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Case Report

Pancreatic intraglandular metastasis of the ductal adenocarcinoma: cases of 2 and literature review

Yang Lv[1*], Baobao Xin[1*], Jian'ang Li[1], Ke Chen[2], Dayong Jin[1], Wenhui Lou[1], Xuefeng Xu[1]

Departments of [1]General Surgery, [2]Pathology, Zhongshan Hospital, Fudan University, Shanghai, People's Republic of China. [*]Equal contributors.

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Abstract: Pancreatic intra-glandular metastasis (PIM) of the primary pancreatic ductal adenocarcinoma (PDAC) is fairly rare and has only been reported twice in English literature. Here this study describes 2 new cases with detailed clinic-pathological data of PIM of PDAC. This report aims to demonstrate the infrequently occurred features of the metastatic pancreatic cancer and distinguish the difference(s) between the PIM and multiple pancreatic ductal adenocarcinomas. Based on the existing 2 papers and our 2 cases, a discussion of the histopathological features, clinical behaviors, treatment and prognosis of this tumor characteristics is presented. Moreover, PIM is a novel conception for metastatic pancreatic cancer with relevant optimal options for diagnosis and treatment undiscovered but should be taken into considerations when multiplicities of pancreatic masses happens, surgery is the optimal curative treatment, and the modalities of resection are still in need of taking numerous factors into accounts and in lack of standard criteria.

Keywords: Pancreatic intra-glandular metastasis, ductal adenocarcinoma, treatment, pathological characteristics

Introduction

Pancreatic ductal adenocarcinoma (PDAC) account for the 90% of the occurrence of the pancreatic cancer, which ranks the fourth driving factors of death, as the 2011th American Cancer Society depicts [1]. Due to 1) the lack of the effective methods of early detection; 2) its highly malignant characteristics [2], PDAC is one of the most devastating diseases occurred in the digestive system. In terms of the regarding factors that validly influence the prognosis, infringement around pancreas (organs, lymph nodes and vessels) are normally considered as the most important factors indicating the poor prognosis. Metastasizing to peripheral organ is commonly thought to be a particularly significant problem in dealing with PDAC. However, pancreatic intra-glandular metastasis (PIM), which is likely to be at an advanced stage, has rarely been noticed when multiplicity of pancreatic cancer occurs.

Intra-organ metastasis, from the literature's perspectives, is often discovered and reported in aggressive cases of hepatocellular carcinoma [3] and lung cancer [4]. The report of the intra-pancreatic metastasis of PDAC is extremely rare. To the best of our knowledge, PIM has only been reported twice in English literature, with actually 22 cases available until now [5, 6]. Here this study presents another 2 cases of PIM with morphological findings and literature review.

Materials and methods

A retrospective review of the clinic-pathological data was performed through the detailed medical records of all the 24 PIM cases (including the 22 published cases and 2 present cases). We described the clinical, imaging, morphological, and immunohistochemistry studies of the 2 PIM cases. The study has obtained ethical approval of institutional review board. All the medical data we've found derive from the computerized pubmed search. By the way, the pathological typing and grading of the primary and secondary carcinoma components were both examined by 2 independent pathologists according to the site of origin and criteria of the World Health Organization (WHO) and graded according to the latest proposal [7]. Both the 2 cases were reviewed through the multidisci-

