Int J Clin Exp Pathol 2016;9(8):8702-8708
www.ijcep.com /ISSN:1936-2625/IJCEP0029627

Case Report

Metastatic cardiac tumor in the right atrium from intraductal papillary mucinous neoplasm of the pancreas

Yuto Monma[1*], Akihiro Nakamura[1*], Sadahide Ono[2], Kenjiro Sato[1], Masanori Kanazawa[1], Kazuki Noda[1], Hideaki Endo[1], Tohru Takahashi[1], Eiji Nozaki[1]

[1]Department of Cardiology, Iwate Prefectural Central Hospital, Morioka, Japan; [2]Department of Pathology, Iwate Prefectural Central Hospital, Morioka, Japan. [*]Equal contributors.

Received April 1, 2016; Accepted June 13, 2016; Epub August 1, 2016; Published August 15, 2016

Abstract: Intraductal papillary mucinous neoplasms of the pancreas (IPMNs) are relatively common neoplasms, and some of IPMNs are known to progress to invasive or non-invasive adenocarcinomas. However, metastases to other organs, especially to the heart were extremely rare. This report describes a case of IPMN with a cardiac metastasis. A 83-year-old man with branch-duct type IPMN was found a tumor in the right atrium adhering to the free wall by transthoracic echocardiography and contrast-enhanced CT scan. The CT images of the pancreas showed no remarkable changes as compared with the previous CT images. Integrated positron emission tomography/computed tomography with 2-^{18}F-fluoro-2-deoxy-D-glucose (FDG-PET/CT) showed a significant FDG tracer uptake in the tumor of the heart, but not in the IPMN lesion. At autopsy, the tumor in the right atrium showed a white multicystic lesion similar to that observed in the pancreas, and it histologically showed the irregular gland structures with cytological atypia compatible with adenocarcinoma. Tumor in the heart showed a strong immunoreactivity for the mucin proteins MUC-1 and MUC-5AC, but focal weak staining for MUC-2. These immunohistochemical findings were similar to those in the pancreas. We concluded that a branch-duct type IPMN transformed into the invasive adenocarcinoma and metastasized to the heart. This is the first report of IPMN with cardiac metastasis to previously undescribed metastatic sites.

Keywords: Cardiac metastasis, intraductal papillary mucinous neoplasm, pancreas

Introduction

Metastasis to the heart is not an infrequent finding. Even though primary cardiac tumors are extremely rare (range from 0.01 to 0.1% on several postmortem studies), the reported incidence of secondary metastatic tumors ranges from 0.7 to 3.5% at autopsy in the general population [1-3]. In regard to the origin of the metastatic cardiac tumors, lung cancer is the most common site followed by breast cancer, malignant melanoma, leukemia, and malignant lymphoma [4]. To date, there are few reports of metastatic cardiac tumors from pancreas, especially those originated from intraductal papillary mucinous neoplasms of the pancreas (IPMNs). IPMNs are the mucin-producing cystic mass originated from the pancreatic ductal system, and they are classified according to the different growth types into three groups (main-duct, branch-duct, and mixed types). Of these subtypes, branch-duct type IPMNs have been believed to progress slowly and to have a better prognosis, and the malignant potential is low [5]. We herein report a rare case of a metastatic cardiac tumor from branch-duct type IPMNs.

Case report

An 83-year-old man who presented a medical history of hypertension, atrial fibrillation, stroke, abdominal aortic aneurysm (AAA), branch-duct type IPMN was admitted to our hospital for a 2-month history of dyspnea, fatigue and loss of appetite. Five years ago, he was incidentally found a cystic lesion connecting to the pancreatic duct in the pancreatic head during a computed tomography (CT) follow-up for AAA (**Figure**

