Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4204-24
Intern Med 64: 1327-1333, 2025
http://internmed.jp

【 CASE REPORT 】

GLUT-1-negative Choroidal Malignant Melanoma with Liver Metastasis Recurrence 12 Years after Surgery without FDG Accumulation in a Recurrent Lesion on FDG-PET/CT

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Abstract:
Choroidal malignant melanoma is a rare malignant tumor that develops in adult eyeballs. It causes early lymph node and distant metastasis. Fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (CT) is widely used for screening malignant melanoma metastases. We encountered a 58-year-old man with choroidal malignant melanoma in whom liver metastasis recurred 12 years after surgery, without any observable FDG accumulation. Immunostaining revealed the absence of glucose transporter type 1 (GLUT-1) expression, crucial for intracellular FDG uptake. The lack of FDG accumulation in the lesion could be attributed to the diminished cellular FDG uptake due to the absence of GLUT-1 expression.

Key words: choroidal malignant melanoma, metastatic liver tumor, PET/CT

(Intern Med 64: 1327-1333, 2025)
(DOI: 10.2169/internalmedicine.4204-24)

Introduction

Choroidal malignant melanoma is a malignant tumor that develops in the eyeballs of adults and it tends to cause lymph node metastasis and hematogenous metastasis to the liver, lungs, and bones from a relatively early period, with liver metastasis being the most common (1). Fluorodeoxyglucose(FDG)-positron emission tomography/computed tomography (PET/CT) is widely used for the screening of metastatic lesions. We herein report the case of a patient with choroidal malignant melanoma who experienced liver metastasis recurrence 12 years after surgery with no detectable FDG accumulation in the liver metastatic lesion.

Case Report

A 58-year-old man had undergone right eye enucleation for primary choroidal malignant melanoma 12 years earlier and received five cycles of dacarbazine, nimustine hydrochloride, vincristine sulfate, and interferon-β treatment as postoperative adjuvant chemotherapy. Subsequently, he underwent annual abdominal ultrasonography screening and a hypoechoic nodule was observed in the left lobe of the liver. The patient was referred to our department for further evaluation. His medical history included cleft lip and left parotid gland adenomas. The patient had no family history of malignant tumors. He had no history of alcohol consumption or smoking. The abdominal examination was unremarkable, and no skin lesions were observed.

Blood tests revealed a mild elevation of liver enzymes. Lactate dehydrogenase(LD), 215 U/L; 5-S-cysteinyldopa(5-S-CD) 2.4 nmol/L and other tumor markers were within the normal range (Table). Contrast-enhanced CT showed a 3-cm low-density nodule in the medial segment of the liver. The contrast effect was indistinct in the arterial phase, and a

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Received: May 30, 2024; Accepted: August 20, 2024; Advance Publication by J-STAGE: October 4, 2024
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mild contrast effect was observed from the portal phase to the equilibrium phase (Fig. 1). Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid contrast-enhanced magnetic resonance imaging (MRI) revealed a nodule with high signal intensity on diffusion-weighted imaging and low signal intensity in the hepatocellular phase (Fig. 2). FDG-PET/CT showed that the nodule in the medial segment of the liver only showed FDG accumulation equivalent to that in the surrounding liver parenchyma(white arrow). No pathological accumulation of FDG indicative of primary or metastatic tumor was thus noted (Fig. 3). Abdominal ultrasonography revealed a hypoechoic nodule in B-mode. Contrast-enhanced imaging using perflubutane (Sonazoid®) revealed that the nodule had no contrast effect in the arterial phase, whereas a contrast effect equivalent to that of the surrounding liver parenchyma was observed in the portal phase. However, the contrast effect was relatively low in the post-vascular phase (Fig. 4).

