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Case Report

Long-term Survival with a Rare Advanced Primary Gastrointestinal Malignant Melanoma Treated with Laparoscopic Surgery/Immune Checkpoint Inhibitor

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Targeted therapies for malignant melanoma have improved patients' prognoses. A primary gastrointestinal malignant melanoma is very rare, with no standard treatment strategy. We treated a 78-year-old Japanese female with advanced primary gastrointestinal melanoma of the descending colon and gallbladder. We administered a multidisciplinary treatment: surgical resection of the descending colon and gallbladder tumors, resection of the metastatic lymph nodes behind the pancreas head, and immune checkpoint antibody-blockade therapy (nivolumab) for ~4 years. PET/CT demonstrated no recurrent lesion for >3 years. Multidisciplinary therapies (*e.g.*, surgery, chemotherapy, radiotherapy, target therapy, and immune checkpoint antibody-blockade therapy) can successfully treat primary gastrointestinal malignant melanoma.

Key words: primary gastrointestinal melanoma, laparoscopic surgery, immune checkpoint antibody-blockade inhibitor

Malignant melanoma is a malignant tumor generating from melanocytes in the skin (termed 'malignant cutaneous melanoma'), and it easily metastasizes to lymph nodes, the lungs, brain, and gastrointestinal tract, resulting in poor prognosis [1-5]. Primary cutaneous malignant melanoma tends to metastasize to digestive organs such as the liver (68%), small intestine (58%), colon (22%), stomach (20%), duodenum (12%), rectum (5%), esophagus (4%), and anus (1%) [1]. In contrast, a primary malignant gastrointestinal melanoma is quite rare, even though the gastrointestinal tract has melanocytes. A primary gastrointestinal malignant melanoma can arise at any site of the gastrointestinal tract, such as the anorectal region (53.6%), pharyngeal cavity (32.8%), esophagus (5.9%), stomach (2.7%), small intestine (2.3%), gallbladder (1.4%), and large intestine (0.9%) [1,5,6]. Primary colonic malignant melanoma is particularly rare; there are only 37 cases in the literature [7-21].

Advances in the basic research into melanoma have dramatically improved the prognosis of patients with malignant melanoma. For example, the recently introduced therapeutic strategies for melanoma use targeted

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treatments such as a BRAF inhibitor, a MEK inhibitor, and immune checkpoint antibody-blockade therapy [22]. However, due to the rarity of primary gastrointestinal malignant melanoma, there is no standard treatment or therapeutic guidelines. Here, we report the case of an elderly female patient with malignant melanoma of the descending colon and gallbladder successfully treated with immune checkpoint antibody-blockade therapy for >4 years.

Case Presentation

A 78-year-old Japanese female with hypertension and hyperlipidemia was referred to our hospital for the examination of a tumor at the descending colon causing uncomfortable bowel distension and lower abdominal pain. There were no significant dermatological findings. The results of blood examinations were normal except for the patient's anemia. The levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were unremarkable. A colonoscopy was performed, and it demonstrated a 5-cm Type 1 mass at the descending colon, occluding the vast majority of the lumen with necrotic tissue; the mass was clinically suspicious for malignancy, but it did not resemble conventional colon cancer (Fig. 1A).

The lesion was biopsied, and the histological findings showed poorly differentiated adenocarcinoma. However, the biopsy results led to the suspicion that it was a malignant tumor. The pathologist suspected that the tumor could be a malignant lymphoma, malignant melanoma, or soft tissue sarcoma. A computed tomography (CT) scan showed that there were 2 large tumors at the descending colon and gallbladder, and the tumor at the descending colon caused tumor-induced invagination and consequently bowel obstruction (Fig. 1C, D).

