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CASE REPORT

Surgically resected pancreatic metastasis from nasal malignant melanoma: case report and literature review

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Abstract
A 13-mm mass was observed in the pancreatic head of a 70-year-old woman who had undergone melanoma resection in the nasal cavity 10 years earlier. Endoscopic ultrasonography (EUS) showed that the mass consisted of multiple hypoechoic nodules. EUS-guided fine needle aspiration and pancreatic juice cytologies revealed neoplastic cells positive for HMB45 and melan-A staining with a few melanin granules, indicating the presence of a metastatic malignant melanoma. These additional stainings were evaluated after surgery. In the surgically resected specimen, the mass had multiple nodule-like structures, some of which were brown colored. Immunocytochemistry and electronic microscopy findings confirmed the diagnosis of malignant melanoma. Microscopic findings were similar to the nasal specimen; therefore, the pancreatic lesion was considered to be a metastasis from the nasal cavity.

Keywords Endoscopic ultrasonography · Pancreatic juice cytology · Endoscopic ultrasonography-guided fine needle aspiration · Pancreatic tumor · Pancreatic cancer · Neuroendocrine neoplasm

Introduction

Melanoma is a rare malignancy that originates from melanocytes. The incidence rate of melanoma per 100,000 persons-year has been reported to be 1–2 in Japan [1, 2]. Although melanoma typically develops on the skin that has been exposed to sunlight, it is less common in areas that have not been overexposed to sunlight, such as eyes, the nervous system, the nose, the mouth, and the digestive system. Melanomas often metastasize to several organs. However, pancreatic metastasis is extremely rare.

We have encountered a case of pancreatic metastasis from nasal melanoma which was resected 10 years ago and present our findings herein. Moreover, pancreatic metastasis of melanoma is reviewed and discussed in reference to previous publications.

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Case report

A 70-year-old Japanese woman visited our hospital for investigation of a pancreatic mass which was identified on screening abdominal ultrasound (US). The patient underwent endoscopic removal of malignant melanoma in the right nasal cavity at another hospital when she was 60 years old. Since the melanoma regionally recurred 9 months after removal, she received five courses of chemotherapy using dacarbazine, nimustine and vincristine (DAV) after heavy particle radiotherapy. Heavy particle radiotherapy was performed again because of recurrence in the right ethmoid sinus 50 months later. As the patient did not recognize these previous treatments as being for melanoma, although she had received full explanation in the previous hospital, she told us "I have only received treatment for a nasal polyp" before surgery. This history was clarified by contacting the hospital where she received the previous treatment after surgery for a pancreatic lesion.

US showed a 13-mm, well-demarcated, round-shaped, hypoechoic mass in the pancreas neck. Using endoscopic ultrasound (EUS), this mass was visualized as being hypoechoic on the whole, although it consisted of multiple hypoechoic nodules surrounded by slightly hyperechoic

septum-like structures, forming a honeycomb-like texture, when closely examined (Fig. 1a). From dynamic contrast-enhanced computed tomography (CT), the mass was found to be hypovascular with gradual enhancement in the pancreatic neck (Fig. 2a). From magnetic resonance imaging (MRI), the mass had a low intensity level in both T1- and T2-weighted images and was related to restriction of water proton diffusion, as determined from diffusion-weighted images (Fig. 3). A small notch was observed in the main pancreatic duct (MPD) at the pancreatic neck during endoscopic retrograde pancreatography (ERP), although the MPD was not dilated even on the tail side (Fig. 4a). Cytologies using aspirated pancreatic juice (PJC) and using an EUS-guided fine needle aspiration (EUS-FNA) specimen obtained utilizing a 22-gauge needle with three punctures were performed with preparation using the cell block method. The results showed atypical cells different in size, which were determined to be neoplastic cells, although definite diagnosis could not be confirmed because there were no positive markers specific for epithelial neoplasms, neuroendocrine neoplasms, nor solid pseudopapillary neoplasm (Table 1; Fig. 5). We strongly recommended surgical resection. However, since the patient rejected surgery, the lesion was observed regularly.

Ten months later, the mass increased to 17 mm in size, as determined using US, EUS, and dynamic CT (Figs. 1b, 2b). It massively invaded into the MPD, accompanied by MPD dilation at 4 mm in diameter on both the ampullary and tail sides. On ERP, the notch in the MPD enlarged with MPD dilation, possibly occurring in association with a small filling defect floating on the ampullary side (Fig. 4b).

Serum levels of tumor markers, including carcinoembryonic antigen, carbohydrate antigen 19-9, DUPAN-2, SPan-1, and α-fetoprotein, were all within normal limits.

