Radiology Case Reports 18 (2023) 4422–4430

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Case Report

Pancreatic mixed acinar-neuroendocrine carcinoma with intraductal growth: A case report with radiologic–pathologic correlations ☆

Hiroshi Baba, MD[a], Yasunari Yamada, MD[a,], Kazuhiro Tada, MD[b], Yusuke Kuboyama, MD[c], Kengo Fukuzawa, MD[b], Kentaro Iwaki, MD[b], Mitsuteru Motomura, MD[d], Ryo Takaji, MD[e], Ryuichi Shimada, MD[e], Hajime Takaki, MD[a], Yoshiki Asayama, MD[e]*

[a] *Department of Radiology, Oita Red Cross Hospital, Chiyo-machi, Oita, Japan*
[b] *Department of Surgery, Oita Red Cross Hospital, Chiyo-machi, Oita , Japan*
[c] *Department of Pathology, Oita Red Cross Hospital, Chiyo-machi, Oita, Japan*
[d] *Hepato-Biliary-Pancreatic Internal Medicine, Oita Red Cross Hospital, Chiyo-machi, Oita, 870-0033, Japan*
[e] *Department of Radiology, Oita University Faculty of Medicine, Yufu, Oita, 879-5593, Japan*

ARTICLE INFO

Article history:
Received 13 June 2023
Revised 9 September 2023
Accepted 12 September 2023
Available online 9 October 2023

Keywords:
Pancreas
Mixed acinar-neuroendocrine carcinoma
Intraductal growth
Computed tomography
Magnetic resonance imaging
Radiologic–pathologic correlation

ABSTRACT

Pancreatic mixed acinar-neuroendocrine carcinomas are rare malignant tumors of the pancreas. They are composed histologically of both acinar and neuroendocrine cells. The pancreatic duct is known to be an important site of tumor growth for acinar cell carcinomas, neuroendocrine tumors, and intraductal tubulopapillary neoplasms. To the best of our knowledge, there has been only 1 report of a mixed acinar-neuroendocrine carcinoma growing into the pancreatic duct and no reports detailing imaging findings with this tumor. We here report a 69-year-old man who presented with worsening glycemic control. Multiphase contrast-enhanced computed tomography and magnetic resonance imaging revealed a well-circumscribed mass with poor contrast enhancement in the pancreatic tail region of the pancreatic duct. The intraductal mass showed diffusion restriction on magnetic resonance imaging. These imaging findings are consistent with the expansive, smooth-surfaced polypoid tumor of low vascularity and high cellularity that was diagnosed pathologically. Mixed acinar-neuroendocrine carcinomas should be included in the differential diagnosis of intraductal tumors of the pancreas with poor contrast enhancement and diffusion restriction.

☆ Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

* Corresponding author.
E-mail address: yasunari@oita-u.ac.jp (Y. Yamada).

https://doi.org/10.1016/j.radcr.2023.09.032

Introduction

The exocrine component of the pancreas is composed of ductal and acinar cells and the endocrine component of neuroendocrine cells [1,2]. Ductal adenocarcinomas are the commonest malignancies of the pancreas (>75%), followed by neuroendocrine tumors (NETs) (7%) and acinar cell carcinomas (ACCs) (1%) [1]. Pancreatic neoplasms can exhibit more than 1 line of cellular differentiation [1–3]. Combinations of acinar-endocrine, acinar-ductal, acinar-endocrine-ductal, and ductal-endocrine cells have been reported [4–6]. It has been established that approximately one-third of ACCs express neuroendocrine markers [7]. According to the World Health Organization (WHO) classification, mixed acinar-endocrine carcinomas (MAEC) is a variant of ACC in which endocrine component comprises more than 30% of the tumor and a rare neoplasm [1,8]. To the best of our knowledge, there has been only 1 report of an MAEC growing into the pancreatic duct [9] and no reports detailing the imaging findings of these tumors. Here, we report a patient with a pancreatic MAEC that was growing into the pancreatic duct and the associated radiologic-pathologic findings.