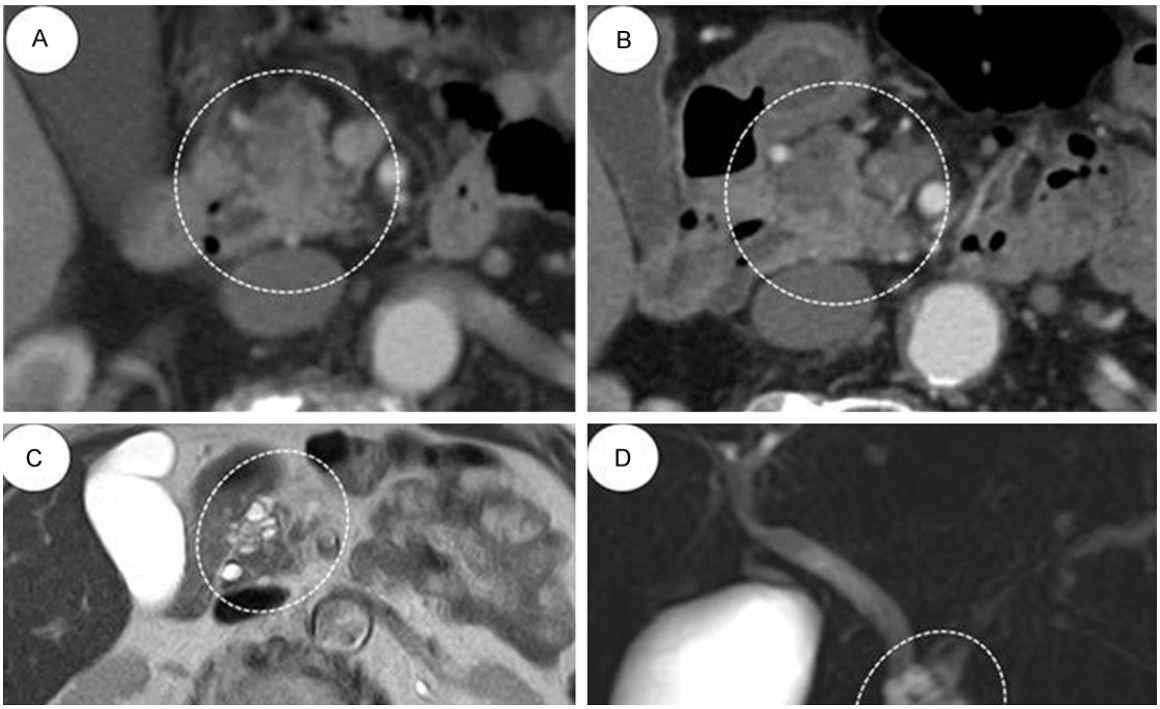

Figure 1. Computed tomography (CT) and magnetic resonance cholangiopancreaticography (MRCP) images of intraductal papillary mucinous neoplasms of the pancreas (IPMN) (dotted-line circle). A. At five years ago, axial contrast-enhanced CT image showed a multichambered lesion located in the head and in the uncinate process of the pancreas. B. Axial contrast-enhanced CT image on the same abdominal level taken during hospitalization. C. T1-weighted image shows a hypointense mass in the uncinate process of the pancreas. D. MRCP image shows dilatation of the pancreas duct and the multilocular cystic lesion in the head of the pancreas, indicating a branch-duct type IPMN.

1A). Magnetic resonance cholangiopancreatography (MRCP) showed the fusiform dilatation of the Wirsung duct at the head of the pancreas and the cystic lesion (**Figure 1C**, **1D**). As a result of CT and MRCP findings, he was diagnosed as having a branch-duct type IPMN.

After admission, he needed the oxygen therapy for hypoxia at rest (oxygen saturation < 93% when breathing room air) and administration of diuretic drug for pitting edema on the lower legs. The level of brain nautriuretic peptide was mildly higher than normal (170.9 pg/ml), and a chest X-ray showed the presence of pleural effusions with the radiographic signs of pulmonary congestion. A CT scan images of the pancreas with a multichambered lesion located in the head of the pancreas (**Figure 1B**) showed no remarkable changes as compared with the previous CT images (**Figure 1A**). Transthoracic echocardiography showed a high echogenic mass in the right atrium adhering to the free wall (**Figure 2A**). Contrast-enhanced CT scan identified it as a large mass attached to the right atrium (**Figure 2B**, **2C**), and it also showed a small mass in the left adrenal gland. The level of cancer antigen 19-9 (CA 19-9, reference values ≤ 37 U/ml) which is a tumor marker associated with pancreatic cancer, was high (31,000 U/ml). Integrated ^{18}F-fluorodeoxy glucose positron emission tomography-computed tomography (FDG-PET/CT) showed a significant FDG tracer uptake in the mass of the heart and the adrenal gland but not in the pancreatic cyst (**Figure 2D**, **2E**). On the day 12, hemorrhagic diathesis was suddenly observed, and the laboratory data was as follows: platelet count, 50,000/μl; prothrombin time international normalized ratio, 1.96; activated partial thromboplastin time, 50.9 sec; fibrinogen, 104 mg/dl; fibrinogen degradation products, 117 μg/ml; D-dimer, 49.9 μg/ml; antithrombin III, 89%; thrombin antithrombin complex, 65.6 ng/ml. He was diagnosed as disseminated intravascular coagulation caused by tumors. He was treated with blood transfusion, platelet transfusion, fresh frozen plasma infusion, nafamostat mesilate and dalteparin, however, on the day 15, he

