Adrenal Gland Metastasis of Merkel Cell Carcinoma Diagnosed by Endoscopic Ultrasonography-guided Fine Needle Biopsy

Masashi MORIMACHI, Momoka KAKIZAWA, Yumi TSUJI, Yosuke TAZAWA, Yoshihiro SHIRATAKI, Aya KAWANISHI, Ryuzo DEGUCHI and Tatehiro KAGAWA

Department of Internal Medicine, Division of Gastroenterology and Hepatology, Tokai University School of Medicine

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A man in his 70s came to our department with jaundice. He was diagnosed with Merkel cell carcinoma in the left eyebrow area 3 years ago and was followed up after tumor resection. Endoscopic retrograde cholangiopancreatography was performed because the computed tomography and abdominal ultrasonography revealed bile duct dilatation. However, the duodenum was too narrow and deformed to reach the ventral papilla. Percutaneous transhepatic cholangiodrainage was performed, and bile cytology revealed no malignant findings; however, it did not sufficiently reduce the jaundice. Subsequently, endoscopic ultrasound-fine needle biopsy was performed on his right adrenal mass, which led to a diagnosis of the rare Merkel cell carcinoma. In summary, we report here of a case in which endoscopic ultrasound-fine needle biopsy led to the diagnosis of Merkel cell carcinoma recurrence.

Key words: Merkel cell carcinoma, adrenal gland metastasis, EUS-FNB

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare, rapidly progressing neuroendocrine malignancy of the skin that occurs in sun-exposed areas (head, neck, and extremities) in older people and rapidly metastasizes to hematogenous and lymphatic sites [1]. Previous retrospective studies have reported distant metastases in 24.3–27.8% of MCCs, with about half of these metastases being intraperitoneal. Peritoneal, abdominal lymph nodes, liver, kidney, and adrenal glands have been reported as sites of intraperitoneal metastasis [2, 3]. On the other hand, few reports exist of endoscopic ultrasound-guided fine needle biopsy (EUS-FNB) leading to the diagnosis of MCC recurrence. Herein, we report a case in which EUS-FNB led to the diagnosis of MCC recurrence, with a review of the literature.

CASE REPORT

A man in his 70s was urgently admitted to our hospital with jaundice and abnormal hepatobiliary enzyme. His past medical history included hypertension and MCC. He was diagnosed with MCC 3 years ago and the malignant tumor in the left eyebrow region was resected along with neck dissection, followed by postoperative radiation therapy (Fig. 1). He had a postoperative scar on the left eyebrow area. An eye examination revealed no signs of anemia; however, the eyes and skin were markedly affected by jaundice. The abdominal wall was soft and flat, with no pain. No edema was observed in the lower legs. He had no fever, and his vitals were normal.

Blood tests are shown in Table 1. The patient had marked jaundice and elevated hepatobiliary enzymes. The tumor marker values were suggestive of a primary malignancy of the biliary tract and pancreas. Abdominal ultrasonography revealed dilated intra- and extrahepatic bile ducts. Additionally, a hypoechoic area with indistinct borders extending from the right adrenal gland to the periportal area was observed (Fig. 2). A contrast-enhanced computed tomography (CT) of the head and pelvis was then performed. There were no obvious findings in the head and neck region. Wall thickening with intrahepatic bile duct dilation and contrast effect in the lower common bile duct were observed. Soft shadows were scattered around the

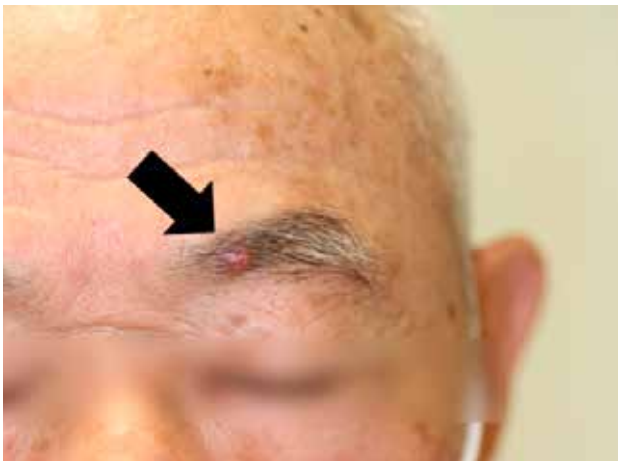

Fig. 1 MCC before resection. A well-defined, 5 x 5 mm size, reddish, raised mass was seen above the left eyebrow.