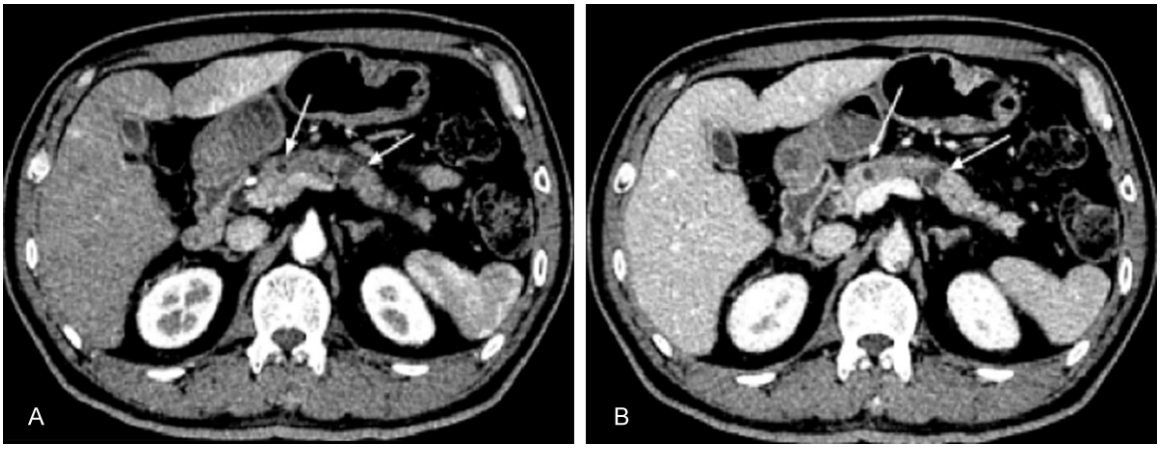

Figure 1. A (arterial phase) and B (venous phase). Contrast CT of case 1 showing 2 separate low-attenuation masses locating at the neck and caudal of pancreas with unclear dilated pancreatic duct.

plinary conference and the pathological sections are re-examined. Following the consensuses and personal experiences, the ultimate pathological diagnoses were the PIM.

Demographic and clinical data, pathological diagnosis and the lesions sites were collected. All data including the common information and tumor characteristics were imported into the computer and a database was established. The statistical analysis was performed using the SPSS 19.0 for Windows statistical software. Continuous data were expressed as mean ± SD.

Result

Case 1

A 65-year-old Chinese man was admitted to our hospital in July 2015 for epigastric pain and distension. No other sign or symptom was displayed. Preoperative laboratory test results included hemoglobin 13.1 g/dL (normally 12-15 g/dL), hematocrit 39% (normally 37-47%), serum total bilirubin 9.4 μmol/L (normally 3.4-17.1 μmol/L), serum direct bilirubin 3.3 μmol/L (normally 0-6.8 μmol/L), glycosylated hemoglobin 10% (normally <6%), glycated albumin 30.2% (normally 11-16%). The serum carbohydrate antigen 19-9 (CA19-9) at that time was 332.6 U/ml (normally <37 U/ml); The serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and cancer embryo antigen (CEA) levels were within normal ranges. The preoperative coagulation function tests and serologic tests for hepatitis B and hepatitis C were negative. Enhanced Computed tomography (CT) of abdominal and pelvis identified a suspicious hypo-attenuation mass in the neck of pancreas accompanied by another lesion of similar density located in the caudal of the pancreas (**Figure 1A**, **1B**). Full preparation and close monitor before the operation was performed on account of his underlying diseases such as diabetes and hypertension. Having underwent a distal pancreatectomy and splenectomy, the patient had a nonspecific recovery period. In the specimen of surgical excision, primary pathological examination using Hematoxylin-eosin staining (**Figure 2A**, **2B**) demonstrated that the ductal adenocarcinoma in the lesion located at both the neck and caudal of the pancreas, with separately grade II and III differentiation, respectively. The PIM speculation were finally confirmed through the immunehistochemical findings that the larger masses were found with CA199 (+++), Muc-2 (-), Muc-5 (+++), Muc-6 (+), Muc-4 (+++), Ki-67 (30%), SMAD4 (-), CK19 (+++), which is actually the same immunohistochemistry expression as the other mass excepting the Muc-4 (-) expression found in this lesion. Through the further histological examination and multidisciplinary conference on the whole surgical specimen, other malignant lesions, such as intra-ductal papillary mucinous neoplasm (IPMN) and neuroendocrine neoplasms (NENs), were not observed around any of the lesions. Nine resected lymph nodes were found negative for metastasis. Based on these findings, the larger mass (2×1.2×1 cm) in the pancreatic body was thought to be the primary lesion, and the other