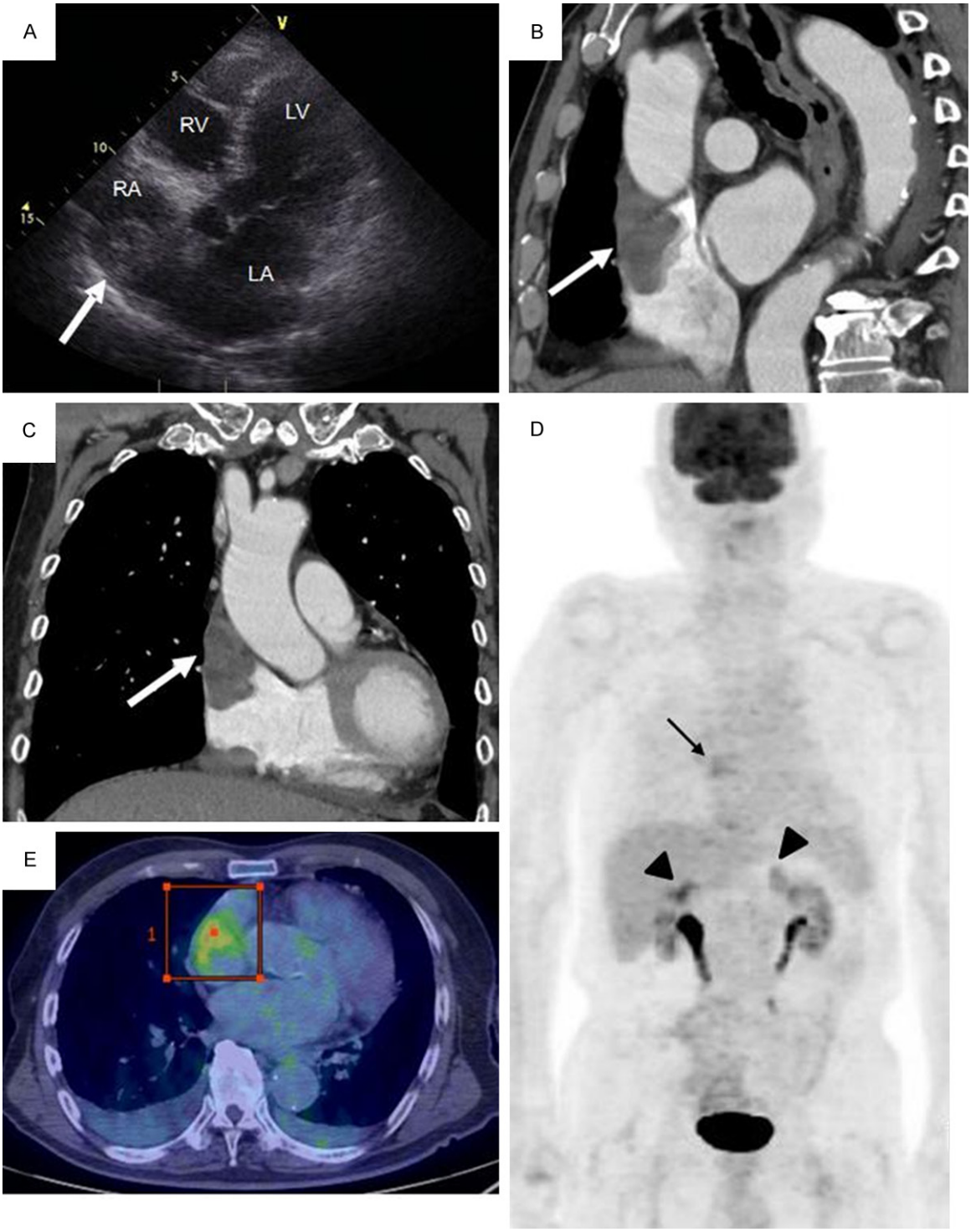

Figure 2. Transthoracic echocardiography (TTE), Computed tomography (CT), and Integrated ^{18}F-fluorodeoxy glucose positron emission tomography-computed tomography (FDG-PET/CT) images of cardiac lesion. (A) Apical 4-chamber view TTE shows a high echogenic mass (arrow) in the right atrium. RV, right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium. (B, C) Sagittal (B) and coronal (C) contrast-enhanced CT images show tumor mass (arrow) attached to the right atrium. (D, E) Coronal PET (D) and apical PET/CT (E) images show high concentration of FDG in the heart (arrow in D; square in E) and the right and left adrenal gland (arrowhead in D).