Masashi MORIMACHI, Department of Gastroenterology and Hepatology, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan Tel: +81-463-93-1121 Fax: +81-463-93-7134 E-mail: m.morimachi@tokai.ac.jp

Table 1 Patient's laboratory data

Hematology		Tumor markers	
White blood cells (/μL)	6500	Carcinoembryonic antigen (ng/mL)	2.6
Neutrophils (%)	73.5	Cancer antigen 19–9 (U/mL)	230
Lymphocytes (%)	20	SPAN-1 (U/mL)	84
Eosinophils (%)	1.5	DUPAN-2 (U/mL)	62
Monocytes (%)	4.5	Neuron-specific enolase (ng/mL)	45.5
Basophils (%)	0.5	Interleukin 2 receptor (U/mL)	1780
Red blood cells ($\times 10^4$/μL)	305		
Hemoglobin (g/dL)	10.2		
Platelets ($\times 10^4$/μL)	34.3		

Biochemistry		Antibodies	
Aspartate aminotransferase (U/L)	228	IgG (mg/dL)	1151
Alanine aminotransferase (U/L)	219	IgG4 (mg/dL)	17
Lactate dehydrogenase (U/L)	233	IgA (mg/dL)	227
Alkaline phosphatase (U/L)	639	IgM (mg/dL)	159
Gamma-glutamyl transferase (U/L)	409	Antinuclear antibody	(-)
Blood urea nitrogen (mg/dL)	12	Anti-mitochondrial antibody	(-)
Creatinine (mg/dL)	1.06		
Albumin (g/dL)	3		
Creatine kinase (U/L)	56		
Amylase (μg/dL)	110		
Total bilirubin (mg/dL)	17.8		
Direct bilirubin (mg/dL)	14.3		
Sodium (mmol/L)	129		
Potassium (mmol/L)	4.2		
Chloride (mmol/L)	95		
Calcium (mg/dL)	8.8		
C-reactive protein (mg/dL)	2.22		

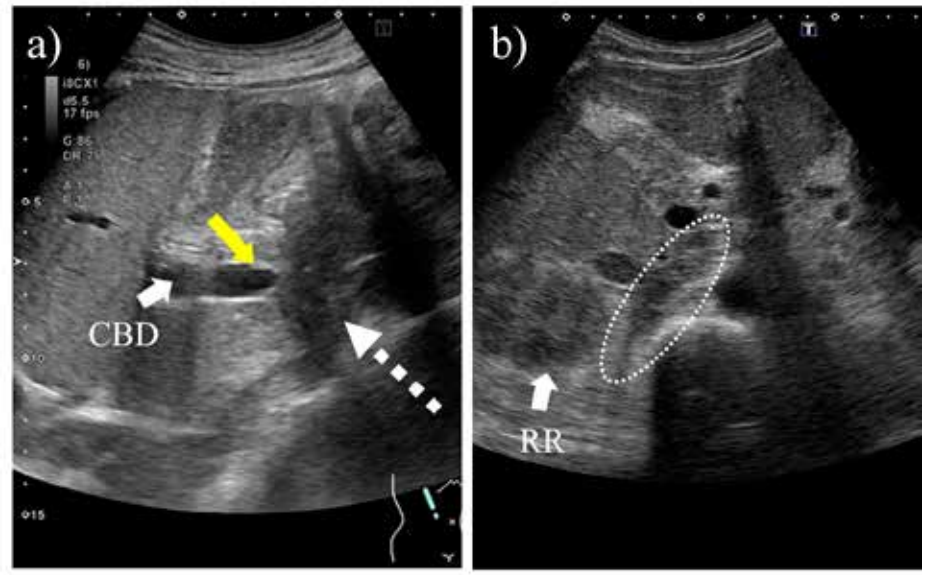

Fig. 2 Abdominal ultrasonography. a: CBD is slightly dilated at 10 mm. The bile duct wall is thickened (yellow arrow). A hypoechoic area is seen around the portal vein (white dashed arrow). b: A 51 × 14 mm hypoechoic area is lumped with the adrenal gland (dashed circle).
CBD: common bile duct, RR: right renal