Considering obvious enlargement of the mass and diameter change of the MPD, subtotal stomach-preserving pancreatoduodenectomy was performed at the patient's request after obtaining written informed consent. From gross observation of the resected specimen, the mass in the pancreatic neck was 14 mm and composed of multiple nodules. Although most of the nodules were grayish, a few were brownish or blackish (Fig. 6a). Microscopic observation revealed that neoplastic cells formed a solid alveolar structure with interstitial fibrous tissue (Fig. 6b). No capsule formation covering the whole mass was observed. There was a cluster of neoplastic cells without continuity with both the main tumor and the MPD wall, which appeared identical to the filling defect floating in the MPD observed during ERP (Fig. 6c). In high power fields, neoplastic cells having a round nucleus irregularly proliferated without intercellular adhesion. Several cells with brownish granules were observed (Fig. 7). Neoplastic cells were positive for HMB45 and melan-A stainings. The brownish color of the granules disappeared after melanin depigmentation using hydrogen peroxide. Electron microscopy revealed melanin granules in the cytoplasm (Fig. 8). Therefore, the diagnosis of a melanoma was pathologically confirmed. The neoplastic cells were diffusely positive for Vimentin and partially positive for CD68 and iron (Fe). The Ki-67 labeling index was approximately 30%, indicating high proliferation potential.

The history of treatment and diagnosis for the nasal lesion were identified by contacting the hospital where endoscopic removal and chemoradiotherapy were performed. The microscopic findings on the specimen of the nasal lesion that was sent from the previous hospital strongly resembled the pancreatic lesion, resulting in a diagnosis of pancreatic metastasis from the nasal melanoma (Fig. 9).

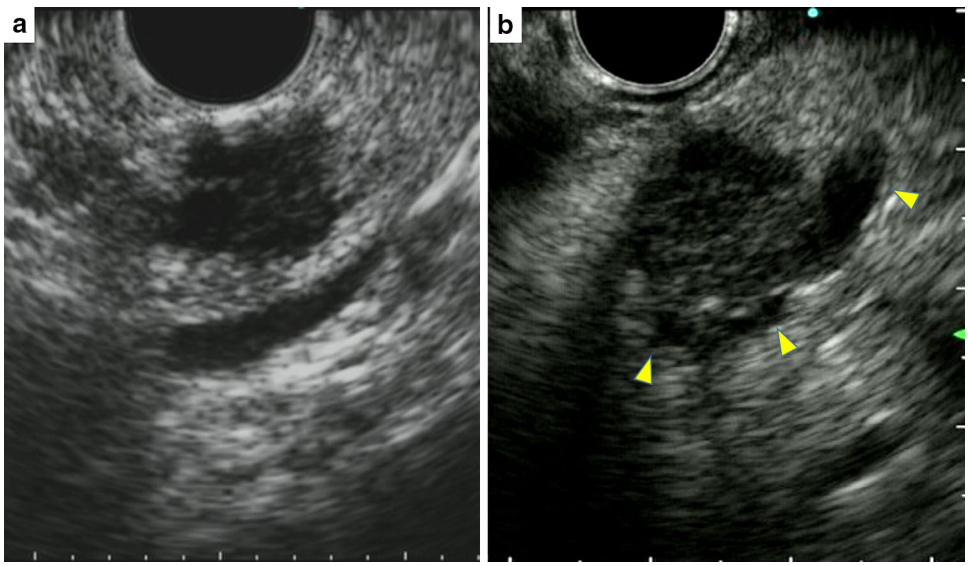

Fig. 1 Endoscopic ultrasonography images: **a** initial examination and **b** examination 10 months after the initial examination. A low echoic mass in the pancreas head consisted of multiple relatively hypoechoic nodules and hyperechoic septum-like structures. The mass invaded the main pancreatic duct (arrow heads) after the follow-up

