

Pancreatic mass as an initial manifestation of polyarteritis nodosa: A case report and review of the literature

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A 66-year-old woman presented with fever, cholestasis and positive MPO-ANCA. Radiological examination showed a pancreatic mass compressing the bile duct. Therefore, we performed pancreatoduodenectomy. Histopathological examination revealed that necrotizing vasculitis predominantly affecting the medium-sized vessels, spared arterioles or capillaries in the pancreas, a finding consistent with PAN. Unexpectedly, renal biopsy revealed small-caliber vasculitis and glomerulonephritis, supporting MPA. The initial manifestation of a pancreatic mass associated with vasculitis has only been reported in 7 articles. Its diagnosis is challenging because no reliable clinico-radiological findings have been observed. Clinicians should be aware of such cases and early diagnosis followed by immunosuppression is mandatory. Our findings may reflect a polyangiitis overlap syndrome coexisting between pancreatic PAN and renal MPA.

Key words: Classic polyarteritis nodosa; Microscopic polyangiitis; Myeloperoxidase anti-neutrophil cytoplasmic antibodies; Pancreatic mass; Polyangiitis overlap syndrome

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Core tip: A 66-year-old woman presented with a pancreatic mass accompanied by fever, cholestasis and positive myeloperoxidase anti-neutrophil cytoplasmic antibodies. The resected pancreas showed extensive fibrosis associated with necrotizing vasculitis, targeting medium-sized vessels but sparing small-caliber vessels, a finding compatible with polyarteritis nodosa. Unexpectedly, renal biopsy revealed small-caliber vasculitis and glomerulonephritis, supporting microscopic polyangiitis. The initial manifestation of a pancreatic mass associated with vasculitis has only been reported in 7 articles. Although rare, vasculitis should be included in a differential diagnosis for pancreatic masses. Additionally, our findings may reflect a polyangiitis overlap syndrome coexisting between pancreatic polyarteritis nodosa and renal microscopic polyangiitis.

Abstract

Classic polyarteritis nodosa (PAN) that targets medium-sized muscular arteries and microscopic polyangiitis (MPA), characterized by inflammation of small-caliber vessels and the presence of circulating myeloperoxidase anti-neutrophil cytoplasmic antibodies (MPO-ANCA), are distinct clinicopathological entities of systemic vasculitis.

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INTRODUCTION

Systemic vasculitis is characterized by a variety of clinical manifestations and courses, depending upon the organ involved. Among the classifications for systemic vasculitis, the Chapel Hill consensus conference (CHCC) nomenclature is widely accepted^[1,2]. Vasculitis affecting small-caliber blood vessels (arterioles, venules or capillaries) often accompanies anti-neutrophil cytoplasmic antibodies which are postulated to play a major pathological role in developing necrotizing vasculitis^[3]. Such ANCA-associated vasculitis includes the following 3 clinicopathological variants: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis^[2]. Among them, MPA is characterized by non-granulomatous inflammation, few or no immune deposits (pauci-immune), glomerulonephritis and the presence of myeloperoxidase (MPO)-ANCA^[2].

Another category of vasculitis, classic polyarteritis nodosa (PAN), targets small and medium-sized muscular arteries, spares small-caliber vessels and causes diffuse vascular inflammation, ischemia or rupture of affected organs^[4]. Although PAN frequently complicates the skin, joints, kidneys and gastrointestinal system, initial and symptomatic involvement of the pancreatobiliary system has only been reported in rare cases^[5-8].

Herein, we report a patient presenting with fever, cholestasis and a pancreatic mass compressing the bile duct as a clinical feature of PAN.