Table. **Laboratory Data.**

WBC	5,060 /μL	BUN	14.2 mg/dL
RBC	446×10^4 /μL	Cr	0.82 mg/dL
Hb	14.1 g/dL	Na	142 mEq/L
Plt	21.9×10^4 /μL	K	4.6 mEq/L
		Cl	107 mEq/L
PT	115.7 %	CRP	0.10 mg/dL
TP	6.9 g/dL	HBsAg	(-)
Alb	4.4 g/dL	Anti-HCV	(-)
T-Bil	0.7 mg/dL		
AST	28 U/L	DCP	22 mAU/mL
ALT	60 U/L	AFP	3 ng/mL
LD	215 U/L	CEA	0.8 ng/mL
ALP	88 U/L	CA19-9	7.1 U/mL
γ-GT	46 U/L	5-S-CD	2.4 nmol/L

Clinical course

Based on imaging findings, liver metastasis of malignant melanoma or exacerbation of a foregut cyst was suspected. However, distinguishing between the two conditions proved to be challenging. A tumor biopsy was also performed. However, owing to concerns regarding the potential risk of tumor seeding and the solitary nature of the lesion, laparoscopic left lobectomy and cholecystectomy were performed as diagnostic therapeutic approaches. The patient recovered satisfactorily and was eventually discharged on postoperative day 8. In the resected specimen, a 30×25 mm well-defined blackish tumor was detected in the left lobe of the liver (Fig. 5). Histologically, tumor cells with melanin granules in the cytoplasm and oval-to spindle-shaped nuclei proliferated in a nest-like manner, thus indicating malignant melanoma.