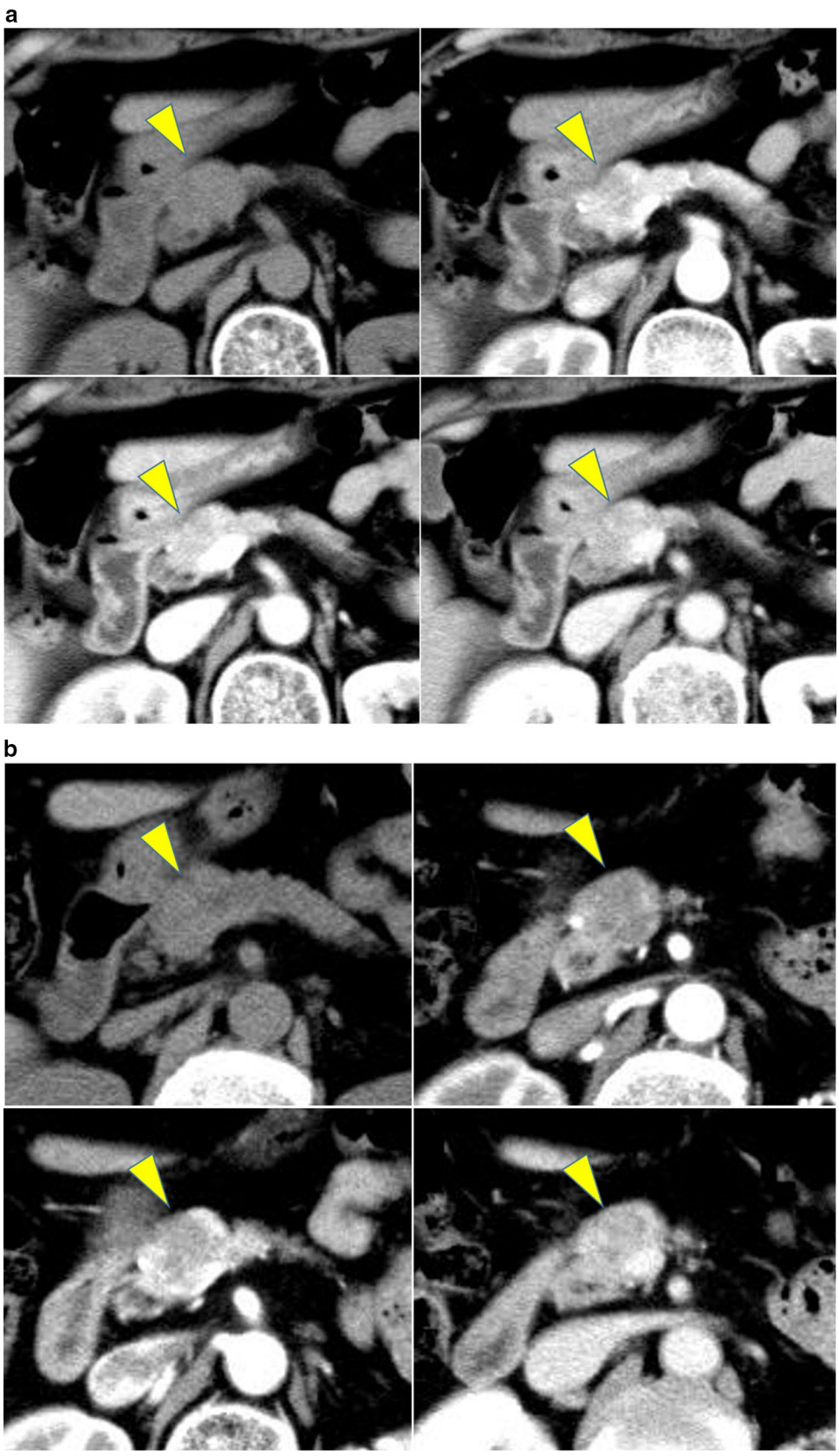

Fig. 2 Dynamic computed tomography scans showing **a** a 13-mm hypovascular mass in the pancreatic head, **b** that grew to 17 mm after 10 months of follow-up. Arrows indicate the mass in the pancreatic head

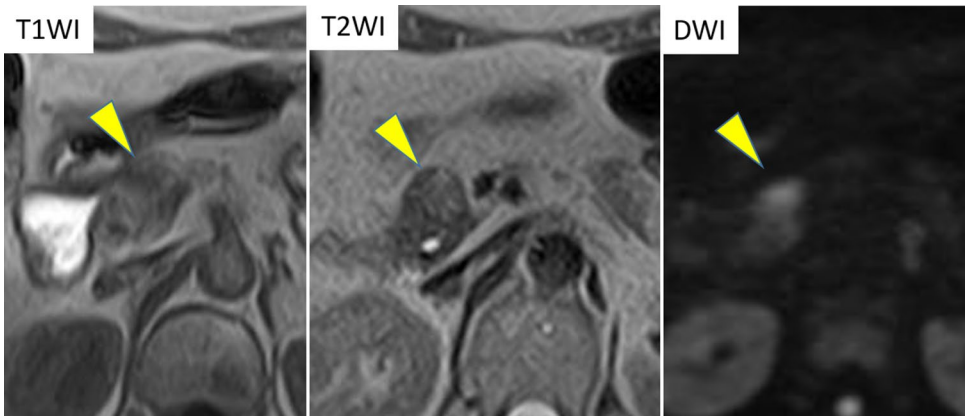

Fig. 3 T1-weighted and T2-weighted magnetic resonance imaging (MRI) scans showed that the mass was hypointense. The signal of the mass was relatively intense in diffusion-weighted MRI scans. Arrows indicate the mass in the pancreatic head