Case report

A 69-year-old man receiving medical treatment for type 2 diabetes mellitus was referred to a local clinic because of worsening glycemic control. He had a history of pulmonary silicosis diagnosed approximately 7 years previously and of prostate cancer diagnosed 3 years previously. He was referred to our hospital for further examination. Laboratory tests revealed high carbohydrate antigen 19–9 (CA19-9) (43 U/mL; reference range <37 U/mL) and HbA1c (10.1%; normal range: 4.0%-6.5%). Serum concentrations of amylase, lipase, carcinoembryonic antigen, DUPAN-2, and SPAN-1 were within the normal range. Computed tomography (CT) revealed a mass with a diameter of 80×20 mm in the main pancreatic duct (MPD) and branch ducts within the pancreatic tail. The intraductal mass showed isoattenuation compared with the adjacent pancreatic parenchyma on noncontrast images, and appeared well-circumscribed and poor contrast enhancement in all phases of triple phase contrast-enhanced CT (CE-CT) (Fig. 1). This intraductal mass showed low signal intensity (SI) on TI-weighted MR images, and inhomogeneous high SI on T2-weighted images (WI) (Figs. 2a and b). Diffusion-weighted images (DWI) and an apparent diffusion coefficient (ADC) map of the intraductal mass revealed diffusion restriction (Figs. 2c and d). No masses were detected in the pancreatic parenchyma on CT or magnetic resonance imaging (MRI). These imaging findings led to a differential diagnosis of ACC, NET, or intraductal tubulopapillary neoplasm (ITPN), the poor enhancement of the intraductal mass favoring the diagnosis of ITPN. Distal pancreatectomy with splenectomy was performed. Gross examination of the resected specimen revealed an expansive and smooth-surfaced polypoid mass (83 × 20 mm in diameter) in the dilated main pancreatic duct and branch ducts within the pancreatic tail (Fig. 3a). Histologically, the tumor showed acinar, cribriform, and solid patterns of growth with high cellularity and low vascularity (Figs. 3b and c). Immunostaining showed extensive expression of trypsin and BCL-10 (markers for acinar cells), together with expression of synaptophysin (a marker for endocrine cells) in more than 30% of the tumor cells (Figs. 3d-f). On the basis of these histopathologic findings and in accordance with the WHO classification [1], the tumor was diagnosed as an MAEC. The intraductal tumor in the pancreatic tail showed minimal invasion of the pancreatic parenchyma. The surgical margins were negative. On follow-up 22 months after resection, an intraductal mass (56×17 mm in diameter) was detected in the remnant pancreatic head. The findings on CE-CT and MRI were similar to those of the previously resected mass (Figs. 4a-d). Positron emission tomography (PET)/CT using 18F-FDG showed an increased maximum standardized uptake value in the delayed-phase (4.0) compared with that in the early-phase (2.9) (Figs. 4e and f). Laboratory tests revealed high serum CA 19–9 (47 U/mL; reference limit <37 U/mL), similar to the previously resected tumor. A MAEC of the remnant pancreatic head was diagnosed on the basis of these findings. Pylorus-preserving pancreato-duodenectomy was considered. However, combined chemotherapy (tegafur–gimeracil–oteracil potassium: TS-1) and radiotherapy (50.4 Gy/28 fr) was considered preferable because of the patient's silicosis-related impaired lung function. The intraductal tumor in the remnant pancreatic head decreased in size from 56×17 mm to 25×5mm on CE-CT performed 1 month after completion of radiotherapy (Figs. 5a and b). Chemotherapy was continued for 1 year, followed by approximately 1 year drug-free. At the last follow-up visit, approximately 4 years after resection of the intraductal tumor of the pancreatic tail, a further CE-CT showed no evidence of intraductal tumor in the remnant pancreatic head (Figs. 5a and d).

Discussion

MAECs are rare pancreatic malignancies. They were first described in the early 1990s by Klimstra et al. [8] and are composed of both acinar and neuroendocrine cells, each component constituting more than 30% of the tumor [1]. Pancreatic ACCs and NETs are rare pancreatic neoplasms, accounting for less than 1%-2% [6,10] and 1%-5% of primary pancreatic neoplasms, respectively [11,12]. MAECs are generally considered a variant of acinar cell carcinoma and make up 5%-20% of ACCs [13]. MAECs are reportedly more common in middle-aged and older patients (median age, 65 years; range, 45-89 years) and more frequently occur in men (76%) [14]. They are most commonly located in the head of the pancreas and are usually of large volume when diagnosed, with a median diameter of 7.3 cm [14]. In previous reports, MAECs have characteristic findings such as a well-defined expansive mass with capsule, and a lack of or relatively mild vascular and bile duct encasement [15,16]. Hara et al. [14] reported MAEC showed an expansive lobular mass and infiltrated the spleen and the splenic vein and had multiple liver metastases. Some previous reports have described MAECs appearing as hypervascular masses on CE-CT [14,17]. To the best of our knowledge, only