We classified the clinical stage of the primary colon cancer as cT3(SS) N0 M0 (Stage II) and a gallbladder tumor. At the same time, a multidisciplinary team was organized consisting of staff of our hospital's departments of gastroenterological surgery, gastroenterology, medical oncology, and anesthesia and the perioperative management center for the design of the therapeutic

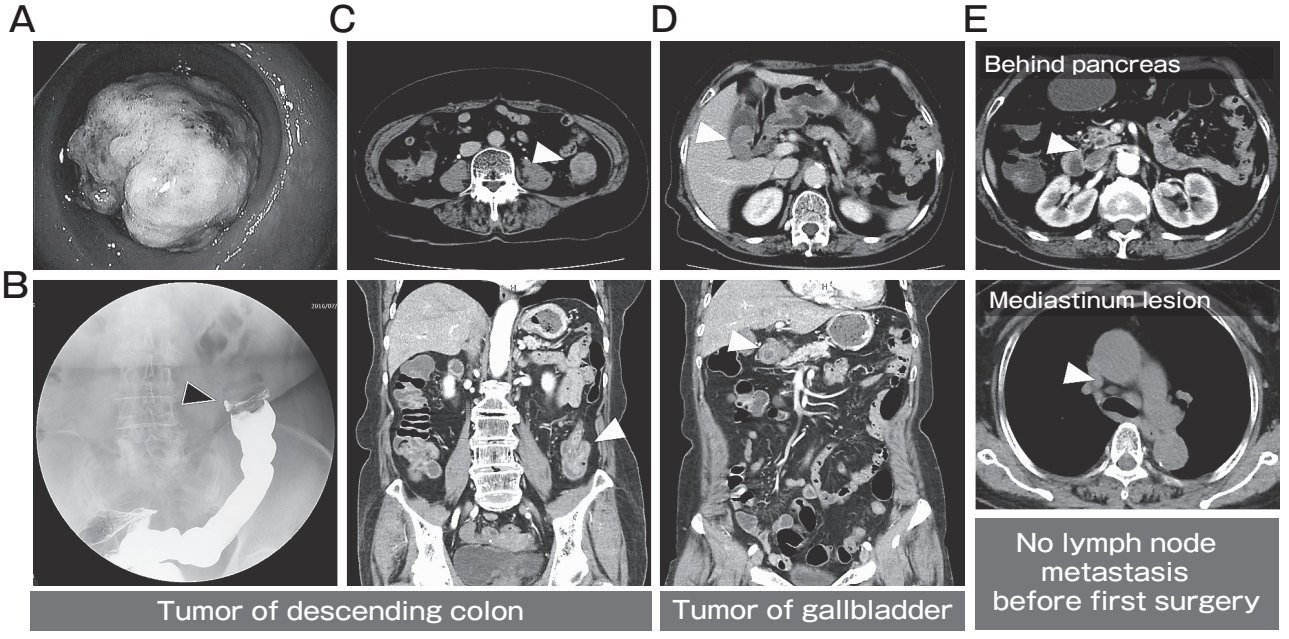

Fig. 1 Clinical findings. **A**, Colonoscopy view of the descending colon showing the 5-cm mass with necrotic tissue at the surface, occluding the majority of the colonic lumen; **B**, Barium X-ray examination demonstrating the mass at descending colon occluding the majority of the colon (*arrowhead*); **C**, CT scan showing the 5-cm tumor at the descending colon (*arrowhead*). *Upper*: Vertical view. *Lower*: Sagittal view; **D**, CT scan showing the 4-cm tumor at the gallbladder (*arrowhead*). *Upper*: Vertical view. *Lower*: Sagittal view; **E**, CT scan showing that there is no remarkable lymph node behind the pancreas head (*upper*) and a small lymph node at the mediastinum lesion before the first surgery (*lower*).

strategy. We decided to perform a laparoscopic left hemicolectomy and cholecystectomy to treat the tumor-induced invagination and obstruction, and to determine the precise diagnoses of the tumors of the descending colon and gallbladder.

The patient then underwent a laparoscopic left hemicolectomy and D3 lymphadenectomy with a colocolonic anastomosis, and a cholecystectomy. The postoperative course was unremarkable, and the patient was discharged on postoperative day 14. The surgical specimen showed that descending colon had a 35-mm tumor and the gall bladder had a 40-mm tumor (Fig. 2A, C). Hematoxylin and eosin (HE) staining of the descending colon tumor, the gallbladder tumor, and lymph nodes in mesocolon of descending colon, revealed that the tumors were comprised of small, round, monoclonal cells with a high nuclear/cytoplasm (N/C) ratio (Fig. 2B, D).