Table 1 Immunochemistry results of preoperative cytological examinations

	Pancreatic juice	EUS-FNA
Ki67 labeling index	5%	< 1%
p53	–	–
MUC1	NA	–
CK	NA	–
CAM2.5	–	–
Chromogranin A	NA	–
Synaptophysin	NA	–
NCAM	NA	–
Vimentin	d++	f+
LCA	–	–
CD3	–	–
CD10	f+	d+
CD20	–	–
S-100	–	–
NSE	–	–
β-Catenin	NA	-
HMB45[a]	d++	d++−
Melan A[a]	d+	f+

All specimens were prepared using the cell block method

EUS-FNA endoscopic ultrasonography-guided fine needle aspiration; *NA* not available; − negative; *f*+ focally positive; *d*+ diffusely positive

[a]Additional postsurgical examination

Pre-operative cytology using pancreatic juice and an EUS-FNA sample was not evaluated specifically for melanoma because previous history of treatment for nasal melanoma was masked. Results of additional evaluation using HMB45 and melan-A stainings were similar, supporting the diagnosis of melanoma (Table 1; Fig. 5). A few cells with brownish granules were identified in careful observation.

Further adjuvant chemotherapy was considered less worthy and was not performed because of previous full DAV therapy. Melanoma did not recur during close follow-up for 7 months. However, the patient's family let us know by phone that she suddenly succumbed for an unknown reason 8 months after surgery.

Discussion

Metastatic pancreatic tumors are rare, involving only 2% of the pancreatic tumors [3–6]. Armed Forces Institute of Pathology (AFIP) (4th edition) has reported that the origins of metastatic pancreatic tumors are a lung (25%), a breast (13%), and melanoma (11%) among 819 autopsy cases (Table 2) [7]. They report that the rates for the originating organ in 190 surgery cases are 23% from a lung, 15% from a kidney, and 5% from a melanoma. On the other hand, the organs to which the melanomas metastasize are commonly skin, lymph nodes, and the digestive system, and they rarely metastasize to a lung, the liver, the brain, and a bone. Pancreatic metastasis has been reported to be extremely rare [8].

In previous retrospective studies on metastatic melanoma including few pancreas cases, the survival period has been found to be prolonged in patients with an isolated metastatic melanoma when the metastasis is completely removed [9–11]. Factors related to better prognosis have been reported to be the absence of lymph node metastasis, a long interval between the treatment for the primary lesion and appearance of metastasis, slow progression of the metastatic lesion, and a low level of serum LDH [9–11]. However, evidence for metastatic melanoma in the pancreas has been insufficient because of a lack of reports due to its rarity [12, 13].

From a MEDLINE search using "melanoma," "metastasis," and "pancreas" as search criteria, 45 cases of resected pancreatic metastasis of melanoma were found between 1960 and December 2018 [14–42] (Table 3). The originating organ, the size of the metastatic mass, and the interval to metastasis highly differ. Similar to common melanoma, the character of metastatic melanoma varies with each case because of the genetic heterogeneity. Among 34 patients with descriptions of the follow-up outcomes after resection,

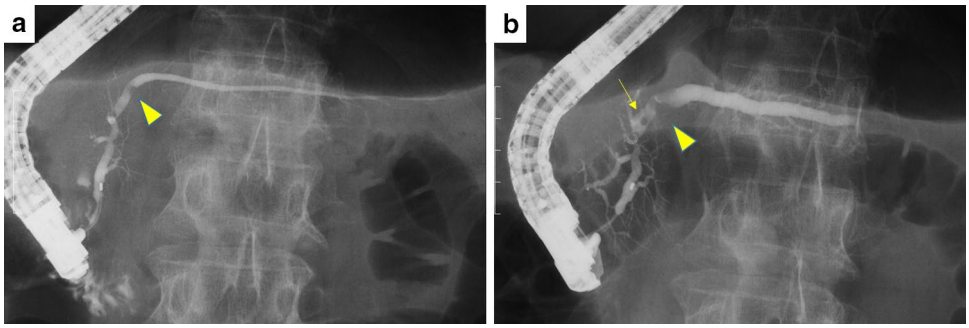

Fig. 4 Endoscopic retrograde pancreatography: **a** the main pancreatic duct was not dilated on the initial examination, although there was a notch in the pancreatic neck, which indicated tumor invasion (arrow head). **b** The main pancreatic duct was clearly dilated and the notch (arrow head) was enlarged at the 10-month follow-up. A small round-shaped filling defect floating in the main pancreatic duct (arrow)