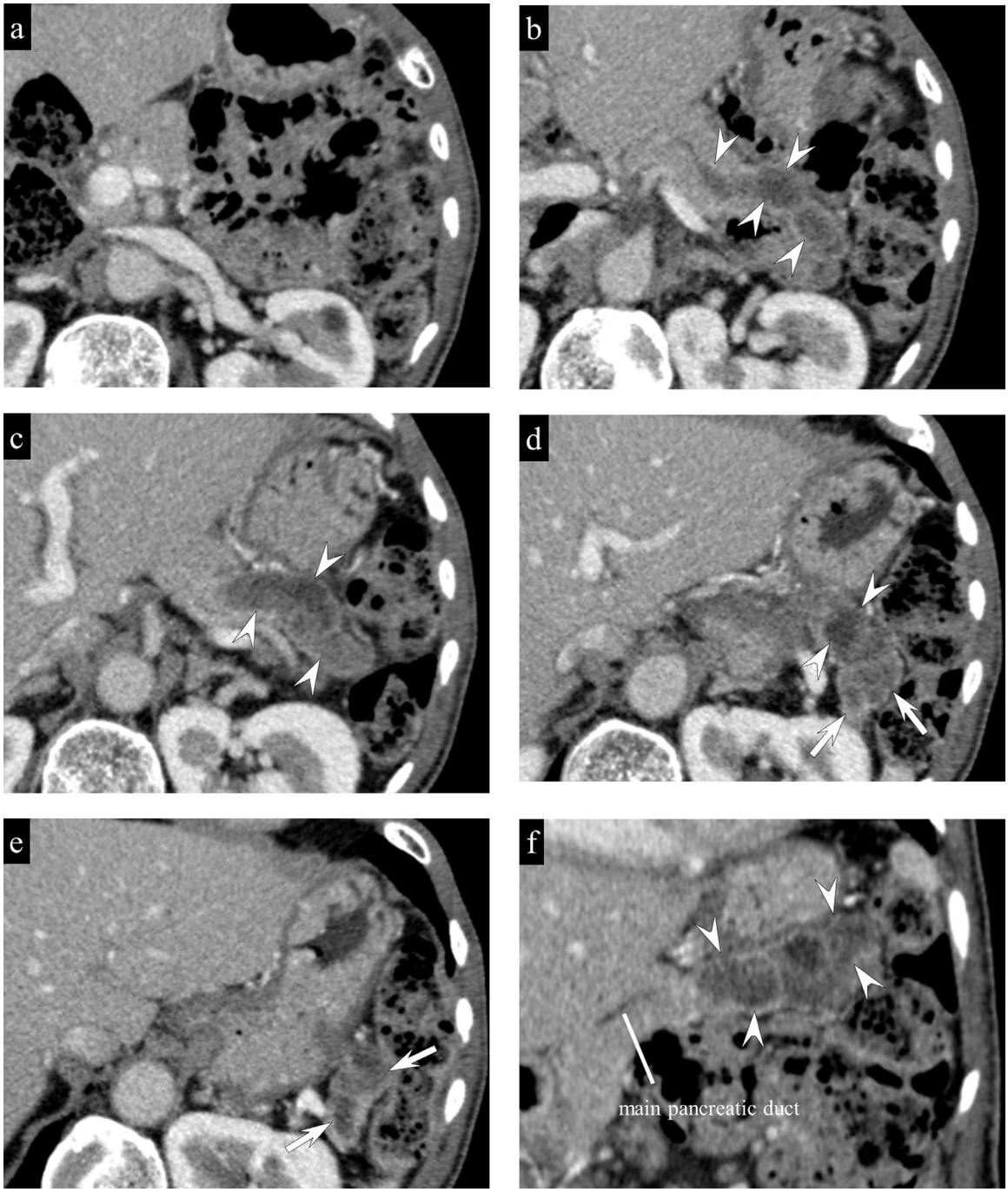

Fig. 1 – Portal venous contrast-enhanced axial (a-e) and paracoronal CT images (f) show an 80 × 20 mm mass in the main pancreatic duct (arrowheads) and branch ducts (arrows) of the pancreatic tail, and pancreatic parenchymal atrophy. The intraductal mass shows well-circumscribed poor enhancement. Mean CT attenuation of the 3 regions in the intraductal mass were 27 Hounsfield unit (HU) on noncontrast enhanced images, 46 HU in the pancreatic parenchymal phase, 45 HU in the portal venous phase, and 44 HU in the equilibrium phase. No mass was detected in the pancreatic parenchyma.