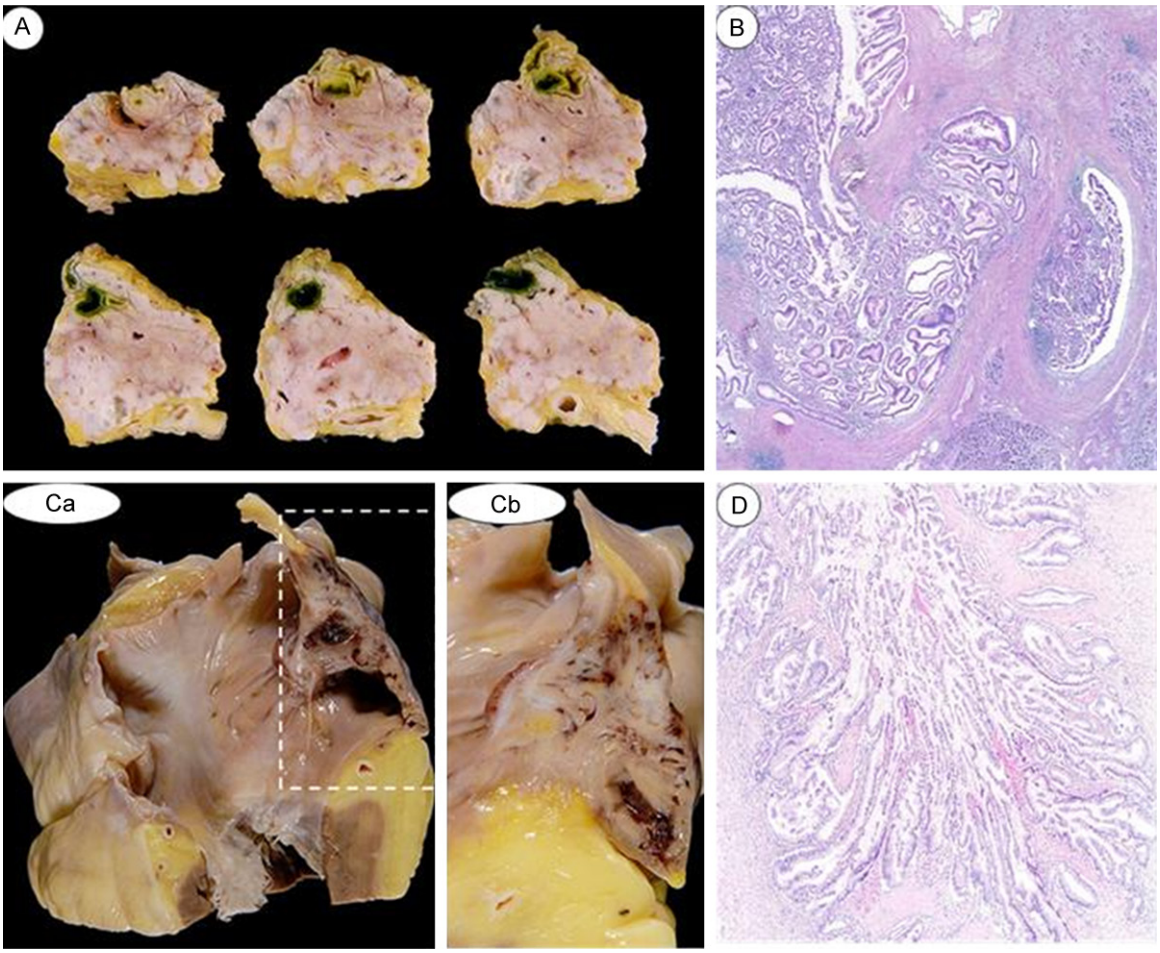

Figure 3. Macroscopic and microscopic examination of the pancreatic and cardiac tumor. (A) The cut sections of the pancreatic tumor located in the head show a white multicystic lesion. (B) Histological finding of the pancreatic tumor shows high-grade dysplasia of IPMN (hematoxylin and eosin stain, × 20). (C) Macroscopic view of the right atrium. The cardiac tumor is shown in dotted-line square (Ca). (Cb) Shows the gross image of the cardiac tumor. (D) Histological finding of the cardiac tumor shows the small gland ductal structures with cellular atypia, which is compatible with that of adenocarcinoma (hematoxylin and eosin stain, × 20).

died of a cerebellar hemorrhage and alveolar hemorrhage.

Pathological findings

Macroscopic examination of the pancreas showed a white multicystic lesion of 15 × 20 mm in diameter located in the head (**Figure 3A**). The right atrium showed an ill defined white cystic leasion which was similar to the one observed in the pancreas (**Figure 3Ca**, **3Cb**). This cystic lesion was also observed in the cortex of the left adrenal gland. These tissue samples were fixed in