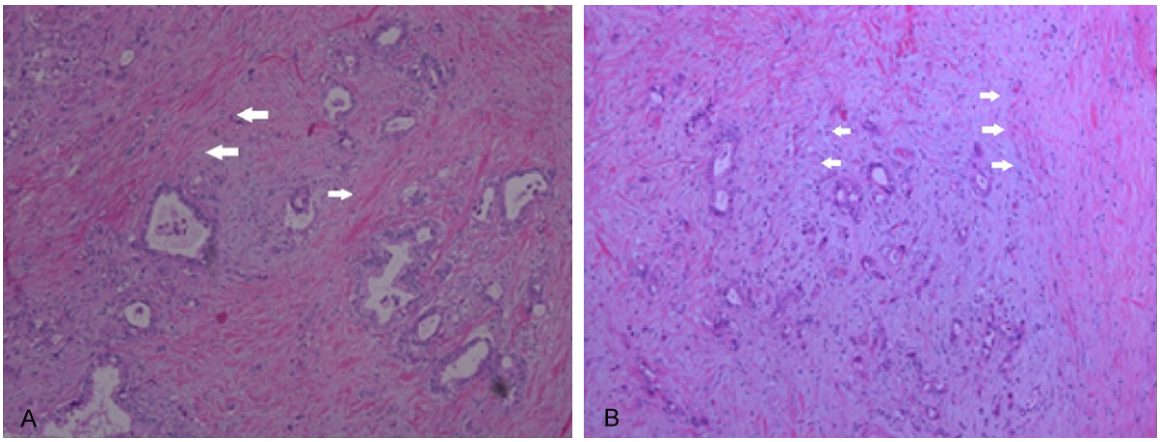

Figure 2. (A and B) Representative case of P-IM (case 1). Histopathological features of the primary tumor (A) and P-IM (B). Poorly differentiated ductal adenocarcinoma infiltrated into the pancreatic parenchyma with an obvious desmoplastic reaction. Similar features are evident in both the primary tumor and the P-IM (marked by arrow). Small monotonous and round shaped cells were arranged in sheet pattern, with relatively basophilic cytoplasm compared with the normal pancreatic parenchyma (Original magnification, ×100).

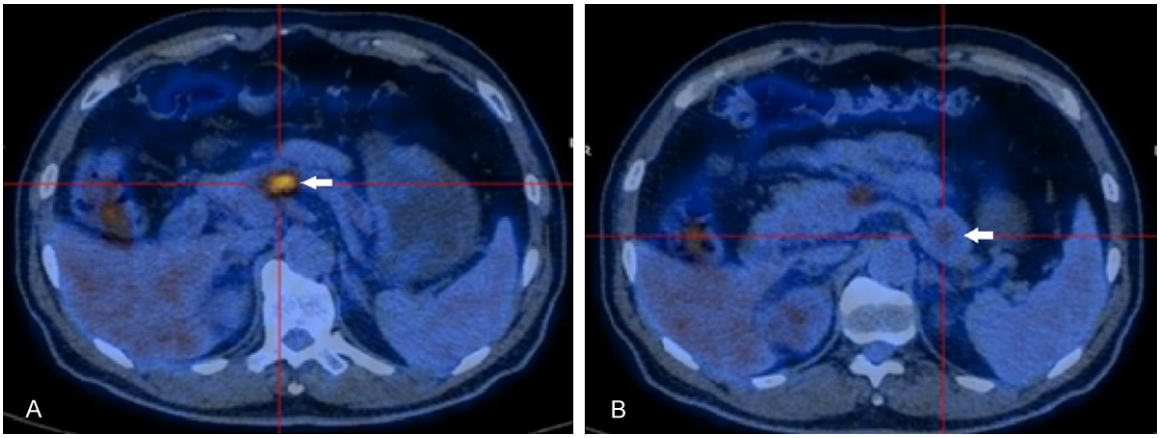

Figure 3. A and B (^{18}FDG-PET). PET-CT showing 2 hypermetabolic masses at the body and tail of pancreas (marked by arrow and at the center of crosshair).

(1.5×1.3×1 cm) were considered to be metastasis.