1 case of a MAEC growing into the main pancreatic duct, as in the present case, has been reported. That intraductal tumor showed low attenuation with medium peripheral enhancement on CE-CT [9]. In the present case, the intraductal tumor was well-circumscribed and had poor enhancement on multiphase CE-CT and MRI. DWI and an ADC map of the intraductal mass revealed diffusion restriction. The well-circumscribed appearance was consistent with the macroscopic findings of an expansive and smooth-surfaced polypoid mass. The imaging findings of poor enhancement and diffusion restriction may reflect the low vascularity and high cellularity found on pathological examination [18,19]. NETs, ACCs, and ITPNs are

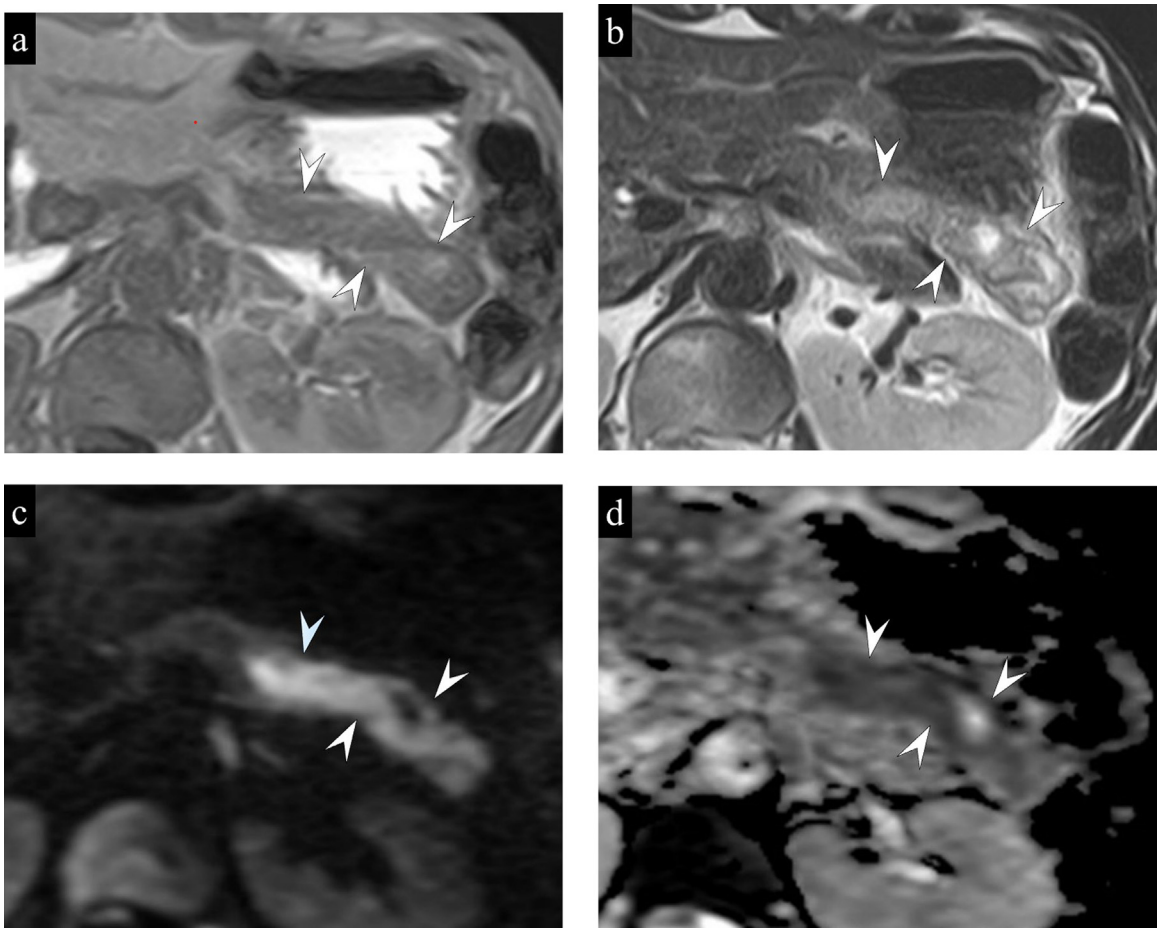

Fig. 2 – On TI-weighted images (a), the intraductal mass (arrowheads) shows low signal intensity (SI) and on T2-weighted images inhomogeneous high SI (b) compared with the adjacent pancreatic parenchyma. Diffusion-weighted image (c) and apparent diffusion coefficient map (d) of the intraductal mass (arrowheads) reveal diffusion restriction.

known to extend into the main pancreatic duct [4,20–26]. Tumor growth into the pancreatic duct is reportedly identified in 10% of ACCs by CT imaging [22] and 54% by histological examination [4]. In previous reports, intraductal tumors in the ACCs show mild enhancement in the pancreatic parenchymal phase on CE-CT [23,24]. Intraductal tumors in the NETs show strong enhancement in the pancreatic parenchymal phase on CE-CT, hyperintense on T2-WI and diffusion weighted MR images, and greater SUV max on F18-FDG PET/CT images [21]. The enhancement pattern in the intraductal tumor in the present MAEC differed from those reported for intraductal tumors in the ACCs