CASE REPORT

A 66-year-old woman presented with a 2 wk history of intermittent high-grade fever (approximately 39 °C). She did not report arthralgia, myalgia or abdominal symptoms. Approximately 1 mo before admission, she underwent tympanotomy for left otitis media. Her medical history was noncontributory. She denied alcohol and drug use. Laboratory examination showed elevated biliary enzyme levels, including an alkaline phosphatase level of 717 U/L (115-359 U/L), gamma glutamyl transpeptidase levels of 238 U/L (10-47 U/L) and C-reactive protein (CRP) levels of 8.30 mg/dL (< 0.30 mg/dL). Serum levels of amylase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, carcinoembryonic antigen, carbohydrate antigen 19-9 and procalcitonin were normal. The levels of glycated hemoglobin were slightly elevated. Leukocytosis and eosinophilia were not present. Immunological data

showed slight elevations of IgG [1902 mg/dL (820-1740 mg/dL)] and IgA [628 mg/dL (90-400 mg/dL)], but IgM and IgG4 levels were normal. Autoimmune investigations showed elevated MPO-ANCA levels [473 IU/mL (< 3.5 IU/mL)] in addition to a slight elevation of anti-nuclear antibodies (1:64) and rheumatoid factor. Proteinase 3-ANCA, serum hepatitis B surface antigen and hepatitis C virus antibodies were not detected. No bacteria grew on blood culture. Urinalysis revealed proteinuria (2+) and hematuria (2+) with hyaline casts.

A hypoechoic 2.0 cm mass was observed in the pancreatic head on an abdominal ultrasonogram (Figure 1A). The corresponding lesion was an ill-defined hypodense mass with poor enhancement, observed by using a CT scan, and it compressed the distal common bile duct (CBD) and pancreatic duct (PD) (Figure 1B-E). The walls of the gallbladder and bile duct were thickened (Figure 1D, E). A chest CT scan showed slight changes, including bronchial dilation and peripheral inflammation with a centrilobular distribution. Angiographic reconstruction using a CT scan showed normal visceral arteries of the superior mesenteric artery (SMA) and celiac systems. Vascular stenosis or aneurysms were not detectable. Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated a double duct sign with compression of the distal CBD and tortuous dilation of the PD (Figure 1F). Bile cytology and culture were negative according to the results obtained after using the sample *via* naso-biliary drainage.

We could not exclude the possibility of pancreatic cancer as a cause of the patient's fever and therefore we performed a pylorus-preserving pancreatoduodenectomy. The pancreatic mass was soft on palpation and did not invade the adjacent tissues. Intraoperative ultrasonography revealed an ill-defined pancreatic mass with low echogenicity. The postoperative course was uneventful and the patient's fever completely resolved with a reduction of CRP levels.

In the resected pancreas, the focal stenosis in the CBD was approximately 2 cm distal to the ampulla of Vater. There was marked fibrosis adjacent to the intrapancreatic CBD and PD (Figure 2A). The affected small to medium-sized arteries in the fibrosis were characterized by necrotizing arteritis with subintimal fibrinoid necrosis, disruption of the elastic laminae, perivascular fibrosis and inflammatory cell infiltration (Figure 2A, B). Vessel occlusion or thrombus was also observed (Figure 2A). Small-caliber vessels such as the arterioles, capillaries or venules were spared. Granulomatous inflammation and significant eosinophil infiltration were not found. The fibrotic lesion extended longitudinally towards the hepatic hilus along the bile duct. Necrotizing vasculitis was also observed in the walls of the proximal bile duct and gallbladder but their mucosal layers were well preserved (Figure 2C). The duodenum also showed arterial changes. These vascular changes were compatible with classical PAN.

To confirm systemic vasculitis, a renal needle biopsy was performed. Global sclerosis affected 20% of the