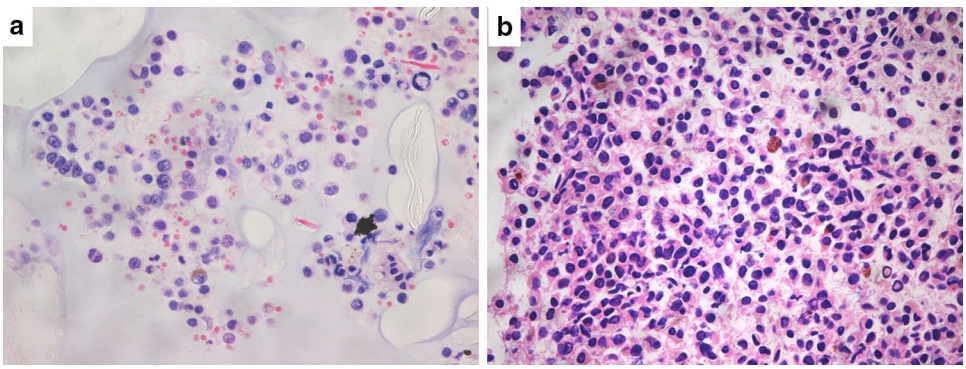

Fig. 5 Preoperative cytology specimen prepared using the cell block method showing round-shaped atypical cells and a few melanin granules (hematoxylin–eosin staining): **a** pancreatic juice cytology and **b** endoscopic ultrasound-guided fine needle aspiration

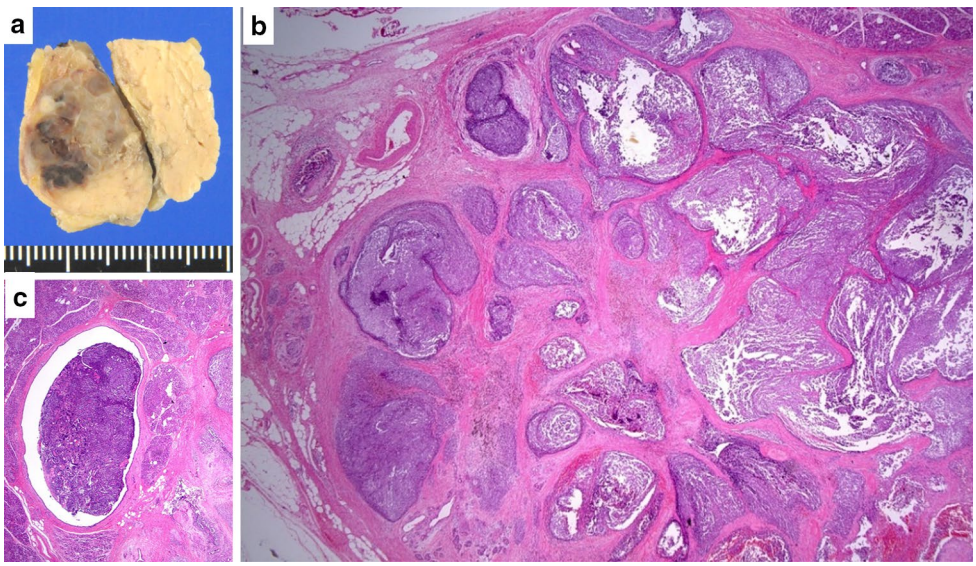

Fig. 6 Surgically resected specimen of a pancreatic mass: **a** gross appearance, **b** hematoxylin–eosin (HE) staining, × 1.25, and **c** HE staining, × 1.25. The mass consisted of multiple nodular structures divided by fibrotic tissue (**a, b**). A cluster of neoplastic cells without continuity with both the main tumor and the MPD wall (**c**)

18 patients died from recurrence. The median survival period after resection was 10 months (range, 3–25 months) in 16 cases. Of the 34 with outcomes, 13 of the remaining patients were alive without recurrence during 6- to 108-month follow-up periods, and the other 3 were alive with recurrence (the follow-up period was 8 months, 12 months, and unknown). Although most patients developed recurrence shortly after resection of pancreatic metastasis, 3 patients were alive for > 5 years (76 months without recurrence, 96 months without recurrence, and 108 months with recurrence) among 26 patients with descriptions of the follow-up periods. Surgical resection was found to be effective for a