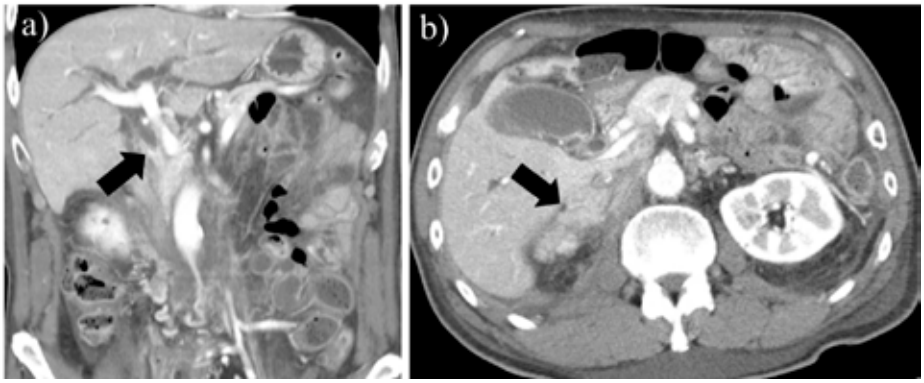

Fig. 3 Contrast-enhanced CT tomography a: Stenosis and wall thickening of the common bile duct. b: A soft shadow was observed in the area corresponding to the right adrenal gland.

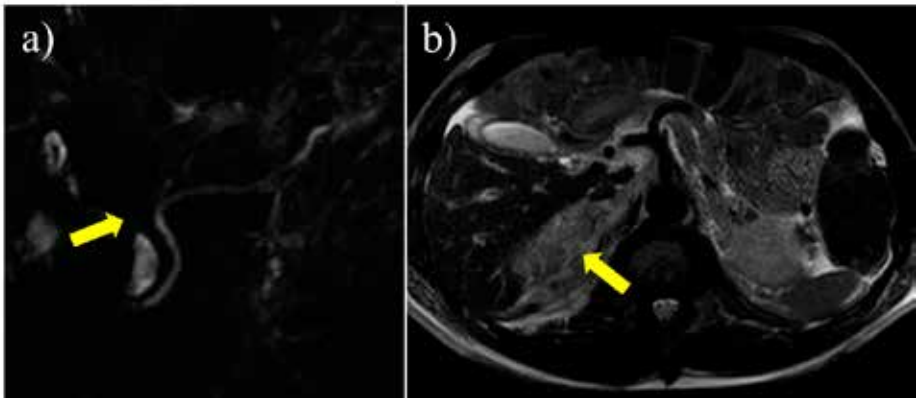

Fig.4 a: Magnetic Resonance Cholangiopancreatography findings. No obvious abnormality in the pancreatic duct. The common bile duct was obstructed (yellow arrow). b: MRI T2 weighted image findings. Soft shadows extended from the right renal portal to the periaortic area. A soft shadow in the area corresponding to the right adrenal gland was also observed (yellow arrow).

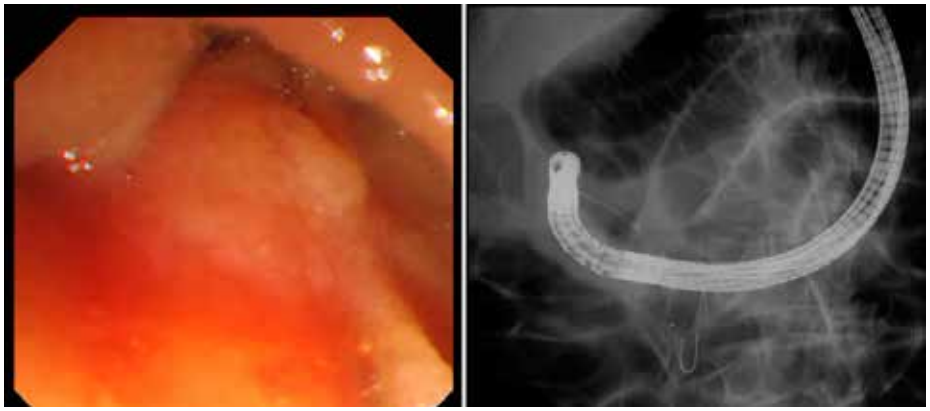

Fig. 5 ERCP findings on the 2nd day. There was a stenosis in the second part of the duodenum and the scope (TJF-260V, OLYMPUS) did not pass. The mucosa was normal.

right kidney, from the abdominal aorta to the inferior vena cava, and around the rectum (Fig. 3). Abdominal magnetic resonance imaging (MRI) revealed similar findings. Soft shadows extended from the right renal portal to the right ureter and periaortic area. There was also a soft shadow in the region corresponding to the right adrenal gland (Fig. 4). There were no obvious abnormal findings in the pancreas.