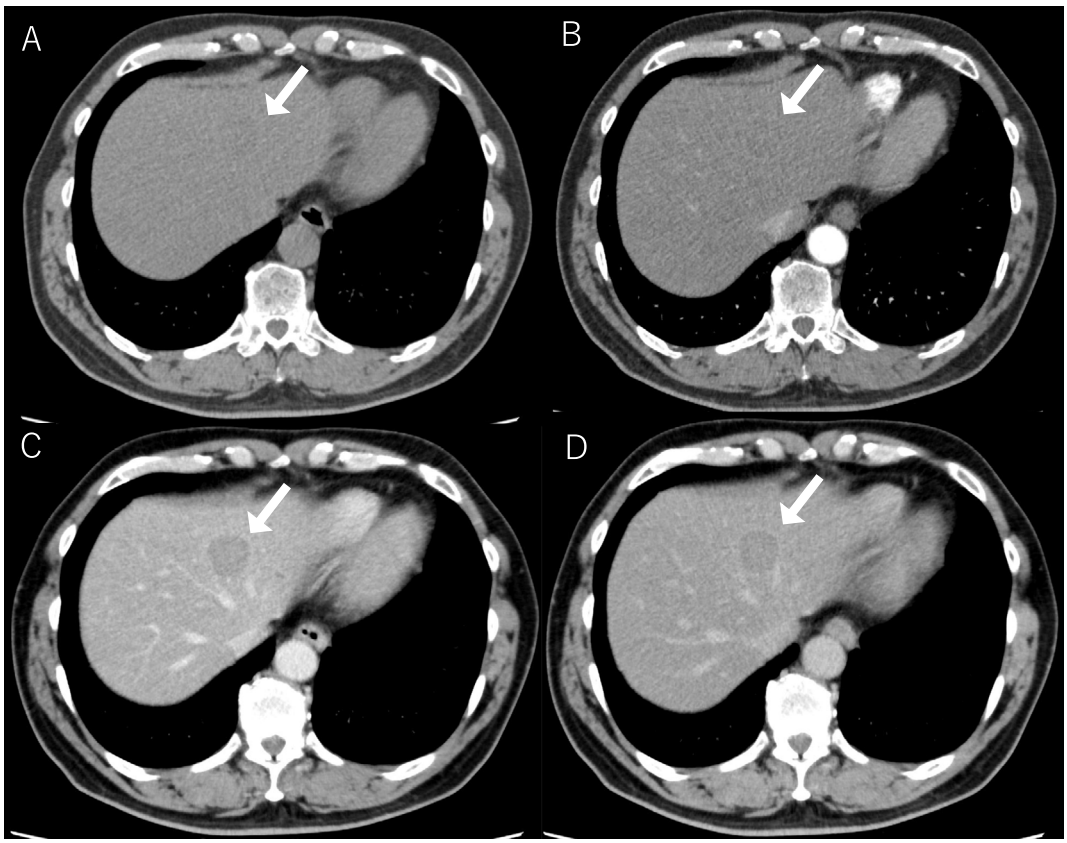

Figure 1. **Computed tomography. A 3-cm low-density nodule is located in the medial segment of the liver (white arrow). The contrast effect is indistinct in the arterial phase (B), while a very mild contrast effect is observed from the portal phase (C) to the equilibrium phase (D).**

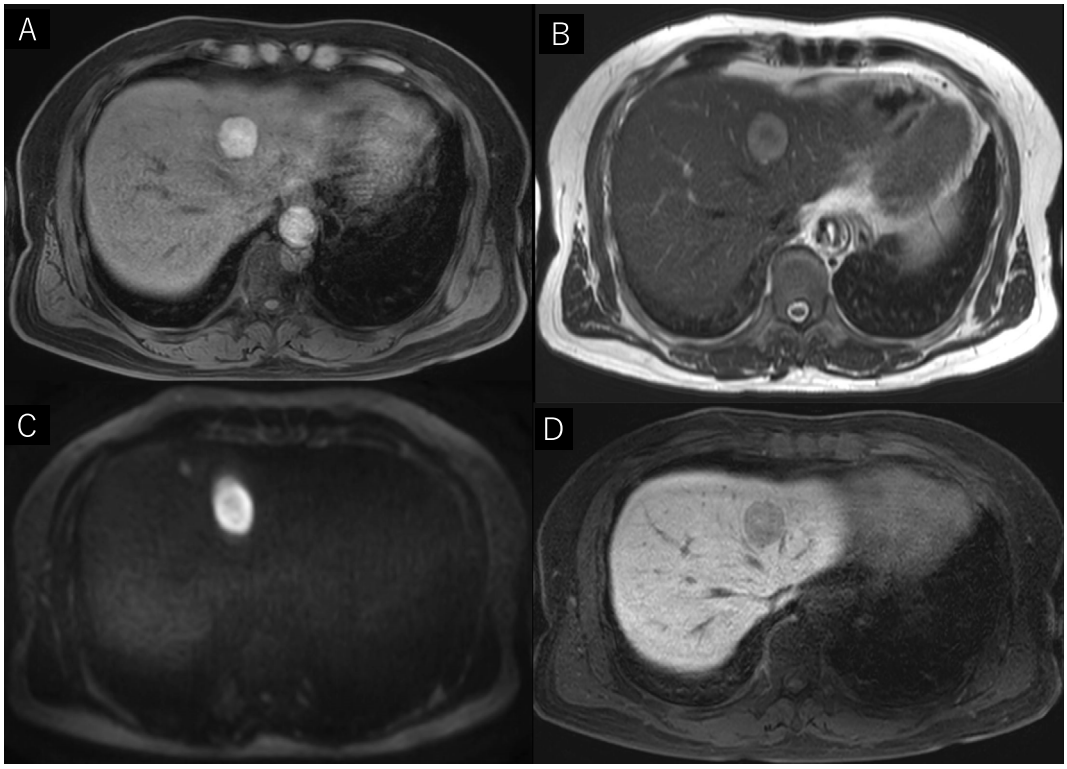

Figure 2. **Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid contrast-enhanced magnetic resonance imaging. The nodule exhibits high signal intensity on T1-weighted imaging (T1WI) (A), high signal intensity in the peripheral phase and low signal intensity in the interior phase on T2WI (B), high signal intensity on diffusion-weighted imaging (C), and low signal intensity in the hepatocellular phase.**