One of the 21 dissected lymph nodes was positive for metastasis. The immunohistochemistry analysis showed that most of the cancer cells from the gallbladder tumor were positive for S100, human melanocyte black (HMB)-45, and melanoma antigen recognized by T-cell-1 (MART-1), which are highly sensitive and specific for the diagnosis of melanoma (Fig. 3). In contrast, most of the gallbladder tumor cells were negative for α-SMA and desmin (Fig. 3). The histological findings from the gallbladder tumor revealed the same appearance as the descending colon tumor. We thus diagnosed these tumors as malignant melanoma, but we were unable to determine which was the primary tumor (descending colon or gallbladder).

A PET/CT examination conducted 1 month postsurgery revealed the acceleration of glucose uptake in the lymph node behind the pancreas head and a mediastinum lesion (Fig. 4). Therefore, immune checkpoint antibody-blockade therapy using nivolumab (ONO pharmaceutical Co., LTD, Osaka, Japan) was administrated intravenously every 3 weeks. PET/CT scans performed after nine cycles of nivolumab demonstrated

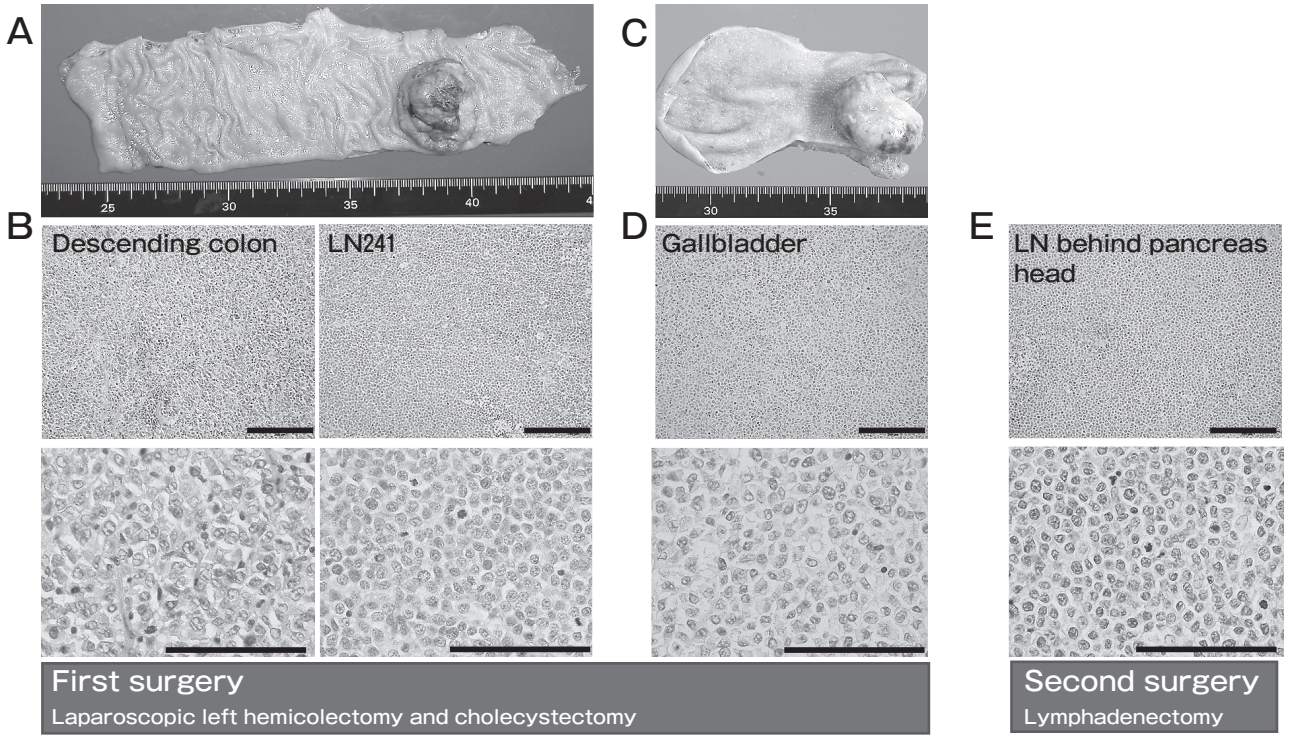

Fig. 2 Macroscopic and microscopic appearance of the primary tumors and metastatic lymph nodes. **A**, Macroscopic appearance of the tumor of the descending colon; **B**, Representative images of hematoxylin-eosin (HE) staining of the tumor of the descending colon (*left panels*) and metastatic lymph node (*right panels*); **C**, Macroscopic appearance of the gallbladder tumor; **D**, Representative images of HE staining of the gallbladder tumor; **D**, Representative images of HE staining of a metastatic lymph node behind the pancreas head. Scale bars: =200 μm.