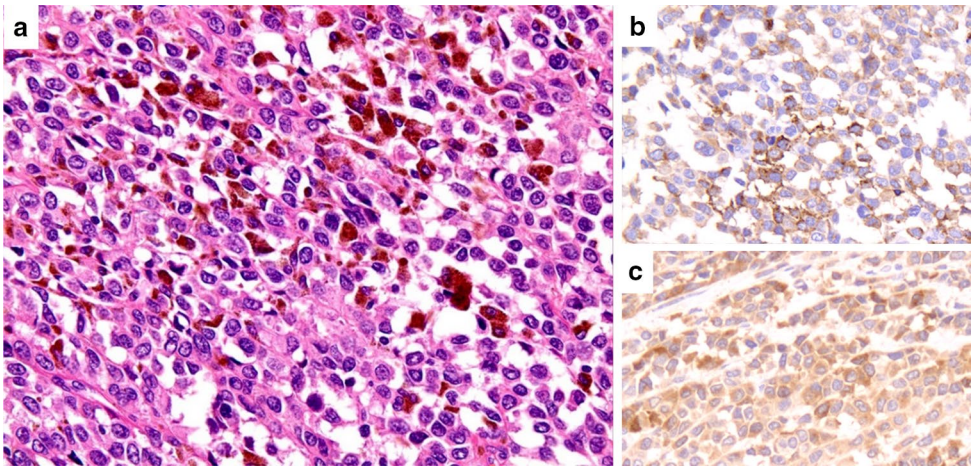

Fig. 7 Surgically resected specimen of a pancreatic mass. **a** hematoxylin–eosin (HE) staining, × 40. **b** HMB45 staining, × 20. **c** Melan-A staining, × 20. Neoplastic cells having a round nucleus irregularly proliferated without intercellular adhesion. Several cells with brownish granules were observed

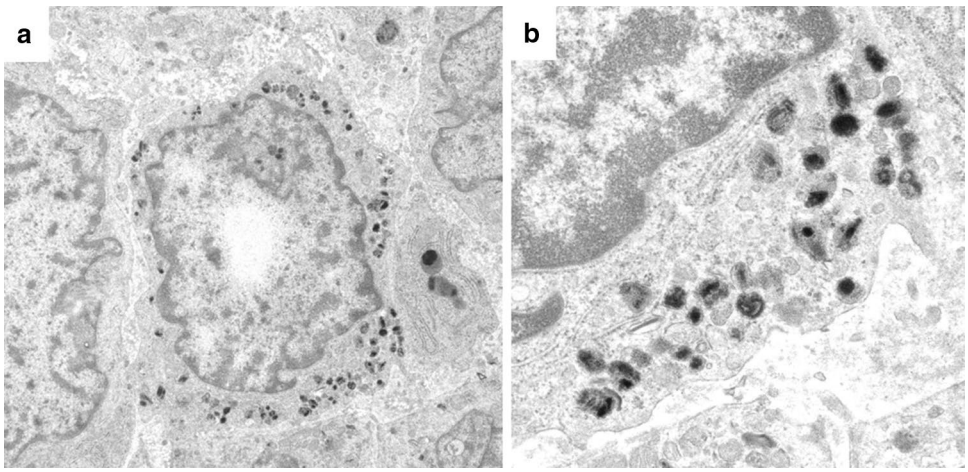

Fig. 8 Electronic microscopic views of the surgically resected specimen revealing melanin granules