The patient's course after admission was as follows. On the 2nd day, endoscopic retrograde cholangiopancreatography (ERCP) was performed. Although the mucosa was normal, there was marked duodenal stenosis and deformation, and the papilla of Vater could not be reached (Fig. 5). Therefore, during hospitalization, the patient was prohibited from taking anything by mouth except water. Nutrition was managed by peripheral and total parenteral nutrition. ERCP was performed again on the 6th day; however,

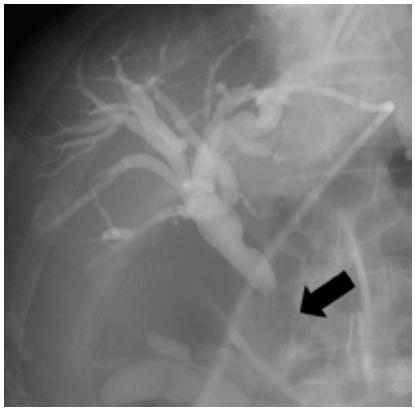

Fig. 6 Findings of PTCD performed on the 6th day. The lower bile duct is obstructed.

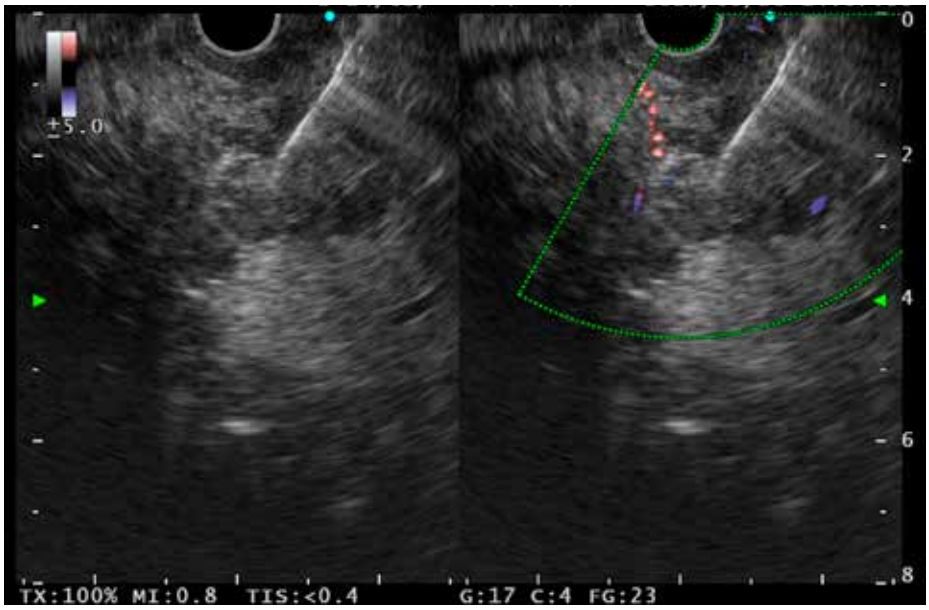

Fig. 7 EUS-FNB findings on the 66th day. A soft tissue mass around the right adrenal gland was biopsied (Scope: GF-UCT260, OLYMPUS. Needle: 22G SonoTip TopGain, MediGlobe).