The patient was discharged with no further treatment after surgery and the 18-fluorodeoxyglucosepositron emission tomography-computed tomography (^{18}FDG PET-CT) performed 4 months after the operation has demonstrated a hyper-metabolic mass measuring approximately 1.9×1.7 cm located in the head of the pancreas with the manifestation of elevated CA199 (253 U/ml), which is suspicious of the tumor recurrence. On account of his poor health status and impossibilities of surgical treatment, the patient has no choice but to elect to interventional therapy.

Case 2

A 56-year-old Chinese man was admitted to our hospital because of the abnormal elevated serum CA199 level (58.3 U/ml) discovered through a regular medical checkup. During a close follow-up period with no clinical manifestations in one month, the patient underwent a magnetic resonance imaging (MRI) and CT in his local hospital, both which indicated only one 1.2×1.0 cm mass located in the pancreatic body with dilated main pancreatic duct, which is firstly suspicious of the IPMN.

Upon arrival, for further diagnosis and treatment of the pancreatic lesion, the patient went

Table 1. The common pathological information of 24 PIM patients

Case	Age/ sex	Primary tumor location	Primary tumor size (cm)	No. of PIM	PIM location (direction)	PIM size (cm)	Distance from the primary tumor (cm)
1	82/M	Head	4.4	1	Cranial	0.1	1.4
2	75/F	Head	1.5	1	Caudal	0.2	1.0
3	62/M	Head	3.4	1	Left	0.5	0.9
4	79/M	Body	2.5	3	Left	0.4/0.3/0.2	1.1/2.1/3.6
5	78/M	Body	3.5	1	Left	1.0	1.0
6	74/F	Body	3.0	1	Left	0.2	2.0
7	72/M	Head	1.8	2	Cranial and Caudal	0.5/0.1	0.5/1.5
8	61/M	Head	3.2	2	Caudal	0.2/0.1	1.4/1.4
9	54/M	Head	3.5	1	Caudal	0.5	0.7
10	61/M	Head	2.0	1	Caudal	0.4	1.3
11	60/M	Head	3.0	1	Caudal	0.1	1.2
12	67/M	Head	3.5	1	Caudal	0.2	1.2
13	66/M	Head	11.4	1	Left	0.1	0.5
14	74/M	Head	3.7	1	Left	0.5	0.5
15	69/M	Head	3.0	1	Left	0.1	0.6
16	62/F	Head/Body	7.8	1	Left	0.9	1.5
17	58/M	Body	3.5	1	Left	0.3	2.5
18	68/M	Head	5.0	2	Caudal	0.4/0.4	0.8/0.7
19	67/F	Head	4.0	1	Caudal	0.7	1.0
20	58/M	Head	2.8	1	Caudal	0.3	1.0
21	61/F	Body	3.1	1	Caudal	0.1	0.6
22	56/M	Body	2.5	3	Caudal	-	0.8
23	65/M	Head/Body	2.0	1	Caudal	2.1	1.0
24	56/M	Body	2.8	1	Caudal	1.5	1.2

Tips: Left is classified as the left direction from the primary tumor location; Caudal is classified as 1) the left direction from the primary location; 2) the secondary tumor(s) location at the very tail of pancreas and(or) near the pancreatic tail; 3) the primary tumor location (Head/Body) is classified at the location in the neck area of pancreas; 4) the first 21 cases were quoted from [6] and the No.23 case were from [5], No.23 and 24 were our cases.

on to have a ^{18}FDGPET-CT which accidentally showed another region of increased focal uptakes by ^{18}FDG at the end of the tail of pancreas, which were not detected by CT and MRI (**Figure 3A**, **3B**). Hepatic cyst and cholelithiasis were also presented through the PET-CT scan. Following the preoperative diagnosis of tumor, distal pancreatectomy and splenectomy were performed. In the specimen of surgical excision, macroscopic examination showed 2 solid tumors which occluded the pancreatic duct, poorly demarcated and about 3.5 cm distance apart from each other, measuring 2.8×1.8×1.8 cm and 2.1×1.5×1 cm, respectively. The incisal margin was drab-yellow, with dilated main pancreatic duct. Nodules of 2 pancreatic ductal adenocarcinomas were present at the mucosa and submucosa with involvement of the nerve tract around the pancreas accompanied by muci-adenomatoid hyperplasia. Immunohistochemistry examinations of the 2 specimen demonstrated the same expression with strong positive reaction for CA199 and CEA, Ki-67 index counting to 60%, diffusely positive for CK7, CK19 and CK20, both which accorded to the characteristics of the ductal adenocarcinoma and were ultimately diagnosed as PIM.