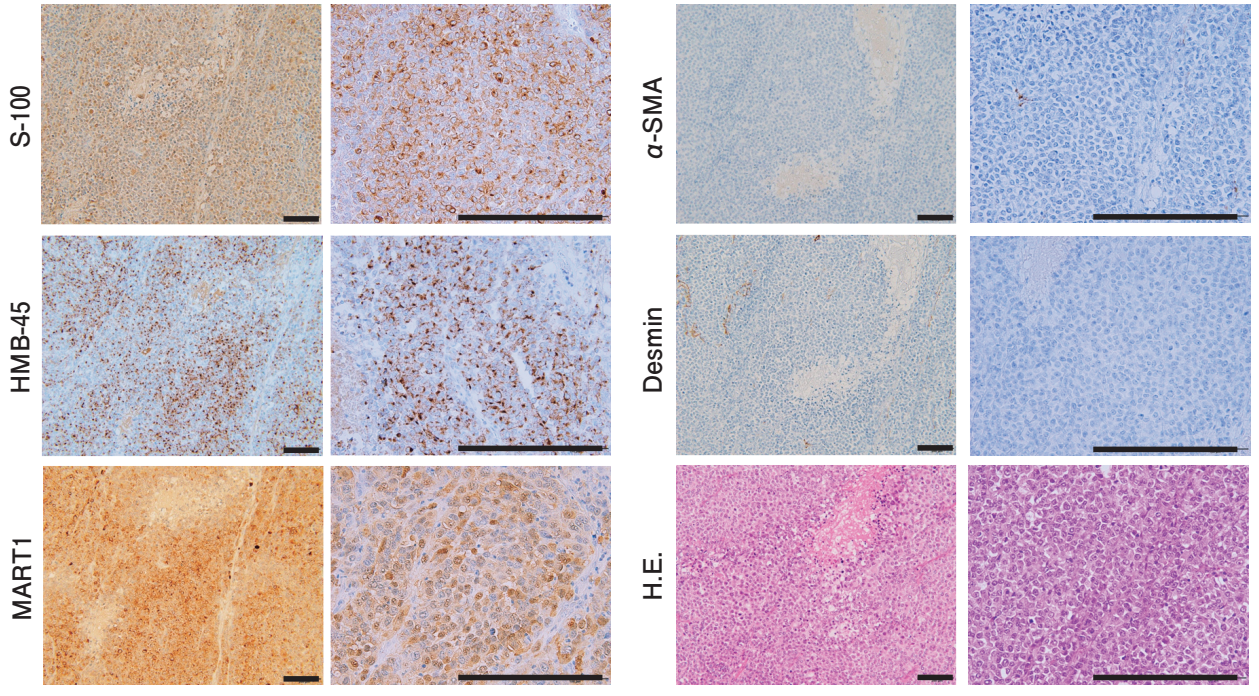

Fig. 3 IHC of the primary tumor at the gallbladder. Representative images of S-100, HMB-45, MART-1, α-SMA, desmin, and HE staining of tumor gallbladder tumor. Scale bars: =200 μm.