it failed. Subsequently, percutaneous transhepatic cholangiodrainage (PTCD) was performed (Fig. 6). Cytology was performed daily on the bile; however, no malignant findings were found in classes II or III. Although PTCD drainage was 200–500 mL every day, total and direct bilirubin remained in the 7.0 mg/dL and 6.0 mg/dL ranges, respectively. In addition, there was a decrease in urine volume and renal function around day 20. Ursodeoxycholic acid and traditional Japanese medicines were ineffective. On the 30th day, suspecting retroperitoneal fibrosis, prednisolone was started at 30 mg/day. Thereafter, renal function continued to deteriorate, and nephrostomy was eventually created on both sides. Urine cytology was performed, but no malignant findings were found in both class II and III. Two weeks after starting steroids, blood test showed a total bilirubin level at 6.2 mg/dL, suggesting sparse improvement in jaundice, and fluoroscopic upper gastrointestinal endoscopy showed no improvement in duodenal stricture and deformation. Therefore, the steroids were judged to be ineffective and tapered off by 5–10 mg per week and terminated. Early in his hospitalization, we thought that EUS-FNB would be difficult because of duodenal stenosis. As hospitalization became more prolonged, the mass in the right adrenal gland increased. On the 66th day, EUS-FNB was performed again successfully (Fig. 7). HE staining revealed an increase in the number of atypical cells with a high N/C ratio. Immunostaining results were chromogranin A(+), synaptophysin(+), INSM1(+), CD56(+), SSTR-2a(2+), and CK20(+), and the Ki-67 index was 30%. The pathological results led to the diagnosis of metastasis of MCC to the right adrenal gland and peritoneum (Fig. 8). Thereafter, despite trial and error, including the replacement of PTCD, the hepatobiliary enzymes did not improve, leading to liver and renal failure, and the patient died on the 82nd day. Pathological autopsy was performed after obtaining the family's consent.

AUTOPSY FINDINGS

The autopsy of the head was not performed at the family's request. There was no recurrence of MCC in the neck or chest. There were no metastases or other cancers in the liver and no abnormalities in the pancreas. The common bile duct had severe adhesions to the surrounding tissue. There was no evidence of primary biliary cancer or autoimmune disease. The mass

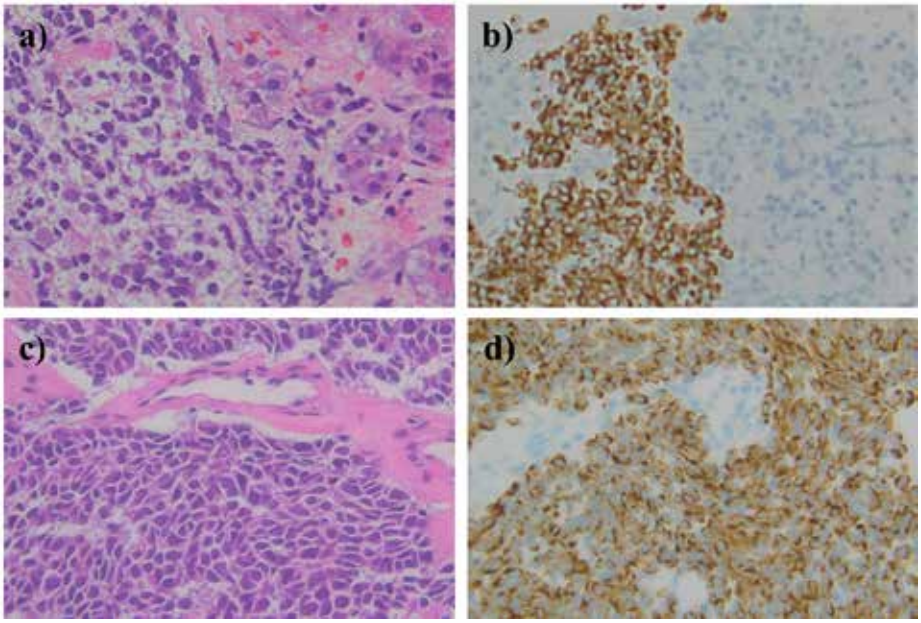

Fig. 8 Pathological findings. a, b: Specimens obtained using EUS-FNB. The specimen collected was of adrenal origin. c, d: Specimen above left eyebrow previously resected.
a, c: High-power views. HE staining revealed an increase in the number of atypical cells with a high N/C ratio. b, d: High-power views. Immunostaining of CK20. Both show positive CK20 staining. These led to the diagnosis of metastasis of MCC.

extended from the right adrenal gland and abdominal aorta to the inferior vena cava and around the bilateral ureters. Moreover, numerous small nodules were scattered in the retroperitoneum and mesentery. Kidneys showed hydronephrosis due to peritoneal metastasis. There was no evidence of retroperitoneal fibrosis. These pathological findings were consistent with that of intraperitoneal metastasis of MCC. No other cancers or diseases were found that may have resulted in his death.