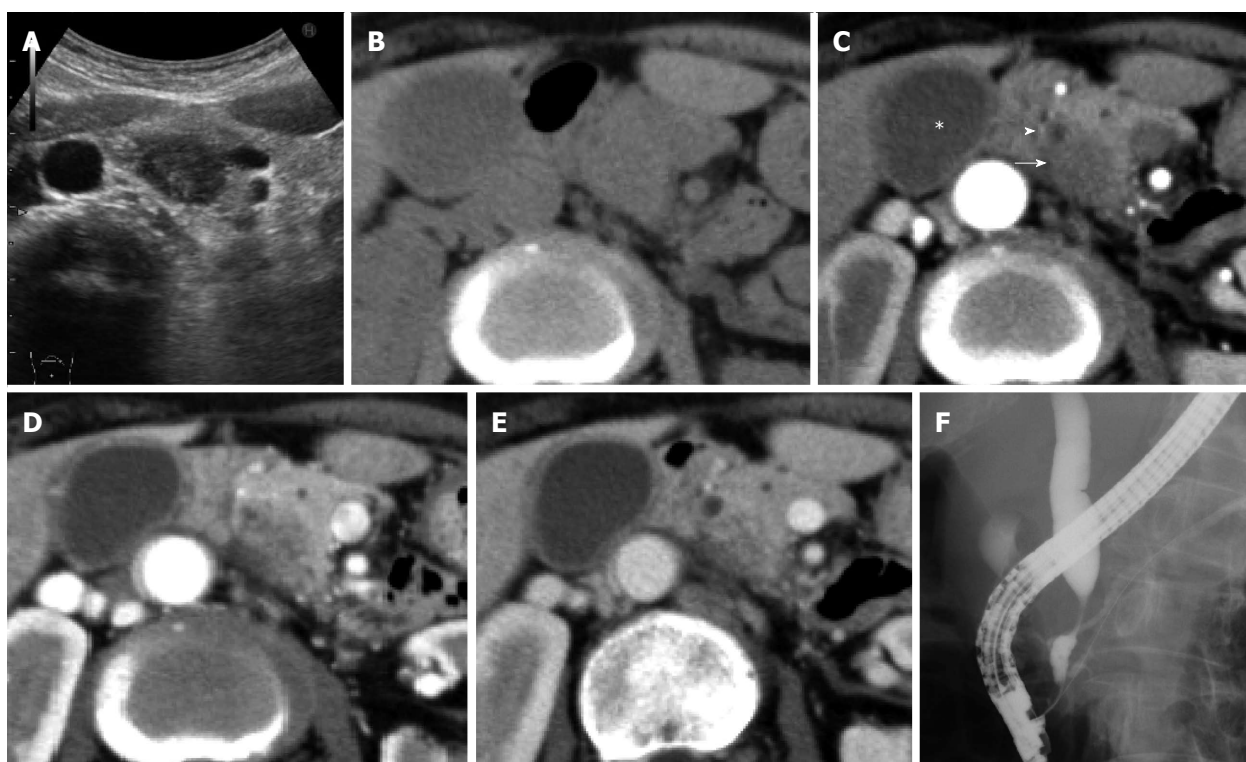


Figure 1 Preoperative images. A: An ultrasonogram showing a slightly ill-defined hypoechoic mass at the pancreatic head; B-E Abdominal CT scans: The pancreatic mass is slightly hypodense on simple CT; C: Enhanced CT shows a non-enhancing mass (arrow) located adjacent to the bile duct (arrowhead) at the arterial phase. Note that the walls of the gallbladder (asterisk) and bile duct are thickened; D and E: The mass has sporadic enhancement at the later phase; F: A Cholangiogram showing a tapered distal biliary stricture consistent with extrinsic compression by the pancreatic mass. CT: Computed tomography.

glomeruli, whereas a cellular crescent was observed in 10% (Figure 2D). Interstitial fibrosis was observed in the tubulointerstitial area. Both active and healed stages of vasculitis were observed in the small arteries and capillaries (Figure 2E). Immune complexes were not detectable. These pathological findings were compatible with the renal changes of MPA according to the CHCC nomenclature^[1,2].

Therapy with prednisone and cyclophosphamide was undertaken to induce remission of the systemic vasculitis. The patient has remained asymptomatic 6 mo after the operation.