formalin and embedded in paraffin. Hematoxylin-eosin and immunohistochemical stains were performed. The pancreas histologically showed the irregular gland structures with cytological atypia and papillary proliferation, which was compatible with branch-duct type IPMN (**Figure 3B**). The tumor lesion in the right atrium showed the small gland ductal structures with cellular atypia, which indicated the metastatic adenocarcinoma (**Figure 3C**). In the left adrenal gland, the similar gland structure was observed.

Immunohistochemical findings

The immunohistochemical staining was performed using a Vectastain ABC kit (PK-4002; Vector Laboratories, Inc., Burlingame, CA, USA). Mouse monoclonal antibody against human mucin (MUC)-1 (clone Ma695, IgG1; Leica Biosystems Newcastle, Ltd., Newcastle, UK),

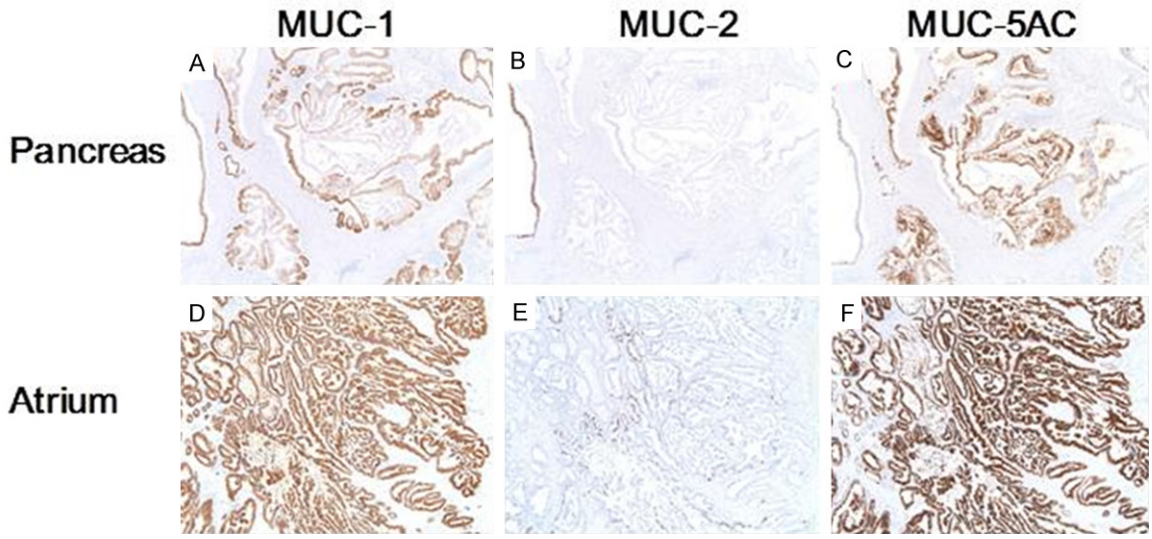

Figure 4. Pathological features of the pancreatic and cardiac tumor. Both the pancreatic and cardiac tumors are immunohistochemically positive for mucin protein, MUC-1 (A, D) and MUC-5AC (C, F). Mucin protein MUC-2 is negative for the pancreatic tumor (B), focally positive for the cardiac tumor (E). (A-F, × 40).