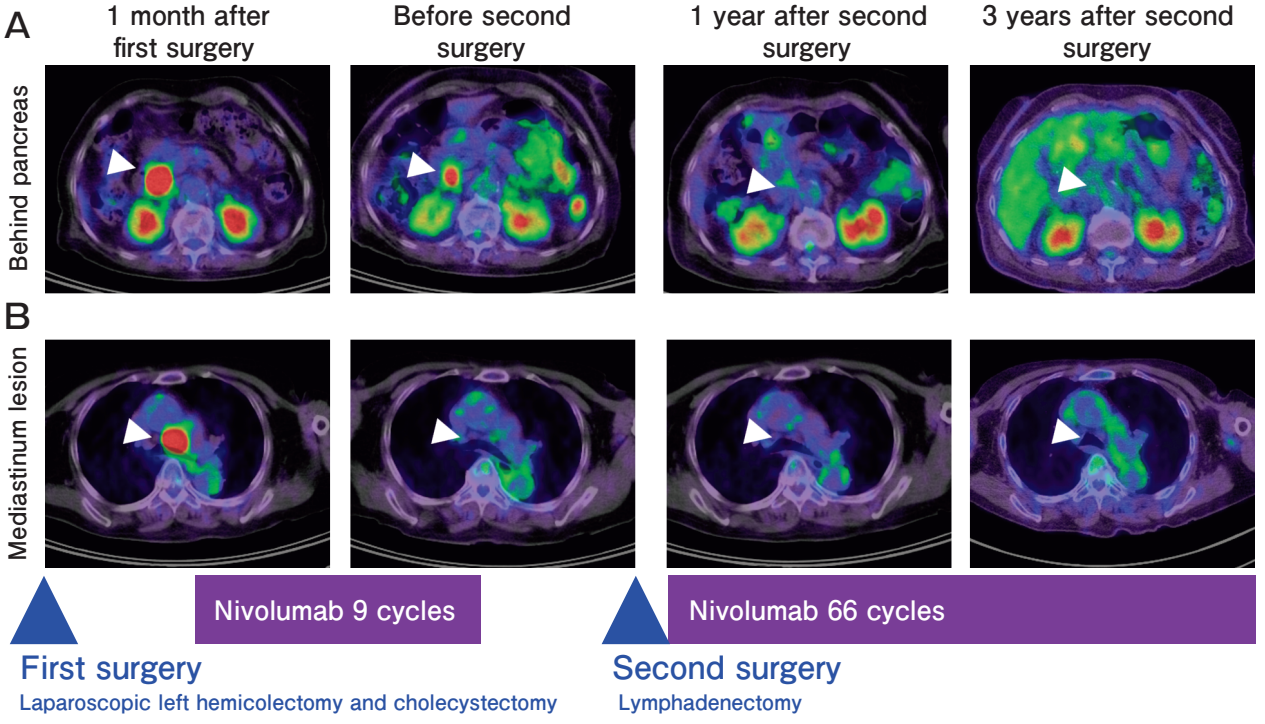

Fig. 4 PET-CT shows the course of the metastatic lymph nodes during the nivolumab treatment. A, PET-CT showing the metastatic lymph node behind the pancreas head (*arrowhead*); B, PET-CT showing the metastatic lymph node at the mediastinum lesion (*arrowhead*).

that (1) the lymph node behind the pancreas head had shrunk, (2) the glucose uptake in the lymph node around the mediastinum lesion disappeared, and (3) there was no other metastasis in the whole body (Fig. 4).

We decided to resect this lymph node behind the pancreas head since there was only one viable metastatic site. We performed a lymphadenectomy around the pancreas head with an open laparotomy. The patient's postoperative course was unremarkable, she was discharged on postoperative day 14. The histopathological analysis showed the same microscopic appearance as the primary tumor. Even though the treatment with nivolumab had reduced the lesion's size and decreased the glucose uptake of the lymph node, most of the melanoma cells were viable, resulting in grade 1a as the histological evaluation of the efficacy of nivolumab (Fig. 2E).

Nivolumab was restarted as adjuvant chemotherapy 1 month after the second surgery. CT scans have been conducted every 3 months and PET-CT has been performed every year. These modalities indicated that the lymph node in the mediastinum lesion has remained as a small nodule and has had no uptake of glucose, and there has not been any other metastasis in the patient's body (Fig. 4). There were no adverse effects from the nivolumab treatment.

Discussion

We have reported a case in which a multidisciplinary treatment approach including surgical resection and immune checkpoint antibody-blockade therapy was effective for a very rare primary gastrointestinal melanoma with distant metastasis. The clinical presentation of a primary gastrointestinal melanoma is not specific. It is sometimes difficult to distinguish a primary gastrointestinal melanoma from conventional gastrointestinal cancer based on the clinical findings [1, 23]. It is therefore indispensable to analyze the tumor specimen with immunohistochemical stains in order to diagnose a primary gastrointestinal melanoma; S-100 is very sensitive to melanoma, and HMB-45 and MART1 are also highly specific to melanoma [24]. In our patient's case, before the surgical resection of the primary tumors, HE staining demonstrated that the tumors were comprised of small, round, monoclonal cells with a high N/C ratio, suggesting diffuse large B-cell lymphoma (DLBL). Immunohistochemistry (IHC) showed that the patient's tumor was positive for BCL6 and MUM1 (which are markers of DLBL), but negative for CD3, CD5, CD10, CD20, CD30, CD38, CD79a, CD138 (markers of hematopoietic cells). The IHC also showed that the patient's tumor was strongly positive for S-100.