DISCUSSION

In the present patient, a pancreatic mass accompanied by fever and cholestasis was observed; surgical removal successfully improved the patient's clinical symptoms and data. Pathological study demonstrated extensive vascular injury in the pancreas, bile duct, gallbladder and duodenum. The affected vessels were small and medium-sized arteries and arterioles and capillaries were spared, a finding consistent with classic PAN^[1,2,4]. Initial clinical manifestation of vasculitis in the pancreatobiliary system is uncommon, with only a few reports documenting pancreatitis or cholecystitis^[7]. Other forms of pancreatic vasculitis, including mass formation, are extremely rare. The articles reporting a pancreatic mass associated with vasculitis were collected through a literature search with

the words “vasculitis”, “pancreas”, “tumor” or “mass” in their title. Among them, 7 articles providing radiological and histopathological descriptions were reviewed (Table 1). Including our case, there were 3 PAN^[5,6], 3 GPA^[8-10] and 2 localized PAN^[11,12]. The former 2 were major vasculitis presenting with a tumor-like lesion in the urogenital system and breast or kidney, respectively^[6]. The median age was 62 years (range: 44-66 years), with a male predominance (5:3 ratio). Three patients were Japanese, 2 were white and 1 was Jewish. The symptoms were varied and nonspecific, including abdominal pain (5 patients), fever (3 patients), otitis media (2 patients) and jaundice (1 patient). All lesions were 2-3 cm in diameter and were localized in the head (6 patients), neck (1 patient) and both body and tail of the pancreas (1 patient). The gallbladder was also affected in 2 PAN patients. Among 4 cases analyzed, ANCA was positive in 3 (GPA, 2; PAN, 1). Use of glucocorticoids and a cytotoxic agent was effective in all cases if treated, otherwise rapid deterioration of necrotizing vasculitis was fatal, as shown in case 5. These findings indicate that early introduction of immunosuppressive treatment based on accurate diagnosis is crucial for a better outcome.

One of the obstacles in treatment strategy for a vasculitis-induced pancreatic mass is the difficulty in diagnosing it. Our review showed that 7 of 8 patients were diagnosed only after surgery or autopsy (Table 1). Besides neoplasm, the pancreatic mass can encompass a variety of diseases, such as an inflammatory pseudotumor