DISCUSSION

In this case, we first considered a tumor of biliary origin as the cause of jaundice based on blood and abdominal ultrasound findings. However, since the daily biliary cytology did not reveal any malignant findings, we suspected retroperitoneal fibrosis based on the CT and MRI findings. Retroperitoneal fibrosis is a disease that causes inflammatory cell infiltration and fibrosis of the retroperitoneum and is most common in middle-aged and older adults. Its causes include malignancies and autoimmune diseases, but most cases are idiopathic with no known cause. CT and MRI show a well-defined soft-tissue mass centered on the aorta, often resulting in renal damage due to ureteral obstruction [4]. The first-line treatment is steroids. Steroids are effective in most cases, often starting at about 30 mg/day [5]. In this case, steroids were administered for suspected retroperitoneal fibrosis; however, it was ruled out following no improvement in the patient's condition.

When the diagnosis was not made based on bile findings, we contemplated another tissue diagnostic method. Initially, the soft intra-abdominal shadows were considered difficult to approach from outside or inside the body due to the proximity of the aorta and the duodenal stenosis. However, as the soft shadow increased with time, we thought there was a chance for puncture and performed EUS-FNB, which successfully biopsied the right adrenal lesion from the duodenal bulb. While puncturing tumors in the abdominal cavity, a short puncture route is often preferred initially in view of bleeding, seeding, and other complications. We opted for EUS-FNB, which resulted in a lengthy diagnostic process. Depending on the overall condition and progression, there may have been room to consider CT-guided or surgical biopsy. We were convinced from the CT and autopsy findings that the puncture was to the right adrenal gland. Adrenocorticotropic hormone and cortisol were measured and confirmed to be normal before puncturing the adrenal gland. However, they may not be an accurate diagnosis because steroids were administered. At least, there were no clinical findings suggestive of abnormal adrenal function. The patient's vitals were also monitored during the EUS-FNB. The definitive MCC diagnosis is based on histopathological examination and is characterized by the presence of cancer cells with delicate chromatin, bright round nuclei, and small, well-defined nucleoli that grow in a cordate or diffuse pattern. In practice, diagnosis is difficult with hematoxylin and eosin staining alone, and is confirmed by immunohistological examination together with findings of CK20(+), synaptophysin(+), chromogranin A(+), and CD56(+) [3, 4]. The histopathological results of this case were consistent with those of MCC, and the immunostaining results of EUS-FNB were also consistent with those of the resection specimen from the left eyebrow region.

Common metastatic sites for MCC are lymph nodes, distant skin, lungs, central nervous system, and bone. Intra-abdominal metastases are also frequent. MCC has been postulated to have a variety of metastatic mo-

dalities, the most common being lymphatic [6]. On the other hand, the adrenal gland is a small but blood-rich organ that has been shown to be a target for metastasis of various cancers through hematogenous spread. Lymphoma, lung cancer, and breast cancer account for the majority of adrenal metastases, but malignant melanoma is also frequently seen [7].

Ultrasound endoscopy is known as one of the diagnostic techniques for intra-abdominal tumors. It used to be called endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA); however, in recent years, due to the evolution of puncture needles, the specimen collection volume has increased and it is now called EUS-FNB. A PubMed search for cases of MCC successfully diagnosed using EUS-FNA or EUS-FNB yielded eight cases. Seven of the cases involved the pancreas and one a peripancreatic nodule. There are no reports of successful diagnosis of MCC by adrenal puncture with EUS-FNB.

The treatment of metastatic or recurrent MCC is chemotherapy. Until now, chemotherapy for neuroendocrine cancer has been used empirically. Recently, the anti-PD-L1 antibody, avelumab, has been approved. The 5-year survival rate of patients with MCC with distant metastases is very poor at 14% [8]. After the introduction of avelumab, the 5-year survival rate was reported to be 26%, which is a remarkable improvement, and future treatments are expected to improve it further [9].

The 5-year recurrence rate for MCC was 40%, especially since 95% of recurrent cases occurred within the first 3 years [10]. Although it depends on the stage of the disease, follow-ups using abdominal ultrasound, CT, MRI, and positron emission tomography-CT every 6 months for at least 5 years after surgery is necessary. In addition, it is recommended that head, chest, and abdominal exams be periodically included, regardless of the primary location [11]. In our case, the original tumor had been completely removed, and there were no findings suggestive of recurrence on the CT scan 4 months earlier.

With the advent of new drugs, long-term survival in MCC appears as a possibility even following metastasis to the abdomen. Therefore, EUS-FNB is a promising and effective diagnostic tool.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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