Along with the decreasing numerical value of CA199, the patient has recovered and been discharged from hospital with no complications. Then the patient has accepted routine chemotherapy (Tegafur 20 mg, Gimeracil 5.8 mg, Oteracil 19.6 mg). So far, after 3 periods of regular follow-up (including physical examination, blood chemistry tests, and measurement of serum CA19-9 and CEA), the patient appears no postoperative progression such as tumor recurrence and loco-regional invasion with clini-

Table 2. Characteristics of 24 patients with Pancreatic intra-pancreatic metastasis of Pancreatic ductal adenocarcinoma

Characteristics	n
Men	19 (79.1%)
Age (years)	n=24
Mean	66.5±7.91
Median	65±7.91
Primary tumor location	n=24
Head	15 (62.5%)
Body	9 (37.5%)
Tail	0
Primary tumor size (cm)	n=24
Mean	3.62±2.11
Median	3±2.11
Secondary tumor size (cm)	n=31
Mean	0.61±0.45
Median	0.35±0.45

cal imaging and carcinoma indexes fairly normal. Furthermore, considering of the tumors' malignant grade and metastatic potential, a further evaluation and close follow-up of the patient's clinical information and performance status should be periodically conducted.

The first PIM of PDAC was reported in 2013 [6], with detailed 21 PIM patients' survival analysis; since then 1 case was also demonstrated in English literature. With the addition of 2 present cases, **Tables 1**, **2** summarize the common information of the PIM of PDAC. 19 males and 5 females (ratio 4:1) patients with a median age of 66 years (from 54 to 82). Of all the 24 consecutive patients, there were 9 (37.5%) patients whose primary tumor location is the pancreatic body and 15 (62.5%) patients' primary lesions located at the pancreatic head. Regarding to intra-pancreatic metastasis, the most common sites of metastasis were at the distal direction of the pancreas (n=22, accounting for approximately 91.6%). The Primary tumor sizes in greatest dimension ranged from 1.5 to 11.4 cm, with an average of 3.62 cm. 19 of all the 24 patients were single metastasis and 5 were diffuse. With a further count, the average diameters of the secondary carcinoma were 0.61 cm.

Discussion

At the time clinicians encountered with a patient with imaging findings showing 2 or more separate masses in pancreas, they may naturally consider 2 possibilities: 1) multiple primary tumors developed in the pancreas; 2) one primary tumor concomitant with PIM. Intra-organ metastasis is not a strange definition listed in the English literature. It has already been shown in some types of tumors, such as the HCC [3] and Lung Cancer [4], and some of those metastasizing mechanism and clinic-pathological characteristics have already been clearly investigated in the literature.

Therefore, synchronously occurred multiple lesions in the pancreas is still a confusion of diagnosis. Due to the deficiency of significant cover published in the literature, there is no standard criteria to diagnose a PIM, but similarity to intra-organ metastasis of HCC and lung cancer is required, which could be supported by morphological and immune-histochemical findings. Until 2013, a randomized clinical prospective trial conducted by Oguro [6] demonstrated that the PIM can be defined as follows: 1) located within the pancreatic parenchyma and separated from the dominant; 2) a histological appearance identical to that of the primary tumor; 3) differentiated to the same degree as or less than the primary tumor; and 4) unaccompanied by premalignant lesions of pancreatic ductal carcinoma, such as SPT and IPMN, the presence of which implies that the tumors may be other primary lesions arising via multi-centric carcinogenesis. Backing up to the above viewpoints, our study suggests that the differences between PIM and multiple pancreatic neoplasms could be identified through thorough pathological examinations from the result of immunohistochemistry and gene analysis.