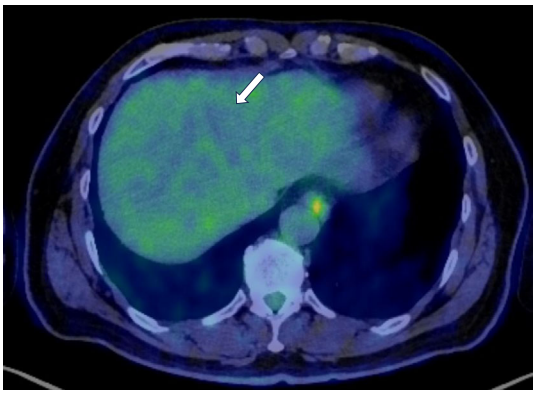

Figure 3. **Fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography. The nodule shows the absence of any FDG accumulation.**

The resection stump was pathologically negative for cancer, whereas programmed death-ligand 1 expression was noted in ≥1% of the tumors (used as a reference value due to the presence of melanin deposition). Glucose transporter type 1 (GLUT-1) staining was negative (Fig. 6). Additionally, the BRAF V600 mutation was negative. In the background liver, approximately 20% of centrilobular macrovesicular fat deposits were present, but no fibrosis was noted. Twelve months after surgery, the patient is still alive and recurrence-free.

Discussion

Primary ocular malignant melanoma rarely occurs among all types of malignant melanomas. Of the 4,594 patients diagnosed with malignant melanoma documented in the Japan Melanoma Study from 2005 to 2017, 45 (1.0%) had primary ocular malignant melanoma (2). Choroidal malignant melanoma tends to cause hematogenous metastasis as it occurs in the choroid, which has abundant blood flow. The liver was the most common site of metastasis, accounting for 87% of all cases, followed by the lungs (46%), bones (29%), and skin (17%). Thus, conducting a systemic metastatic search is crucial for establishing appropriate treatment policies and determining follow-up strategies to evaluate recurrence after surgery (1). The distant metastasis rate increased as the diameter of the primary lesion increased. The primary lesion in the present patient had a tumor diameter of ≥10 mm, with metastasis rates of 35% at 5 years, 49% at 10 years, and 67% at 20 years (3). Patients with liver metastasis have a poor prognosis, with a median overall survival of 4.9 months if left untreated (4). Clinical practice guidelines for melanoma in Japan mainly focus on managing primary cutaneous malignant melanoma. These guidelines do not specify the necessity of performing routine imaging tests in asymptomatic patients beyond 5 years after surgery. A recurrence of liver metastasis occurred in patients with primary choroi-