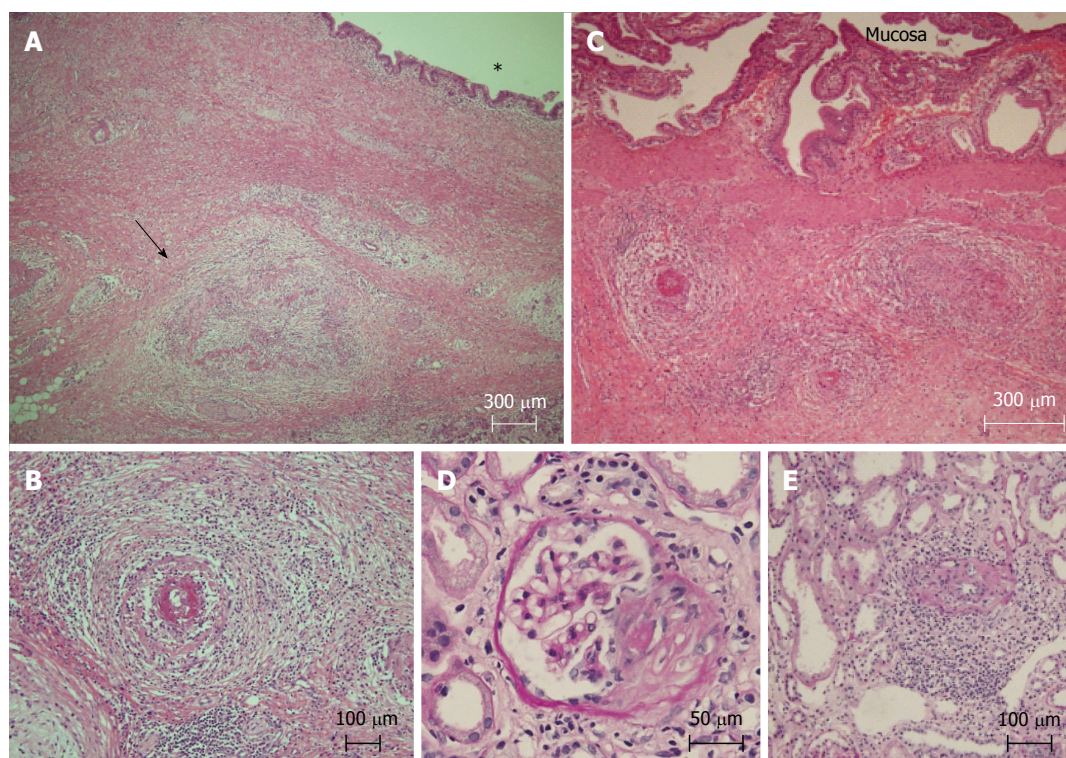


Figure 2 Histological findings of the pancreas, gallbladder and kidney. A: Pancreatic fibrotic changes adjacent to the bile duct (asterisk) are evident. An obliterated medium-sized artery (arrow) is accompanied by cellular infiltration and destruction of the wall. The bile duct mucosa is intact (hematoxylin-eosin stain; original magnification, $\times 40$); B: The affected small-sized artery in the pancreatic fibrosis is characterized by necrotizing arteritis with subintimal fibrinoid necrosis and inflammatory cell infiltration (hematoxylin-eosin stain; original magnification, $\times 100$); C: The arteries of the gallbladder are also involved: the mucosa is preserved (hematoxylin-eosin stain; original magnification, $\times 40$); D and E: Renal biopsy showed segmental sclerosis and collapse with a fibrocellular crescent (D: Periodic acid-Schiff's stain, original magnification, $\times 200$) and vasculitis of a small-sized artery (E: Periodic acid-Schiff's stain, original magnification, $\times 100$).

Table 1 Reported cases of pancreatic tumor associated with vasculitis

Ref.	Age/sex/race etc.	Final diagnosis	Symptoms	Sites involved	Prior diagnosis	Tumor size	Diagnostic criteria	Outcome	
								Pancreas	Patient
Ito <i>et al</i> ^[11]	44/M/ Japanese	Localized PAN	Epigastralgia	Head	No	ND	ND	Underwent PD	Discharged
O'Neil <i>et al</i> ^[8]	62/M/ White	GPA	Jaundice Otitis media Nasal ulceration	Head Gallbladder	No	ERCP: CBD stenosis 3 cm CT: mass US: hypoechoic ERCP: CBD stenosis	ANCA (+) Needle biopsy: non diagnostic Renal biopsy: confirmed	Improved on CYC + CS	Improved on CYC + CS
Damani <i>et al</i> ^[5]	46/F/ ND	PAN	Right upper abdominal pain	Neck	No	2 cm US: hypoechoic CT: low attenuation, nonenhancing mass	Needle biopsy: non diagnostic Postoperative histopathology	Cholecystectomy Distal Px	Died (20 d) Various complication
Kariv <i>et al</i> ^[6]	65/M/ Jewish	PAN	Epigastralgia Weight loss Low grade fever	Head	No	3 cm CT: mass	Needle biopsy: chronic pancreatitis	Underwent PD	Remission on CS
Matsubayashi <i>et al</i> ^[9]	65/M/ Japanese	GPA	Left abdominal pain Constipation Low grade fever Tympanitis	Body and Tail	S/O GPA	ND CT: Enlargement of pancreas with sporadic low density lesions	¹²⁵ I-PR3-ANCA (+) Autopsy	No	Died Hemorrhagic pneumonia Diffuse necrotizing pancreatitis
Tinazzi <i>et al</i> ^[10]	48/F/ ND	GPA	Mid-epigastric pain	Head	No	2 cm: US: Hypoechoic MRCP: Obstruction of pancreatic duct	Postoperative histopathology	Underwent PD	Improved on CYC + CS
Gonzalez-Gay <i>et al</i> ^[12]	75/M/ White	Localized PAN	Epigastralgia	Head	No	ND	Postoperative histopathology	Underwent PD	Discharged

Our case	66 /F/ Japanese	PAN Renal MPA	Otitis media Fever	Head Gallbladder Bile duct Duodenum	No	2 cm US: Hypoechoic CT: Hypodense Non-enhancing	MPO-ANCA(+) Postoperative histopathology	Underwent PD	Improved on CYC + CS Discharged
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PAN: Polyarteritis nodosa; ERCP: Endoscopic retrograde cholangiopancreatography; CBD: Common bile duct; PD: Pancreatoduodenectomy; GPA: Granulomatosis with polyangiitis; US: Ultrasonography; ANCA: Anti-neutrophil cytoplasmic antibody; CYC: Cyclophosphamide; CS: Corticosteroids; Px: Pancreatectomy; S/O: Suspect of; PR3: Proteinase 3; MRCP: Magnetic resonance cholangiopancreatography; MPA: Microscopic polyangiitis; MPO: Myeloperoxidase.