There are three other tumors with overlapping clinical features: gastrointestinal stromal tumor (GIST), epithelioid malignant peripheral nerve sheath tumor, and clear cell sarcoma (CCS) [1, 25]. GISTs are sometimes is positive for S-100, our patient's tumor was strongly positive for HMB-45 and MART1 [26, 27]. Epithelioid malignant peripheral nerve sheath tumor also is positive for S-100, but it has areas of necrosis and a larger vascularity , unlike malignant melanomas [27]. CCS is a rare primary soft tissue sarcoma with melanin, and it is very rare in the gastrointestinal tract [27-32]. A primary soft tissue CCS can be positive for S-100, HMB45, and MART-1, but a primary gastrointestinal CCS can be negative for HMB45 and MART-1 [30-32]. We thus diagnosed these tumors as primary gastrointestinal malignant melanoma. Moreover, it was recently reported that the expression of SOX10 or the existence of EWSR1-CREB1 or EWSR1-ATF1 fusion genes is useful to diagnose CCS [33-35]. We further checked EWSR1-ATF1 fusion genes by reverse transcriptional polymerase chain reaction (RT-PCR). RT-PCR showed that this patient did not have EWSR1-ATF1 fusion genes (Fig. 5). Therefore, we thus diagnosed these tumors as primary gastrointestinal malig-

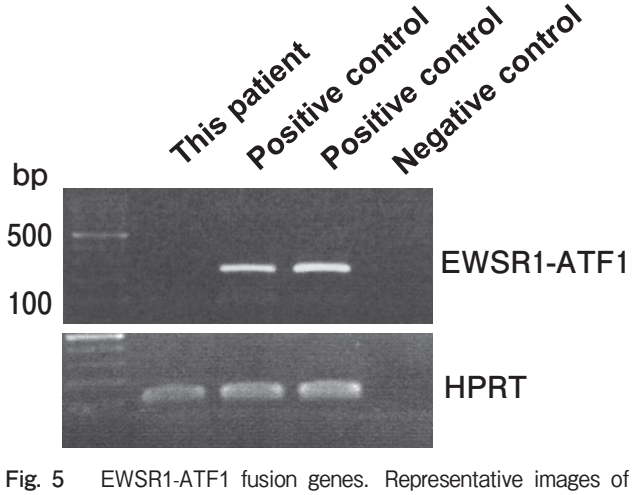

Fig. 5 EWSR1-ATF1 fusion genes. Representative images of EWSR1-ATF1 fusion genes by reverse transcriptional polymerase chain reaction (RT-PCR).

nant melanoma at that time. However, in the present case it was not possible to determine whether the tumor was primarily generated from the descending colon or the gallbladder.

Ozdemir proposed criteria to differentiate primary bronchial melanoma from secondary melanoma: (1) the lesion must be solitary in the surgical specimen, (2) there must be no previously excised skin melanoma, (3) no previous or concurrent ocular tumor is present, (4) the morphology must be compatible with that of a primary tumor, (5) there must be no other demonstrable melanoma at the time of surgical exploration, and (6) the findings should be confirmed by a careful autopsy for patients who succumb to the disease [36]. In our patient's case, surgical resection was necessary to treat the tumor-induced invagination and obstruction, diagnose the colon and gallbladder tumors, and establish the further therapeutic strategy. Moreover, endoscopic surgery was feasible for this patient [36, 37, 39]. We thus performed a laparoscopic left hemicolectomy and cholecystectomy (less invasively than an open laparotomy), and the patient could therefore receive immune checkpoint antibody-blockade therapy within 1 month after the surgery. However, the lymph node lesions recurred just 1 month after the surgical resection of the primary tumor.

