

CASE REPORT

Idiopathic Acute Recurrent Pancreatitis - A paraneoplastic Syndrome?

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ABSTRACT

A Forty-seven-year-old male patient presented for evaluation of recurrent episodes of acute pancreatitis. Imaging studies including EUS and laboratory evaluation did not reveal any clear etiology. The patient was felt to have idiopathic acute recurrent pancreatitis. A few months later he was diagnosed with metastatic non-small cell lung cancer with pancreatic metastases. While it is possible that the initial presentation could have been due to metastatic cancer, this was felt to be unlikely given the negative workup. The possibility of acute pancreatitis as a para-neoplastic syndrome was considered. A detailed discussion and literature review follows.

INTRODUCTION

Acute recurrent pancreatitis may sometimes be due to a more sinister underlying problem. We present a case of a patient with unexplained acute recurrent pancreatitis who unfortunately went on to develop metastatic non-small cell lung cancer with pancreatic involvement.

CASE PRESENTATION

A Forty-seven-year-old gentleman presented for evaluation of acute recurrent pancreatitis of unclear etiology. He denied significant alcohol intake and imaging studies/laboratory data did not suggest gall stone disease. As per the radiology report, MRI/MRCP done at an outside facility was concerning for a small non-visualized segment of main pancreatic duct in the body but was otherwise normal.

EUS (endoscopic ultrasound) evaluation of pancreas at our institution was normal (**Figures 1, 2, 3**). Reactive peri-pancreatic lymphadenopathy was noted. A diagnosis of idiopathic recurrent pancreatitis was considered. The patient did not want to pursue genetic studies.

The gentleman re-presented 5 months later for celiac plexus neurolysis (CPN) for pain relief. By this time, unfortunately, he had been diagnosed with metastatic non-small cell lung cancer (NSCLC of the left upper lobe) with neuroendocrine features. He continued to have attacks of recurrent acute pancreatitis. He had also undergone an

ERCP (endoscopic retrograde cholangio-pancreatography) at the referring hospital. As per the procedure report, the pancreatogram was normal and a pancreatic stent was placed (for post ERCP pancreatitis prophylaxis).

At the time of repeat endosonography, the pancreatic stent was removed. EUS guided CPN was performed. EUS evaluation of the pancreas revealed at least 2 discrete less than 10 mm hypoechoic oval/round lesions in the pancreatic body that were not previously seen (**Figure 4**). The main pancreatic duct appeared normal. Findings were consistent with metastases to the pancreas. Diagnostic confirmation with FNA (fine needle aspiration) was not performed given documented metastatic lung cancer, poor functional status and risk of pancreatitis associated with EUS-FNA.

The disease progressed despite palliative chemotherapy and the patient subsequently passed away.

DISCUSSION

Metastases to the pancreas are rare and reported incidence ranges from 2 to 5% [1, 2].



Figure 1. Normal pancreatic body.

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Abbreviations CPN celiac plexus neurolysis; EUS endoscopic ultrasound; FNA fine needle aspiration
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Figure 2. Normal pancreatic head.



Figure 3. Normal gallbladder.



Figure 4. EUS 5 months later – hypoechoic lesions in the pancreas.

Common primary cancers known to metastasize to the pancreas include renal cell cancer, melanoma, lung cancer, colorectal and breast cancer.

Up to 12% of patients with pancreatic metastases can present with synchronous extra-pancreatic metastases [3, 4].

Most patients (up to 35%) are asymptomatic. Common symptoms include jaundice, abdominal pain, gastrointestinal bleeding, weight loss and pancreatitis [3]. There appears to be some correlation between size of metastatic lesions and clinical symptoms [5].

Three different types of pancreatic metastases have been described based on review of CT findings [6]. A single localized metastasis is most common (50 to 70%). Diffuse homogeneous attenuation of the pancreas (15 to 40%) and multifocal metastases (5 to 10%) has also been recognized. Pattern of vascular enhancement may be useful in identifying the primary tumor [4].