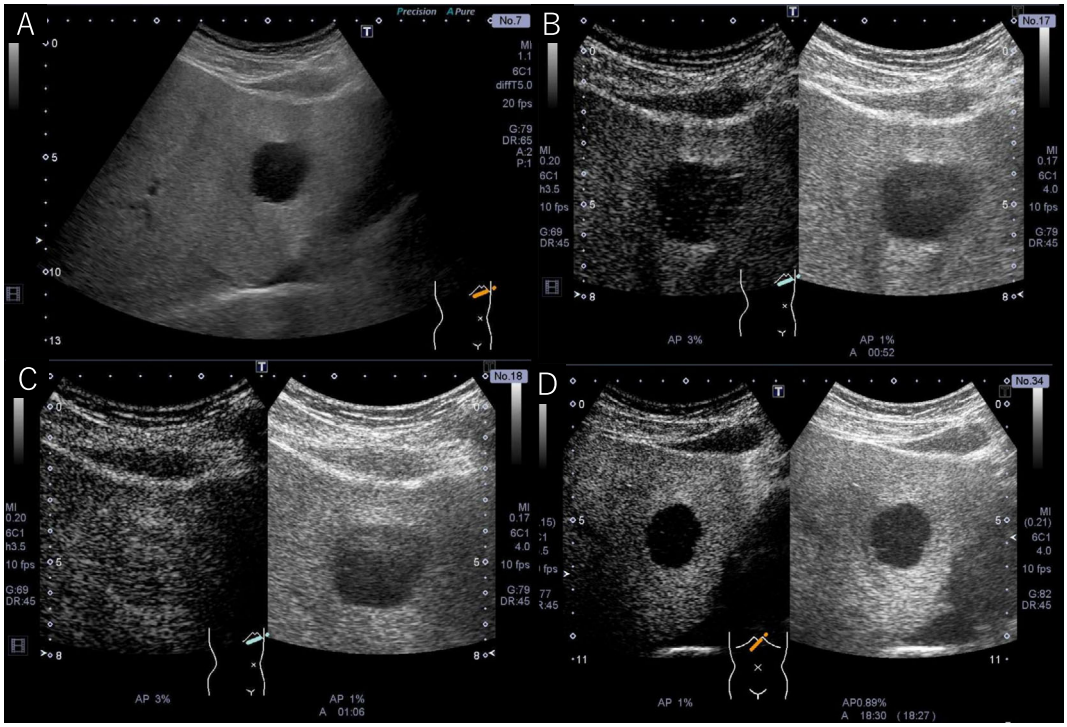

Figure 4. **Abdominal ultrasonography. A well-defined, smooth, hypoechoic nodule was observed in B-mode (A). Contrast-enhanced ultrasonography showed that the nodule had no contrast effect in the arterial phase (B). A contrast effect equivalent to that of the surrounding liver parenchyma was noted in the portal phase (C), but it was deficient in the post-vascular phase (D).**

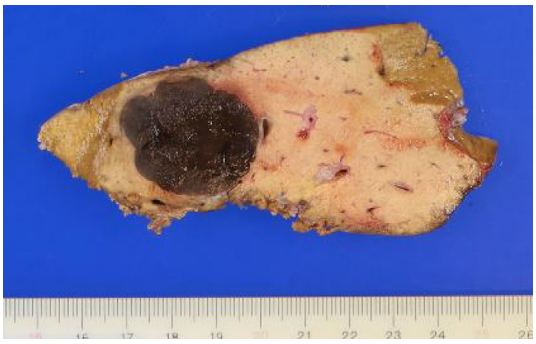

Figure 5. **Pathological specimen. The nodule in the left lobe of the liver appears blackish and well-defined.**

dal melanoma ≥10 years after surgery. Crowley et al. reported a case of primary ocular malignant melanoma that recurred 47 years after surgery (5). Although long-term follow-up is necessary from the viewpoint of cost-effectiveness, it is not realistic to perform a whole-body search more than once a year for patients more than 10 years after surgery. In addition, there was a case of lung metastasis after the age of 25 years. In our opinion, annual abdominal ultrasonography + CT of the thorax and abdomen may be considered to search for metastasis, including in the lungs and bones (6-11).

In this case, screening for liver metastasis by abdominal ultrasonography was continued once a year after surgery, and a recurrence of liver metastasis was confirmed in the 12 th year after surgery. Considering the hypervascular nature of choroidal malignant melanoma, the primary lesion, it was anticipated that the metastatic lesion would also exhibit hypervascularity. However, contrast-enhanced CT and MRI imaging revealed a poor contrast effect in the liver lesions. In addition, blood tests revealed no elevation in the levels of 5-S-CD and LD, which are used as biomarkers for malignant melanoma. At first onset, 5-S-CD 4.1 nmol/L and LD 193 U/L, which were within normal range. 5-S-CD and LD levels are more commonly elevated in the advanced stages of malignant melanoma, and their association with prognosis has been demonstrated (12, 13). However, Umemura et al. reported that when metastasis/recurrence of malignant melanoma was confirmed, the 5-S-CD level was elevated in 11 of 14 patients, whereas the LD level was elevated in only 3 of 14 patients. Even in patients with stage IV disease, 5-S-CD demonstrated a sensitivity of 70%, whereas LD demonstrated a sensitivity of 50%. In cases of melanin-producing malignant melanoma, the levels of these biomarkers may not necessarily be elevated (14).

In this case, owing to the risk of tumor seeding, biopsy was not performed, and surgery was selected for diagnostic and therapeutic purposes. Prior to surgery, FDG-PET/CT was performed to detect malignant findings in other organs or metastatic lesions. However, no significant FDG accumulation was observed in the liver metastatic lesions.