and NETs. In contrast, it has been reported that pancreatic ITPNs show low attenuation compared with the adjacent pancreatic parenchyma on unenhanced CT and iso to low attenuation in all phases of multiphase CE-CT [25,27]. The signal intensities of most of these lesions are high on T2WIs and low on T1WIs [25,26], whereas DWI shows diffusion restriction [26,28]. 18F-FDG uptake on PET-CT ranges widely from no to strong uptake [29,30]. Therefore, it was difficult to differentiate our tumor from an ITPN on imaging findings.

Intraductal papillary mucinous neoplasms (IPMNs) are also representative of pancreatic tumors with intraductal tumor growth into the MPD [1] and have high frequency of MPD dilatation of not only the upstream but also downstream of the tumor owing to mucin hypersecretion [31–33]. Co-occurrence of IPMN and NET is a very rare entity [34,35] and Boge et al. [36] reported that neuroendocrine carcinoma was identified as a mural nodule measuring 1.5cm in the dilated pancreatic duct and had marked contrast enhancement with on MRI. In the present case, intraductal tumor causes dilatation of the pancreatic duct simply due to tumor mass itself with poor contrast enhancement and has no dilatation of downstream of the tumor owing to mucin hypersecretion.

The gold standard treatment for MAEC has not yet been established. It is generally agreed that resection is the first-line treatment for resectable MAECs [14,37]. In the present case, we performed a distal pancreatectomy for the intraductal tumor in the pancreatic tail. Because so few cases have been reported, the role of chemotherapy for unresectable MAECs has not yet been established. Given that MAECs have 2 cellular components, chemotherapy regimens that are effective