Several mechanisms have been hypothesized for metastases induced pancreatitis. Direct obstruction of main pancreatic duct by the metastases or peri-pancreatic compression secondary to lymph nodes can cause activation of proteases and secondary autolysis. This is the most likely pathway and has been noted in up to 40% of patients [7]. Vascular compromise due to neoplastic destruction can cause pancreatitis. Other causes include alcohol, gall stone disease and medications such as anti-neoplastic agents.

In a few patients, pathologic investigation has not shown evidence of metastatic tumor deposits [8], raising the possibility of acute pancreatitis as a para-neoplastic syndrome. This phenomenon might have been at play in our patient with negative index EUS evaluation who subsequently developed metastatic lung cancer.

Small cell lung cancer appears to be the predominant type of lung cancer causing pancreatic metastases (up to 50%) [9] although metastases have been noted with other types of lung cancer [10]. Our patient was noted to have non-small cell lung cancer.

In a post-mortem series, pancreatic metastases were noted in 25 to 40% of small cell lung cancer [11]. However metastases induced acute pancreatitis (MIAP) occurred in only 0.12% in a study of patients with lung cancer [12]. The severity of pancreatitis in MIAP tends to be mild to moderate. To the best of our knowledge, there is one case report of severe pancreatitis with pseudocyst and pancreatic ascites (autopsy findings) in the literature. The patient had a history of heavy alcohol consumption which may have contributed to severity of pancreatitis [13]. Extensive metastatic tumor deposits were noted adjacent to and within the main pancreatic duct with obstruction, severe ductal dilation and rupture.

Focal necrosis of pancreatic parenchyma and peri-pancreatic adipose tissue has been noted (on autopsy) in patients with MIAP [14].

Further studies are needed to clarify why only a small fraction of patients with metastases develop acute pancreatitis - MIAP. The mechanisms underlying MIAP as a paraneoplastic syndrome remain unclear. Malignancy can cause secondary hypercalcemia and acute pancreatitis [15] without pancreatic metastases. Para-neoplastic

amylase and lipase production in small cell lung cancer has been reported without documented acute pancreatitis [16]. In these patients, abdominal pain from other causes and coincidental hyperamylasemia and hyperlipasemia can be mistaken for acute pancreatitis. The tumor cells are known to express antigens of neural crest and epithelial origin. Whether they produce other humoral factors that can cause pancreatitis remains unclear. Acute pancreatitis has been reported in hypersecretory hormonal states such as gastrinoma [17] and Cushing's syndrome [18]. Autoimmune mechanisms could have an etiologic role in pancreatitis in patients with documented cancer. Steroid responsive acute severe pancreatitis has been reported in leukemic transformation of myelodysplastic syndrome [19]. In patients with MIAP from lung cancer the primary tumor was noted to predominantly involve the left lung [20] (as was the case with our patient). This raises the possibility of lymphatic communication between left lung and the pancreas facilitating direct spread of tumor cells/humoral factors causing pancreatitis.

Imaging modalities including CT, MRI, EUS and FDG-PET have been useful for diagnosis of pancreatic metastases. Although pancreatic metastases can be confirmed by EUS-FNA, it is often difficult to obtain tissue diagnosis in these seriously ill patients due to high morbidity and false negative rate on biopsy [21].

Overall prognosis in patients with MIAP is poor with mean survival of 2.2 months (survival range from 8 days to 8 months) [22]. Chemotherapy may confer survival benefit in patient with lung cancer [22, 23, 24]. Despite increased morbidity surgical resection of metastases may be helpful in patients with metastatic renal cell cancer [25]. In patients with MIAP and pancreatic duct stricture, endoscopic pancreatic stenting is beneficial [10]. In our patient (despite questionable MRCP findings of focal non-visualization of main pancreatic duct) index EUS exam was normal and subsequent pancreatogram at ERCP did not reveal any abnormality and pancreatic stenting did not provide the desired therapeutic effect.

While MIAP as the cause of acute recurrent pancreatitis is rare, it should be considered in patients with negative work up. It is unclear as to which subset of such patients should be screened for occult malignancy.

CONCLUSION

Idiopathic acute pancreatitis can rarely be a harbinger of a more sinister underlying problem. Paraneoplastic syndrome and metastatic cancer need to be considered in patients with acute recurrent pancreatitis of unclear etiology.

Conflict of Interest

The authors declare that they have no conflict of interest.

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