The diagnostic performance of FDG-PET/CT in the diagnosis of primary lesions of uveal melanoma varies according to tumor size, and a systematic review reported a pooled sensitivity of 45% (95% CI: 41-50%). Regarding liver me-

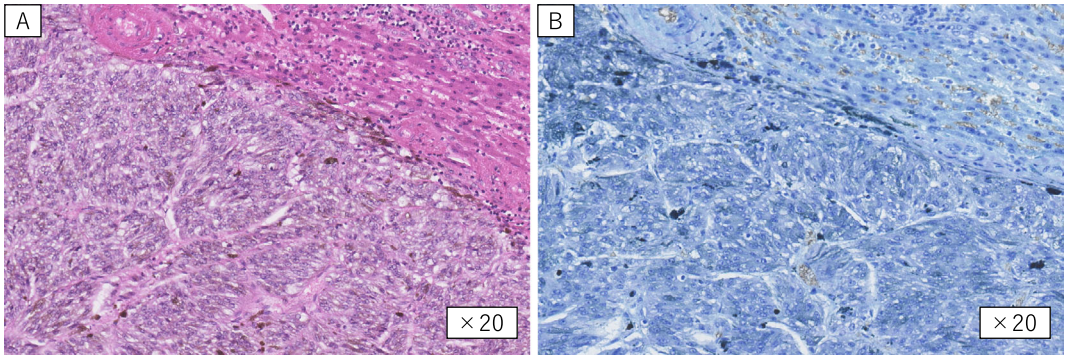

Figure 6. **Pathological findings of liver metastasis. Hematoxylin-eosin stain (A) shows tumor cells containing intracellular melanin granules and oval- to spindle-shaped nuclei. Glucose transporter type 1 (GLUT-1) stain (B) was negative in the tumor cells.**

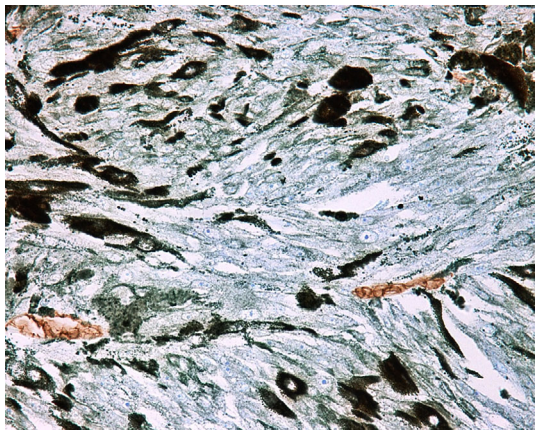

Figure 7. **Pathological fingings of primary lesion. GLUT-1 was not expressed in the tumor cells.**

tastases, the pooled sensitivity and specificity were 96% (95%CI: 81-99%) and 100% (95%CI: 94-100%), respectively (15). If the primary lesion had occurred at a location other than the eye, the pooled sensitivity and pooled specificity were 70% (95%CI: 57-80%) and 94% (95%CI: 88-97%) for the entire lesion (including primary tumor, lymph node metastasis, and distant metastasis), 84% (95%CI: 72-92%), and 93% (95%CI: 83-97%) for distant metastasis (16). Standardized uptake value (SUV) max of liver metastases is also associated with the prognosis. Del Carpio et al. reported that patients with a high SUVmax (8.5 ≤) had a significantly worse prognosis, and SUVmax was an independent prognostic factor according to a multivariate analysis (17). Patients without FDG accumulation may have a relatively long-term survival potential, and radical resection may be a feasible treatment option.

FDG-PET/CT detects tumors through the accumulation of ^{18}F-FDG inside the cells. This accumulation occurs after ^{18}F-FDG is transported into the cells by GLUT on the cell membrane surface and subsequently phosphorylated by hexokinase. Among glucose transporters, GLUT-1 is upregulated in various tumors. Generally, FDG accumulation is enhanced in tumors with a high GLUT-1 expression. Additionally, a correlation between the GLUT-1 expression level and the PET/CT maximum standardized uptake value has been shown in malignant melanoma (18, 19).