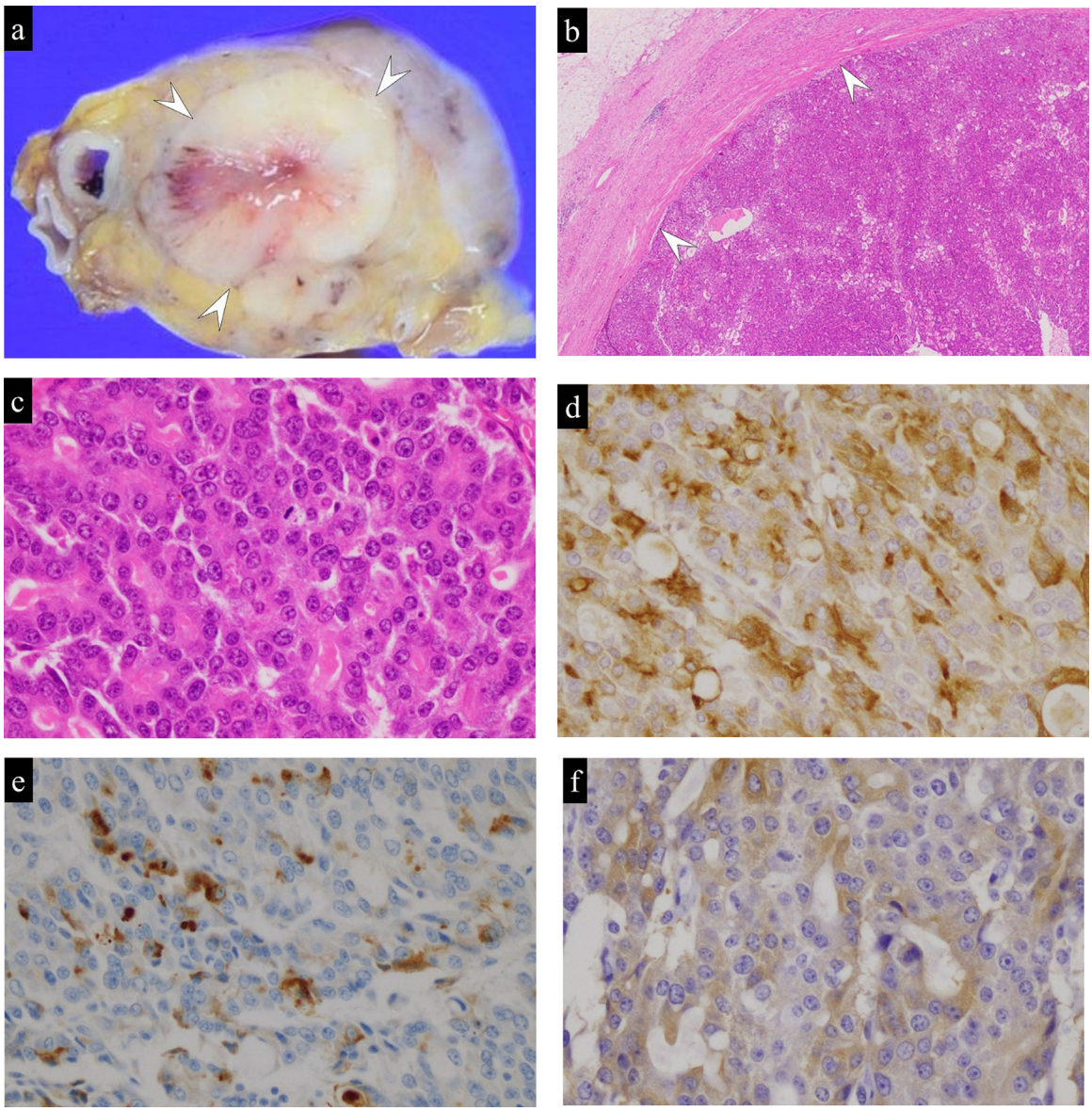

Fig. 3 – Photomicrographs of sections of the resected specimen (a), hematoxylin and eosin stain, ([b] low-power photomicrograph, [c] high-power photomicrograph), and immunostaining for trypsin (d), bcl10 (e), and synaptophysin (f). Grossly, the tumor appears as an expansive polypoid lesion (arrowheads) in the dilated main pancreatic duct (a). Histologically, the tumor cells are growing in solid nests and surrounded by fibrotic pancreatic parenchyma (arrowheads in b). The tumor shows acinar, cribriform, and solid patterns of growth with high cellularity and low vascularity (c). Immunostaining showed extensive expression of trypsin (d) and BCL-10 (e), followed by expression of synaptophysin in more than 30% of the tumor cells (f).

against both elements are ideal [38]. Some studies have documented responses of MAECs to TS-1 chemotherapy [38,39]. It has been suggested that TS-1 may be less effective for the neuroendocrine components of MAECs [39]. In the present case, the patient underwent both radiotherapy and chemotherapy with TS-1 for the intraductal tumor in the remnant pancreatic head. This resulted in the intraductal tumor no longer being detectable on CE-CT. The reported prognosis of patients who have undergone resection of an MAEC is an 80% 1-year overall survival rate and 60% 3-year survival rate according to the Kaplan–Meier method [14]. At a follow-up visit approximately 4 years after resection of the tumor and chemoradiotherapy, the present patient was symptom-free and imaging studies revealed no evidence of tumor recurrence.

