. He has been recurrence-free for 8 months since surgery.

Discussion

Malignant melanoma is a tumor with a poor prognosis that can metastasize early to any organ. The most common sites of metastasis are lymph nodes, lungs, liver, and brain. However, metastasis to gastrointestinal organs is rare (4.4%), with small intestine (35.0%), colorectum (14.5%), and stomach (7.0%) being more common; gallbladder metastasis is extremely rare [1].

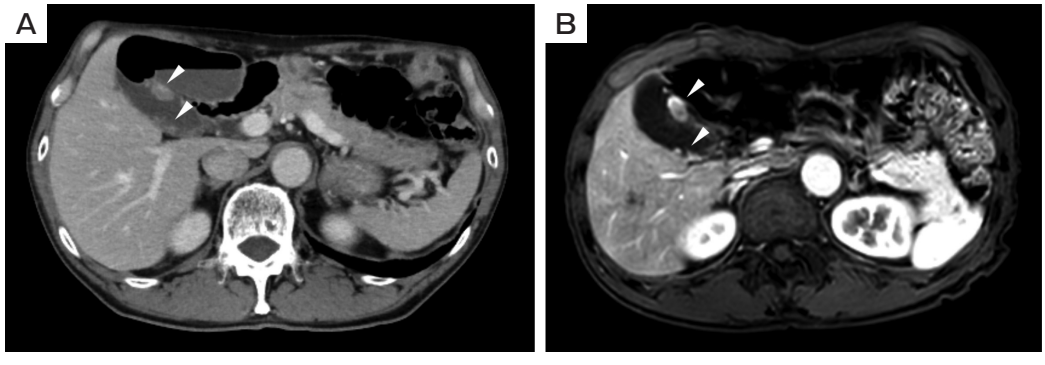

Fig. 1 **A**, Contrast-enhanced CT scan showed multiple nodules with contrast effects up to 15 mm in size in the gallbladder (white arrowheads); **B**, Contrast-enhanced MRI showed multiple nodules in the gallbladder similar to CT, with contrast effect and diffusion limitation (white arrowheads).

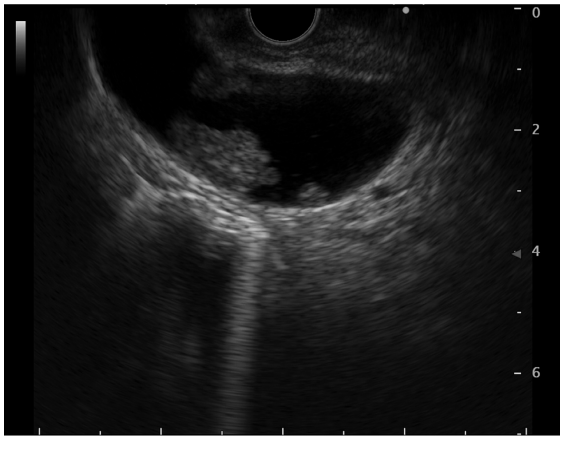

Fig. 2 Endoscopic ultrasonography revealed multiple semi-pedunculated tumors in gallbladder. The outermost layer was preserved, and the depth of the tumors was determined to be the mucosa to the muscular layer.

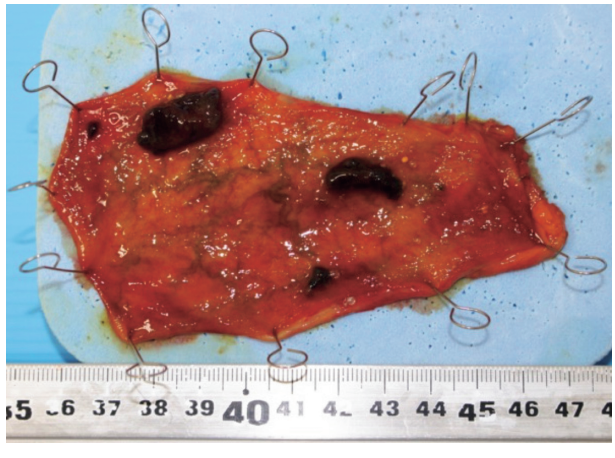

Fig. 3 Photograph of the excised specimen. Multiple dark brown elevated lesions were observed on the mucosal surface of the gallbladder.

A search of Japanese and English papers using the keywords "gallbladder", "malignant melanoma", and "metastasis" revealed 16 cases reported in Japan between 1970 and 2021. The 17 cases, including ours, are summarized in Table 1 [2-13].

The median age of patients was 68 (41-87) years, and the primary sites were the skin in 9 patients (52.9%), gastrointestinal tract in 4 patients (23.5%), and nasal