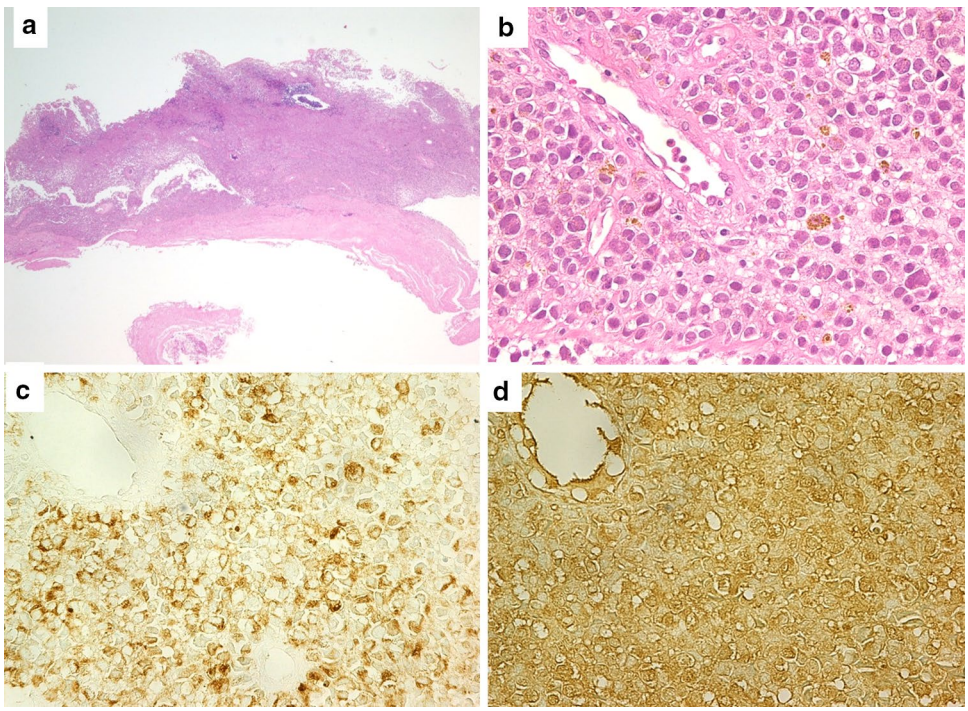

Fig. 9 Specimen of the nasal lesion that was endoscopically resected 10 years before the metastatic lesion to the pancreas was identified. **a** hematoxylin–eosin (HE) staining, × 1.25. **b** HE staining, × 40. **c** HMB45 staining, × 40. **d** NSE staining, × 40

Table 2 Origin of pancreatic metastases (summarized from Reference 7)

Autopsy series ($n=815$)		Surgical series ($n=190$)	
Lung (%)	25	Lung (%)	23
Breast (%)	13	Kidney (%)	15
Melanoma (%)	11	Breast (%)	8
Stomach (%)	10	Colorectal (%)	8
Colorectal (%)	6	Melanoma (%)	5
Kidney (%)	4	Liver (%)	5
Ovary (%)	4	Other (%)	36
Other (%)	27		

few of the patients, although precise selection was difficult before surgery.

On the other hand, recent advances in molecular biology have enabled the development and clinical application of molecular targeted agents for unresectable or recurrent melanoma [43]. In Japan, several drugs, such as the anti-PD-1 antibodies nivolumab, the BRAF inhibitor vemurafenib, the CTLA-4 antibody ipilimumab, and the MEK inhibitor trametinib, have sequentially been approved for melanomas since 2014. Although the present case did not receive additional chemotherapy because she was encountered before such approval, these agents have improved prognosis for similar patients.

It is important to accurately diagnose metastatic melanoma for determining appropriate treatment options, including resection and chemotherapy. In several reports, EUS-FNA has been a useful for making a precise diagnosis before surgery [39, 44]. DeWitt et al. have reported the usefulness of immunohistochemistry with anti-S-100 protein, anti-vimentin, and HMB45 for an EUS-FNA specimen [44]. In the present case, such stainings to evaluate melanoma were not performed before surgery because both clinicians and pathologists did not consider the patient's ultimate diagnosis. However, the tiny specimen obtained using PJC and EUS-FNA was confirmed to be sufficient to preoperatively diagnose the mass as being a melanoma when several stainings were added after surgery. If the previous history of treatment for melanoma had been known, precise diagnosis would have been possible even using such a tiny specimen.

Although such pathological approaches appear useful, specific findings indicating metastatic melanoma using imaging examinations have been unknown. Typical metastatic melanoma resembles common pancreatic cancer because both are similarly hypoechoic in ultrasound-based examinations and hypovascular in contrast-enhanced examinations. In previous reports, metastatic masses in most cases have been solid and well demarcated, although there have been cystic tumors [44] and lesions with diffuse pancreatic swelling [45]. As to MRI findings, melanin pigment which is paramagnetic produces enhances the intensity in T1-weighted images [46, 47]. However, the amount of melanin varies highly among cases, resulting in a variety of signal levels. In the present case, the reason why T1-weighted imaging did not show high intensity at the metastatic mass is probably because of a lack of melanin pigment and the small size of the mass.

In contrast, the multinodular structure may be a key to diagnosing metastatic melanoma in parenchymal organs, such as the pancreas and the brain, unlike skin and luminal organs. This gross appearance was observed using EUS in the present case. Referring to the pictures in several reports, the metastatic tumors appear to have similar multiple nodules, although authors do not mention them [42, 48]. The prevalence of such a structure in metastatic melanomas has not been reported to the best of our knowledge.

In summary, we presented a case of surgically resected melanoma in the pancreas which metastasized from the nasal cavity over a 10-year interval. Gross appearance and microscopic findings showed a multinodular structure which was observed using EUS. There have been cases of pancreatic metastasis of melanoma with a long survival period after resection in previous reports, although it is uncertain whether all patients should be surgically treated or not. Given the recent progress in molecular targeted agents for melanoma, preoperative diagnosis using EUS-FNA or PJC appeared important for determining clinical tactics.