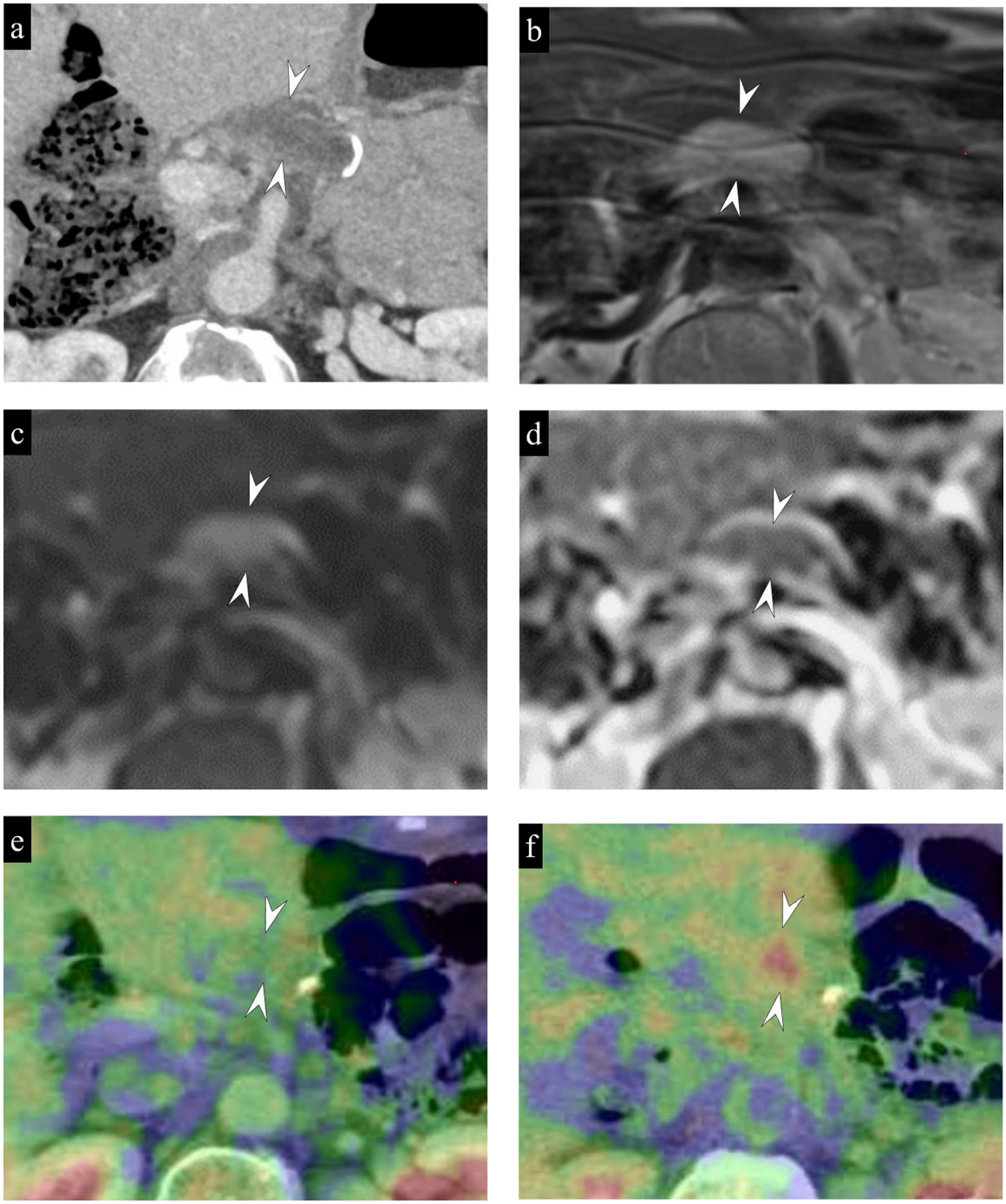

Fig. 4 – Portal venous contrast-enhanced CT on follow-up 21 months postoperatively reveals well-circumscribed 56 x 17 mm mass with poor enhancement in the main pancreatic duct (arrowheads in a). The intraductal mass shows high signal intensity on T2-weighted images (arrowheads in b) and diffusion restriction on diffusion-weighted image (arrowheads in c) and apparent diffusion coefficient map (arrowheads in d). Positron emission tomography/computed tomography using 18F-FDG of the intraductal mass shows a maximum standardized uptake value in the delayed-phase (4.0) (arrowheads in e) compared with the value in the early-phase (2.9) (arrowheads in f).