Like the familiar monotonous ductal adenocarcinoma involving the pancreas, PIM of the PDAC usually presents with nonspecific clinical manifestations, such as epigastric pain, abdominal distension, jaundice, as were the laboratory test, which include the elevated CA19-9, CEA and CK [8].

Given the high mortality of PDAC concomitant with PIM [6], it is of utmost significance to attain the fastest means of diagnosis. In the presence of various diagnostic imaging modalities available, contrast-enhanced computed tomography and magnetic resonance imaging remain the standard noninvasive means of diagnosing,

staging and evaluating the pancreatic metastasis. On the other hand, Lachter [9] has reported that ^{18}FDG-PET imaging was superior to CT in the categories of sensitivity, specificity and positive predictive value, which is similarly confirmed in our cases. Furthermore, PET-CT in conjunction with CT or MRI has been shown to be useful in searching for distant pancreatic metastasis, especially within the peritoneal cavity. EUS-guided Fine needle aspiration was once thought of a helpful method to make a definite diagnosis [10]. However, in consideration of the increased risk of complications and tumor dissemination [11], the decision of whether or not to biopsy is always hard to make.

Because of the small number of cases reported to date and the relative lack of large scale follow-up data after operation, there are still many controversies on the matter of the optimal course of treatment. Surgery is the first line of treatment in all the cases that the mass was elevated to be operable. Nevertheless, the undiscovered mechanism and complicated primary and secondary tumor locations of PIM are stumbling blocks to confuse the surgeons to choose an appropriate surgical decision. No studies describe criteria for resectability of metastatic cancer to the pancreas, Reddy [12] has demonstrated in a systemic review that the resection of metastatic cancer to the pancreas should take numerous factors into accounts, including the tumor involvement (or encasement) with superior mesenteric, common hepatic, or proper hepatic arteries the feasibility of the vascular reconstruction and suitable intraoperative operating clearance. In our 2 cases (both primary PDAC located at the body of pancreas metastasizing to the direction of pancreatic tail), distal pancreatectomy and splenectomy were performed. From the PIM case report with similar locations informed by Morita [5], total pancreatectomy was chosen to be the surgical procedure. Of all the 24 PIM patients with a rough count, approximately 14 (58.3%) patients have underwent pancreatoduodenectomy with or without resection of the pylorus ring, 8 (33.3%) distal pancreatectomy and 2 total pancreatectomy. In terms of the suitable surgical procedure, whether aggressive pancreatic resection of PDAC accompanied by PIM can be performed with low perioperative mortality and morbidity are still unknown and in urgent need of large amount of data analysis. However, Resection of primary and metastasizing lesions, on the other hand, is a good treatment option for selected patients and should be considered in patients presenting with good performance status, stable disease and isolated pancreatic metastases [13]. Besides, the benefits of surgical tumor debulking and local and systemic anti-proliferative therapy are still unknown but worth further evaluation.

It has been reported that the presence of PIM is an independent prognostic factor and that venous and lymphatic invasion and recurrence around the metastatic lesions occurs at high rates, the 2-year and 5-year survival rates for patients having PDAC with PIM were 18% and 0%, separately [6]. In our cases, 1 of the 2 cases appeared local recurrence shortly after the operation, and the prognosis was poor; the other patient was still in the period of routine follow-up with no other abnormalities. In spite of the poor outcome, Shinichi Morita [5] believed that it is critical to detect the intraglandular metastasis in pancreas and make the determined pathological diagnosis, which is necessary guide the whole referred treatment. Further research is warranted to probe into the relative prognosis.

Conclusion

In summary, once multiplicity of pancreatic lesions was discovered from the imaging examination, intra-pancreatic metastasis should be taken into considerations. PIM is a relatively new conception of metastatic pancreatic cancer with the valid methods of diagnosis and treatment undiscovered, continued identification and report should be encouraged and required.

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Disclosure of conflict of interest

None.

Address correspondence to: Xuefeng Xu, Department of General Surgery, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai 200032, People's Republic of China. Tel: +008613061626568; E-mail: xuefengxu87@aliyun.com

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