(IPT). IPT includes autoimmune pancreatitis, groove pancreatitis and lipomatosis^[13]. As shown in Table 1, regardless of different types of vasculitis, vasculitis-associated masses were hypoechoic and hypodense with poor encasement on a CT scan, making it difficult for differentiation from pancreatic cancer or IPT. For a focal pancreatic lesion, fine-needle biopsy is widely used with abdominal or endoscopic ultrasonography and it is useful in autoimmune pancreatitis^[14]. However, fine-needle biopsy has potential sampling error problems; indeed, ultrasound or CT-guided needle biopsy failed to be diagnostic for pancreatic GPA (case 2) and PAN (cases 3 and 4). Negative findings do not exclude the possibility of malignancy and there is a risk of needle tract seeding or dissemination of tumor cells^[15]. Thus, the diagnostic procedure is challenging. Some clinicians do away with the preoperative evaluation in patients with operable focal lesions of a clinically and radiologically suspicious malignancy. The common use of ANCA tests in the future would enhance preoperative diagnosis and avoid unnecessary radical operations.

Another interesting finding in this case was the coexistence of different entities of vasculitis, such as PAN in the pancreatobiliary system and MPA in the kidneys. The renal histopathological findings of small-caliber vessel (arteries and capillaries) vasculitis and positive MPO-ANCA supported the MPA diagnosis^[2,3]. PAN and MPA had often been diagnosed together until the proposal of the CHCC nomenclature and distinguishing between these 2 entities is not clinically always straightforward^[16]. Our case may represent the so-called polyangiitis overlap syndrome which is characterized by systemic vasculitis with features that overlap more than 1 type of vasculitis^[17]. Alternatively, it is possibly a coincidence or part of the MAP or PAN spectrum. Renal MAP has been reported to complicate vasculitic disorders that can be attributed to PAN, such as a rupture of branch of the celiac^[18] or SMA system^[19] and coronary angiitis^[20].

In conclusion, we encountered a patient with a pancreatic mass associated with PAN. A literature review revealed that pancreatic masses have been reported in 7 patients with primary vasculitis. Because of its rarity and lack of reliable discrimination from pancreatic cancer, clinicians should be aware of such cases and that early diagnosis followed by immunosuppressive treatment is mandatory.

COMMENTS

Case characteristics

A 66-year-old woman presented with a pancreatic mass accompanied by fever.

Differential diagnosis

An inflammatory pseudotumor and pancreatic neoplasms, including cancer.

Laboratory diagnosis

Laboratory examination showed elevated levels of biliary enzymes (alkaline phosphatase and gamma glutamyl transpeptidase), C-reactive protein and myeloperoxidase-anti nuclear cytoplasmic antibodies.

Imaging diagnosis

An abdominal computed tomography revealed an ill-defined 2.0 cm pancreatic mass with poor enhancement compressing the distal common bile duct (CBD) and pancreatic duct, as well as the thickened walls of the CBD and gallbladder.

Pathological diagnosis

The resected pancreas revealed extensive fibrosis associated with necrotizing vasculitis targeting medium-sized vessels and sparing small-caliber vessels.

Treatment

The patient underwent surgical resection followed by immunosuppression after pathological diagnosis of polyarteritis nodosa.

Related reports

A pancreatic mass as an initial manifestation of vasculitis is extremely rare, with only 7 cases reported in the literature.

Experiences and lessons

The case emphasizes that vasculitis should be included in the differential diagnosis of a pancreatic mass accompanied by fever.

Peer review

Although immunosuppression is the optimal treatment for a vasculitis-associated pancreatic tumor, the diagnosis is challenging because of its rarity and lack of discrimination from pancreatic cancer.

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