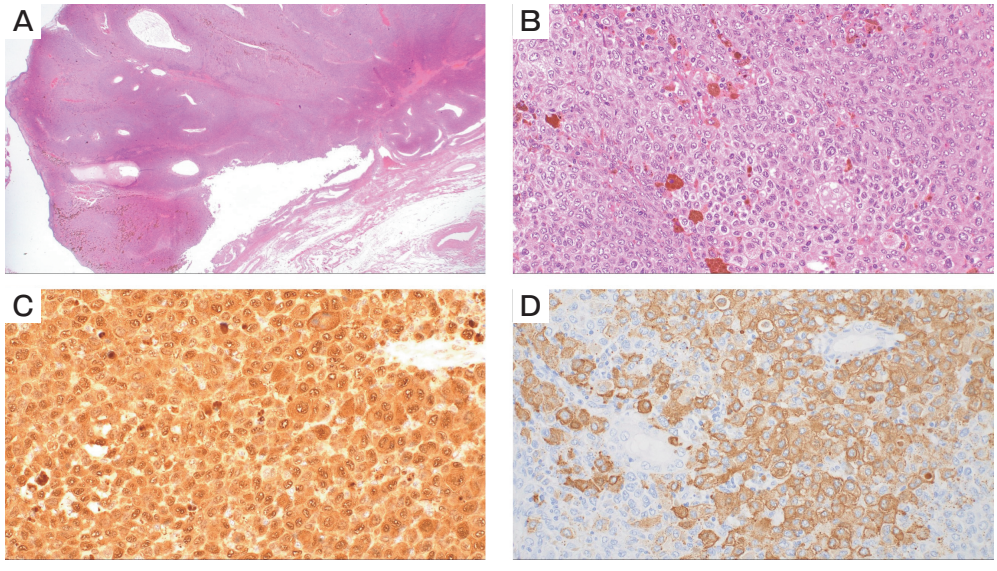

Fig. 4 **A**, Hematoxylin-eosin staining under weak magnification; **B**, The lesions were densely populated with tumor cells with irregular nuclei and weakly acidic spores, accompanied by brown pigmentation. The lesions were confined to the mucosa (HE staining, strong magnification); **C**, Immunostaining was positive for S-100; **D**, Immunostaining was positive for HMB-45.

Table 1 Reported cases of gallbladder metastasis of malignant melanoma in Japan

	Author	Year	Age (y.o.)	Sex	Primary lesion	Duration to metastasis	Metastasis to other organs	Treatment	Prognosis after cholecystectomy
1	Suzuki	1992	71	F	Anal canal	43 months	Lung	Surgery (Unknown)	NA
2	Kato	1993	66	F	Skin (Left lower leg)	60 months	Skin, LN, Bone, Adrenal grand	Surgery (Unknown)	NA
3	Sugihara[2]	2000	43	M	Skin (Back of head)	Synchronous	Brain	Surgery (Laparoscopy)	10 months (dead)
4	Kuze[3]	2000	68	M	Esophagus	Synchronous	LN	Surgery (Open)	5 months (dead)
5	Teruya[4]	2001	69	F	Rectum	24 months	LN	Surgery (Open)	12 months (dead)
6	Hasuo[5]	2002	48	F	Skin (Left abdomen)	204 months	None	Surgery (Laparoscopy)	5 months (alive)
7	Ishikawa[6]	2012	70	F	Skin (Right forearm)	46 months	LN	Surgery (Open)	10 months (dead)
8	Furumoto[7]	2013	77	F	Right nasal cavity	36 months	None	Surgery (Open, Resection of the liver bed, LN dissection)	13 months (alive)
9	Onozawa[8]	2014	58	F	Unknown	Synchronous	Lung, Liver, Bone, Stomach, Colon	Surgery (Laparoscopy)	8 months (dead)
10	Matsui[9]	2016	68	M	Skin (Neck)	Synchronous	None	Chemotherapy	–
11	Nakai	2017	43	F	Skin (Left heel)	12 months	Liver	Chemotherapy	–
12	Otsubo[10]	2019	41	M	Left nasal cavity	36 months	Colon mesentery	Surgery (Open)	7 months (alive)
13	Tsukada[11]	2020	87	M	Skin (Back)	29 months	LN, Brain	Surgery (Open, Resection of the liver bed, LN dissection)	14 months (alive)
14	Nakauchi[12]	2021	68	M	Rectum	Synchronous	None	Surgery (Unknown)	15 months (alive)
15	Takahashi	2021	60	M	Left nasal cavity	24 months	Intra-abdominal LN, Cerebrospinal fluid	Chemotherapy	–
16	Yamagishi[13]	2021	73	M	Skin (Back)	24 months	LN, Skin	Surgery (Open)	24 months (alive)
17	Our case	2022	69	M	Skin (Left Gluteal)	84 months	LN, Lung	Surgery (Laparoscopy)	8 months (alive)

LN = lymph node

cavity in 3 patients (17.6%). Five patients had Synchronous gallbladder metastases and 12 patients had metachronous metastases (median 36 months). Metastases to other organs than the gallbladder occurred at a high rate, and long-term survival was limited to patients whose disease was controlled by surgical resection or chemotherapy of the metastases other than the gallbladder lesions, or who had metastasis to the gallbladder alone.

The route of metastasis to the gallbladder has been discussed by other authors and is thought to be hematogenous [14]. All of the cases reported in Japan, including our case, presented with elevated lesions: this is considered the characteristic form of gallbladder metastasis of malignant melanoma. However, it is difficult to differentiate gallbladder polyps, primary gallbladder cancer, and other metastatic gallbladder tumors by morphology alone. Biliary cytology may provide a clue, as in our case. Diagnosing the depth of the lesion is important in determining the surgical approach, for which EUS is useful.

Regarding surgery, open cholecystectomy is often performed considering the risk of port site recurrence, but Vilar et al. reported the usefulness of laparoscopic surgery in terms of early postoperative recovery and introduction of chemotherapy [15].

According to the NCCN Clinical Practice Guidelines, surgery is indicated for a small number of distant metastases that can be completely resected [16]. In recent years, immune checkpoint inhibitors have been expected to improve the prognosis of malignant melanoma, and resection of gallbladder metastases may improve the prognosis when the disease is controlled in other foci, as in our case.

In conclusion, the possibility of gallbladder metastasis should be kept in mind when gallbladder tumors are recognized during the treatment process of malignant melanoma. In such cases, where other lesions are under control, surgical resection of gallbladder metastases can improve the prognosis.

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