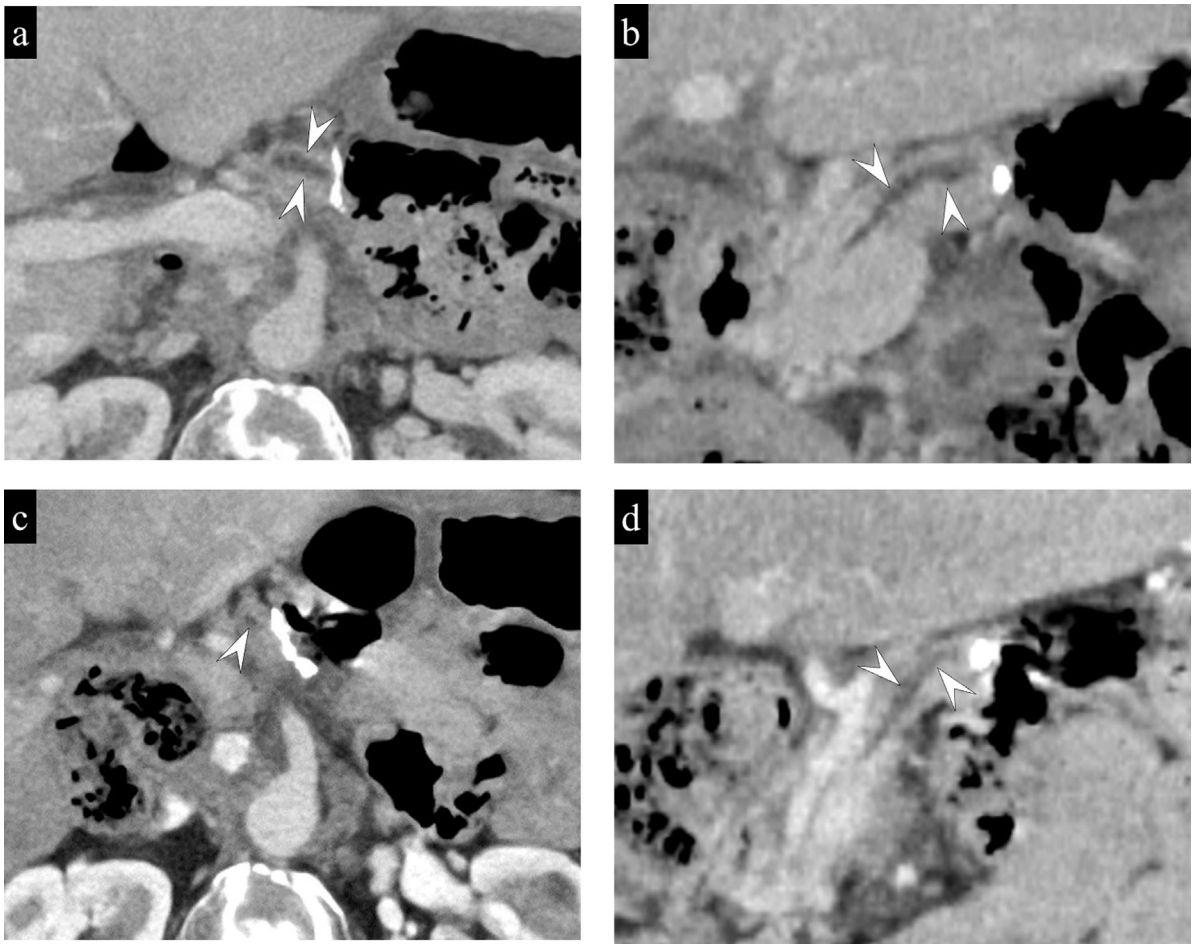

Fig. 5 – The intraductal mass in the remnant pancreatic head decreases in size from 56 x 17 mm to 25 x 5 mm on contrast-enhanced (CE) CT performed 1 month after completion of radiotherapy (arrowheads in a,b). After chemotherapy, the intraductal mass is no longer visible on CE-CT (arrowheads in c,d).

Conclusions

Pancreatic MAECs with growth into the pancreatic duct are rare and few data on imaging findings have been published. Both MAEC and ITPN should be considered in the differential diagnosis of an intraductal pancreatic mass showing poor contrast enhancement and diffusion restriction. Further case studies are required to clarify the imaging characteristics of these rare tumors.

Patient consent

Informed written consent was obtained from the patient for the publication of this report and any accompanying images.

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