mouse monoclonal antibody against human MUC-2 (clone Ccp58, IgG1; Leica Biosystems), and mouse monoclonal antibody against human MUC-5AC (clone CLH2, IgG1; Leica Biosystems) were used as primary antibodies at a 1:100 dilution. The pancreatic tumor tissue expressed MUC-1 (**Figure 4A**) and MUC-5AC (**Figure 4C**), but negative for MUC-2 (**Figure 4B**), and the cardiac tumor tissue showed positivity for MUC-1 (**Figure 4D**), MUC-5AC (**Figure 4F**) and negativity for MUC-2 (**Figure 4E**). The tumor of the left adrenal gland also showed the same immunostaining pattern as that of the pancreas tumor. From these findings, we concluded that IPMN had transformed and metastasized to the right atrium and the adrenal glands.

Discussion

We present here a case of metastatic cardiac tumor in the right atrium from IPMN. Primary cardiac tumors are relatively rare, but secondary or metastatic cardiac tumors occur comparatively more frequently, with an at least 100 times higher incidence than primary tumors of the heart [1-3, 6]. Several autopsy studies showed that the incidences of metastatic cardiac tumors were estimated to range from 1.7 to 14.0% in patients with cancer and that from 0.7 to 3.5% in the general population [3]. Furthermore, metastatic cardiac tumors have recently been increasing due to the prolonged survival of patients attendant upon the improved chemotherapy and radiotherapy, coupled with increasingly sensitive diagnostic modalities [7]. Metastatic cardiac tumors include malignant lymphoma, malignant melanoma, and leukemia, however, overall numbers are greater for lung and breast cancer, reflecting their higher incidence [4], whereas metastasis from pancreas is very rare and metastatic cardiac tumor from IPMN has not been previously reported.

IPMNs are cystic neoplasms arising from the epithelium of the pancreatic ductal system, which are characterized by gross dilatation of the pancreatic duct due to overproduction of mucus from a proliferative epithelium with papillary growth [5]. IPMNs can be classified into main-duct, branch-duct and mixed type, according to the involvement of the pancreatic duct. Main-duct type IPMNs present as a nodule or mass lesion in a dilated duct or cyst, whereas branch-duct type IPMNs show a multicystic lesion with lack of nodular formation. The neoplastic cells in IPMNs show a variety of atypia ranging from low to high grade, which leads to a diagnosis of adenoma or adenocarcinoma depending on the degree of atypia. Most cases of branch-duct type IPMNs show no or low-grade atypia, and rarely high-grade atypia. Terris et al. reported that the incidence of carcinoma in situ in branch-duct type IPMNs was

15%, and that was 37% in main-duct IPMNs [5]. A long term follow up studies showed that the incidence of the progression to invasive carcinomas was between 1.9 to 5.4% in patients with branch-duct type IPMNs [8]. Thus, pathological behavior could be considered less aggressive in branch-duct type IPMNs, especially those without symptoms as compared with main-duct IPMNs [9].

At baseline and follow-up, the observation using imaging modality such as CT or MRCP is useful because the risk of malignant degeneration is closely associated with the size of cysts and other morphologic features such as dilatation of main duct and nodule formation. According to the Sendai Guidelines, the surgical treatment of branch-duct type IPMNsis recommended for the patients with cysts greater than 3 cm, a dilated main duct greater than 6 cm, or nodular component, but the remainder patients can be managed nonoperatively with routine surveillance [10, 11]. In our case, the tumor in the pancreas was diagnosed as branch-duct type IPMN with CT scan and MRCP images, and identified as a tumor with cystic lesion less than 3 cm in diameter and no nodular component. In addition, the CT scan showed no morphological changes in the pancreatic lesion for five years. Therefore, the observation with imaging modality did not enable us to detect the malignant transformation of branch-duct type IPMN during his lifetime.