Targeted therapy is the most promising chemotherapy regimen for advanced melanoma, as such therapy has markedly improved the survival outcome of melanoma. Targeted therapy may be comprised of BRAF and MEK inhibitors (dabrafenib + trametinib, vemurafenib + cobimetinib, or encorafenib + binimetinib), anti-programmed death agent-1 (PD-1), or nivolumab, in combination with anti-cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), or ipilimumab [22]. Several randomized control trials have confirmed that monotherapy or combination therapy with a BRAF inhibitor and MEK inhibitor are effective for advanced melanoma. Combination therapy with a BRAF inhibitor and MEK inhibitor provided a >60% response rate and 22.3-33.6 months as the median overall survival (OS) [22].

Nivolumab monotherapy resulted in a median OS of 36.9 months and a 5-year OS rate at 44% [22]. Combination therapy of nivolumab + ipilimumab also provided a median OS of >60 months, and the 5-year OS rate was 52% [22]. Immune checkpoint antibody-blockade therapy has thus improved the long-term overall survival of patients with advanced melanoma. In our patient, the IHC results demonstrated that the primary tumors of the gallbladder and descending colon were positive for PD-L1 (Fig. 6). We thus administered nivolumab after the first surgery [22]. Nivolumab reduced the size of the lymph node behind the pancreas head and decreased the uptake of glucose, and it also diminished the lymph node at the mediastinum lesion. However, the H.E. stain of the lymph node behind the pancreas head (resected by the second

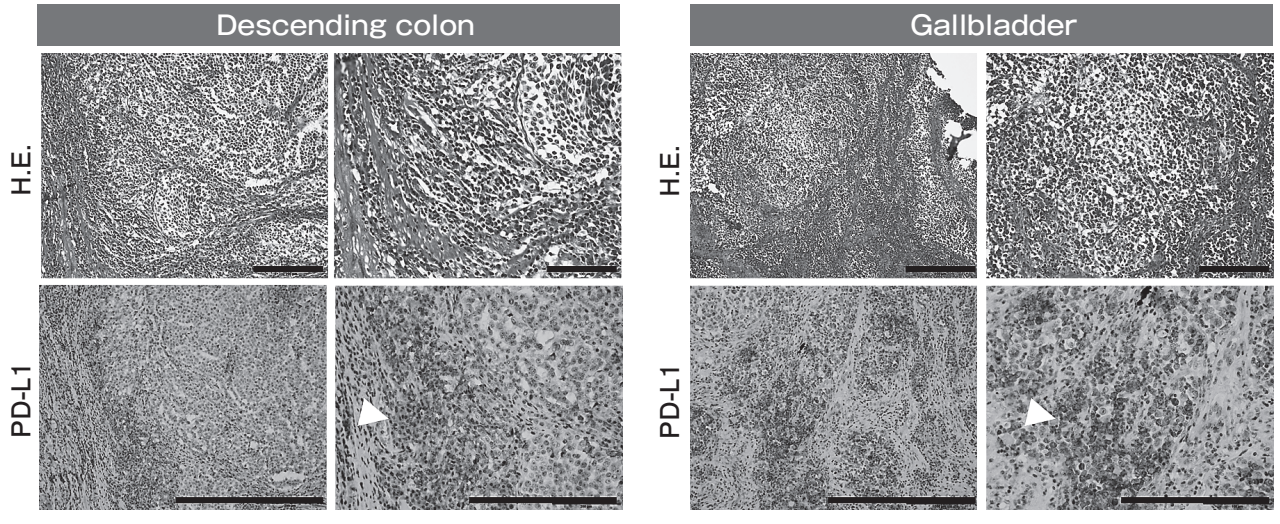

Fig. 6 PD-L1. Representative images of PD-L1 staining of the tumors of the gallbladder and descending colon. Arrowheads indicate PD-L1 positive cancer cells. Scale bars: =200 μm.

surgery) demonstrated that it had viable melanoma cells, and the efficacy of the nivolumab was grade 1A. In contrast, the lymph node at the mediastinum lesion has remained small and does not take up glucose at 4 years after the start of nivolumab treatment. These findings suggest that immune checkpoint antibody-blockade therapy is not always completely effective for a primary gastrointestinal malignant melanoma, and thus the surgical resection of a chemoresistant melanoma should be performed if possible. Our patient's case demonstrates that a combination of radical resection and adjuvant immune checkpoint antibody-blockade therapy is a promising strategy against primary gastrointestinal malignant melanoma.

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