Důra et al. reported that GLUT-1 expression was observed on the cell membrane in 65 out of 225 (30.7%) patients with cutaneous malignant melanoma, while GLUT-1 expression was not observed in all 175 patients with melanocytic nevus. In addition, the GLUT-1 expression correlated with an increased Breslow thickness (pathological tumor thickness), increased local recurrence, distant metastasis recurrence rates, and a shortened survival time. This indicates that GLUT-1 is involved in malignant melanoma progression (20). Although there are no reports on the frequency of GLUT-1 expression in primary ocular malignant melanoma, a higher ratio of GLUT-1 among GLUT-1, 2, 3 expressed in lesions with metastases has been shown, thus suggesting an association with an abnormality of chromosome 3 (monosomy-3) in tumor cells. (21). The primary lesion in this case was also GLUT-1 negative (Fig. 7), and the patient was considered to have a relatively good prognosis, as he had been recurrence-free for 12 years after surgery.

According to Strobel et al., FDG accumulation was observed in the liver metastatic lesions of all patients with primary cutaneous malignant melanoma, whereas no FDG accumulation was noted in the liver metastatic lesion in 59% of patients with primary intraocular malignant melanoma. Additionally, inconsistencies were observed between the presence or absence of GLUT-1 expression in tumor cells and the presence or absence of FDG accumulation (22). FDG accumulation may be absent, even if GLUT-1 is highly expressed in specific cancer types, such as prostate cancer. Moreover, GLUT-1 expressed in cells may not be present or activated in the cell membrane (23). In addition, glucose transporters other than GLUT-1, the activity of intracellular FDG metabolic enzymes, and the degree of tumor differentiation are believed to be involved in FDG accumulation. Even in choroidal malignant melanoma, the degree of FDG accumulation may vary depending on the patient. In this case, GLUT-1 staining was performed to examine the underlying cause of the absence of FDG accumulation in tumors.

The absence of FDG accumulation may be attributed to the lack of GLUT-1 expression in the tumor cells. Thus, FDG-PET/CT was not performed prior to eye enucleation. Thus, it was unclear whether FDG accumulation had been present in the primary lesions.

Therefore, it is crucial to recognize that certain metastatic lesions may not exhibit FDG accumulation as in the present case. It is advisable to not rely solely on the results of FDG-PET/CT. Instead, screening and detailed examinations should be performed in combination with multiple diagnostic modalities.

Regarding the postoperative adjuvant chemotherapy for stage IV malignant melanoma, such as in this case, a phase 3 clinical trial comparing the efficacy of ipilimumab and nivolumab (CheckMate 238 trial) was conducted. The trial demonstrated that recurrence-free survival was significantly longer in the nivolumab group (12-month recurrence-free survival rate: 70.5%) than in the ipilimumab group (12-month recurrence-free survival rate: 60.8%) (hazard ratio: 0.65, 97.56% confidence interval: 0.51-0.83, $p<0.001$) (24). Therefore, nivolumab has been approved in Japan as postoperative adjuvant chemotherapy for malignant melanoma with completely resected lymph node metastasis or distant metastatic lesions. Choroidal malignant melanoma was excluded from the CheckMate 238 trial. Thus, the effectiveness of this treatment in choroidal malignant melanoma with liver metastasis recurrence has not been assessed. Therefore, in this case, liver and brain metastases were monitored using contrast-enhanced MRI every 3 months after surgery, and nivolumab administration was considered at the time of recurrence.

Conclusion

We encountered a patient with choroidal malignant melanoma who experienced a recurrence of liver metastasis 12 years after eye enucleation. The absence of GLUT-1 expression in tumor cells could be one of the reasons why FDG-PET/CT revealed no accumulation. Thus, it is necessary to use multiple modalities to evaluate metastatic lesions.

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

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