It has been recognized that IPMNs differ in their histological and cytological features and in their mucin profile, and four subtypes of IPMNs can be distinguished: an intestinal type, a pancreaticobiliary type, an oncocytic type, and a gastric type. It has been reported that the intestinal type IPMNs are uniformly positive for MUC-2, and some cases focally express MUC-5AC; the pancreaticobiliary type IPMNs are positive for MUC-1; the oncocytic type IPMNs mostly express MUC-1; gastric type IPMNs are positive for MUC-5AC [11, 12]. In our case, the immunohistochemical study showed the positive immunoreactivity for MUC-1 and MUC-5AC in both pancreas and cardiac lesions. The immunoreactivity for MUC-2 was negative in pancreas lesion, whereas it was focally positive in the cardiac lesion. Judging from these results, it seems that the patient in our case had a pancreaticobiliary-type or gastric type IPMN. Although we believe that the same cytological type existed in pancreas and cardiac lesions, further examination with other immunohistochemical marker such as MUC-6, caudal type homebox transcription factor 2 (CDX2) would give us more important information to understand the malignant transformation of branch-duct type IPMNs and metastasis to other organs.

Branch-duct type IPMNs have been thought to be low malignancy potential and few cases of metastasis have been reported. To our knowledge, this is the first reported case of a metastatic cardiac tumor in the right atrium from branch-duct type IPMNs. Although the mechanisms of metastasis to other organs are not clearly known, meticulous observation is mandatory in patients with IPMNs.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Akihiro Nakamura, Department of Cardiology, Iwate Prefectural Central Hospital, 1-4-1, Ueda, Morioka, Japan. Tel: +81-19-653-1151; Fax: +81-19-653-2528; E-mail: Akihiro-Nakamura0223@msn.com

References

[1] Goldberg AD, Blankstein R, Padera RF. Tumors metastatic to the heart. Circulation 2013; 128: 1790-1794.

[2] Bussani R, De-Giorgio F, Abbate A, Silvestri F. Cardiac metastases. J Clin Pathol 2007; 60: 27-34.

[3] Al-Mamgani A, Baartman L, Baaijens M, de Pree I, Incrocci L, Levendaq PC. Cardiac metastases. Int J Clin Oncol 2008; 13: 369-372.

[4] Butany J, Leong SW, Carmichael K, Komeda M. A 30-year analysis of cardiac neoplasms at autopsy. Can J Cardiol 2005; 21: 675-680.

[5] Terris B, Ponsot P, Paye F, Hammel P, Sauvanet A, Molas G, Bemades P, Belghiti J, Ruszniewski P, Fléjou JF. Intraductal papillary mucinous tumors of the pancreas confined to secondary ducts show less aggressive pathologic features as compared with those involving the main pancreatic duct. Am J Surg Pathol 2000; 24: 1372-1377.

[6] Burke A, Virmani R. Tumors of the Cardiovascular System. Atlas of Tumor Pathology. 3rd Series, Fascicle 16. Washington, DC: Armed Forces Institute of Pathology; 1996.

[7] Neragi-Miandoab S, Kim J, Vlahakes GJ. Malignant tumors of the heart: a review of tumor

type, diagnosis and therapy. Clin Oncol (R Coll Radil) 2007; 19: 748-756.
[8] Sohn TA, Yeo CJ, Cameron JL, Hruban RH, Fukushima N, Campbell KA, Lillemoe KD. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. Ann Surg 2004; 239: 788-797.
[9] Arlix A, Bournet B, Otal P, Canevet G, Thevenot A, Kirzin S, Carrere N, Suc B, Moreau J, Escourrou J, Buscail L. Long-term clinical and imaging follow-up of nonoperated branch ductform of intraductal papillary mucinous neoplasms of the pancreas. Pancreas 2012; 41: 295-301.
[10] Tanaka M, Chari S, Adsay V, Femandez-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, Kimura W, Levy P, Pitman MB, Schmidt CM, Shimizu M, Wolfgang CL, Yamaguchi K, Yamano K. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology 2006; 6: 17-32.
[11] Farrell JJ. Prevalence, diagnosis and management of pancreatic cystic neoplasms: Current status and future direction. Gut Liver 2015; 9: 571-589.
[12] Andrejevic-Blant S, Kosmahl M, Sipos B, Klöppel G. Pancreatic intraductal papillary-mucinous neoplasms: a new and evolving entity. Virchows Arch 2007; 451: 863-869.