Table 3 Pancreatic resection for metastatic malignant melanoma (searched on MEDLINE)

Author	Year	Case number	Age/sex	Interval (year)	Primary site	Tumor size (cm)	Surgery	Follow-up (mo)	Outcome
Das Gupta [14]	1964	1	28/M	2	Skin	NA	DP + duodenal resection	10	Dead
Johansson [15]	1970	1	79/F	12	Ocular	NA	PD	11	Alive w/o rec
Lasser [16]	1990	1	NA	8	Skin	NA	PD	10	Alive w/o rec
Bianca [17]	1991	1	48/M	NA	Unknown	3	PD	12	Alive w disease
Brodish [18]	1993	1	75/F	24	Skin	5	DP + S	8	Alive w disease
Harrison [19]	1997	1	NA	NA	NA	NA	PD	108	Alive w/o rec
Medina-Franco [20]	1999	1	60/M	NA	Unknown	8	PPPD	6	Dead
Wood [21]	2001	8	NA	NA	NA	NA	NA	NA[a]	NA
Hiotis [22]	2002	1	NA	NA	NA	NA	PD	NA	Dead
Camp [23]	2002	1	62/F	6	Ocular	5	DP + S	20	Alive w/o rec
Nifkarjam [24]	2003	2	45/F	12	Ocular	3	PPPD	6	Alive w/o rec
			55/M	13	Ocular	NA	TP	7	Alive w/o rec
Carboni [25]	2004	1	55/F	9	Skin	8	PD	4	Dead
Crippa [26]	2006	1	36/F	2.7	Skin	NA	PPPD	14	Dead
Belágyi [27]	2006	1	28/F	6	Skin	6	Enucleation	4	Dead
Eidt [28]	2007	4	NA	3	NA	7	PPPD	12	Dead
			NA	4	NA	5	PPPD	25	Dead
			NA	14	NA	5	PPPD	30	Alive w/o rec
			NA	4	NA	8	PPPD	76	Alive w/o rec
Lanitis [29]	2009	1	69/M	5	Skin	4.5	PD	96	Alive w/o rec
Vagefi [30]	2009	1	57/F	28	Ocular	2.2	DP + S	NA	NA
Sperti [31]	2010	1	48/F	3	Unknown	2.9	DP + S	24	Dead
He [32]	2010	1	39/M	5	Ocular	18	DP + S	25	Alive w/o rec
Goyal [33]	2011	5	33/F	5	Skin	2	PPPD	4.5[†]	Dead
			50/F	3	Skin	NA	PPPD	15[†]	Dead
			69/M	NA	Unknown	4.5	DP + S	26[†]	Dead
			73/F	22	Skin	4	PPPD	3[†]	Dead
			58/F	NA	Unknown	10	PPPD	11.4[†]	Dead
Portale [34]	2011	1	43/F	7	Skin	1.7	DP + S	NA	Alive w/o rec
Moszkowicz [35]	2011	1	44/F	7	Skin	1.3	PD	NA	NA
Fernández-Aceñero [36]	2011	1	58/F	8	Skin	NA	PD	8	Dead
Sugimoto [37]	2012	1	45/M	1	Nasal cavity	3.3	DP + S	10	Dead
Wiltberger [38]	2015	2	NA	5.5	NA	NA	TP	NA	Alive w disease
			NA	19	NA	NA	PPPD	NA	Dead
De Maura [39]	2016	1	58/F	NA	Ocular	4	PD	NA	Alive w/o rec
Yagi [40]	2017	1	55/M	5 mo	Oral cavity	2.8	DP	4	Dead
Ben Salma [41]	2017	1	55/F	NA	Unknown	5.5	PD	15	Dead
Liu [42]	2018	1	54/M	6	Skin	3.1	PD	6	Alive w/o rec
Present case	2018	1	70/F	10	Nasal cavity	1.3	PD	7	Dead

M male; *F* female; *NA* not available; *DP* distal pancreatectomy; *PD* pancreaticoduodenectomy; *S* splenectomy; *PPPD* pylorus-preserving pancreaticoduodenectomy; *TP* total pancreatectomy

[†]The median survival time was 0.9 years; alive w/o rec, alive without recurrence; alive w disease, alive with the recurrent or residual disease

[a]The 5-year survival rate was 37.5%

Compliance with ethical standards

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

Human rights All procedures 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 for all examinations and surgery.

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