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CASE REPORT

Disseminated Metastasis with a History of Pancreatic Carcinoma 15 Years Ago: Diagnostic Challenge

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ABSTRACT

We report on a patient with a history of pancreatic carcinoma 15 years ago, who presented with a fever of unknown origin and was subsequently found to have disseminated metastases from an unknown primary. Multiple investigations performed in response to clinical findings and suspicions indicated that they might be metastases from the pancreatic carcinoma resected 15 years earlier, without there being any evidence of recurrence in the intervening period. In view of the patient's progressively deteriorating general condition, she could only be offered best supportive care. Apart from being rare, this case illustrates possible diagnostic approaches when faced with a patient with metastasis from an unknown primary. For patients with disseminated metastatic disease being considered for palliative chemotherapy, it is important to explore all possible means to identify the primary site and obtain histological confirmation, especially if the origin of the primary tumour is in doubt.

Key Words: *Carcinoma, pancreatic ductal; Neoplasm metastasis; Neoplasm recurrence, local; Neoplasm, unknown primary; Pancreatic neoplasms*

中文摘要

十五年前曾患有胰腺癌的患者發現有全身性轉移癌：診斷挑戰

蕭偉君、簡念慈、歐國雄

本文報告一名病人病發時無明顯原因的發燒，其後發現有不明原發腫瘤引致的全身性轉移。患者十五年前曾患有胰腺癌。根據臨床資料替患者作多項檢查結果顯示，雖然這段期間並無任何復發跡象，其轉移瘤應可能十五年前切除了的胰腺癌引發的。由於患者病情逐漸惡化，唯有給予最佳支持治療。這病例除了罕有之外，也說明了當遇上有不明原發腫瘤的病人，醫生可以採用的診斷方法。患有全身性轉移瘤而須接受緩和性化療的病人，應盡可能找出原發腫瘤的位置及確定其組織學資料，尤其是未能確立原發腫瘤的位置時。

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INTRODUCTION

In general, carcinoma of the pancreas has a poor prognosis. The 12-month survival rate following diagnosis is approximately 23%, and only 5% are alive after 5 years.[1] The recurrence rate after curative resection is high, and over 90% of patients develop their recurrence in the abdominal cavity, either as an isolated lesion at the original site and / or with liver, regional lymph node, or peritoneal involvement.[2,3]

Overall, patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma have a median survival rate ranging from 12 to 20 months, and a 5-year survival rate of 15 to 20%.[4] Most recurrences of pancreatic carcinoma occur within the first one to two years of surgical resection, and experiencing a recurrence after a long disease-free period is very uncommon.

In this report, we describe a patient with disseminated metastases, which was suspected to be an unusual instance of pancreatic carcinoma recurring as multiple distant metastases 15 years after the initial diagnosis.

CASE REPORT

The patient was a 52-year-old woman with a history of a Whipple's operation for carcinoma of pancreas in 1993. She had an episode of adhesive intestinal obstruction with laparotomy and adhesiolysis in 2004. Otherwise she remained clinically stable and free from recurrence of her pancreatic carcinoma; contrast computed tomography (CT) of her abdomen in September 2008 showed no evidence of recurrence.

She was admitted to our hospital in December 2008 complaining of pain over the left palm and left knee for 2 to 3 months, and also had a swinging fever. Subsequent blood culture yielded *Streptococcus bovis* sensitive to penicillin G. Echocardiography was performed twice but no definite oscillating masses or vegetations were identified. As the source of infection remained uncertain, in January 2009 a positron emission tomography (PET) scan was performed as a component of the investigations into her fever of unknown origin (FUO). However, it was reported as showing hypermetabolic nodules in both lungs, a hypermetabolic necrotic lesion in the left apical chest wall (between the first and second ribs), and multiple hypermetabolic destructive bone lesions scattered in the left knee, left pelvis, left hand, and right scapula (Figure 1). There was also a hypermetabolic nodule in the anterior mesentery. These lesions were commented as suspicious metastases. There was also a non-fluorodeoxyglucose–avid complex cystic nodule in the left breast and another tiny nodule in the right breast. Her blood cancer antigen (CA) 15.3 level was slightly elevated at 30 U/ml (normal, <23 U/ml), but her carcinoembryonic antigen, alpha-fetoprotein, and CA19.9 were all within normal limits.

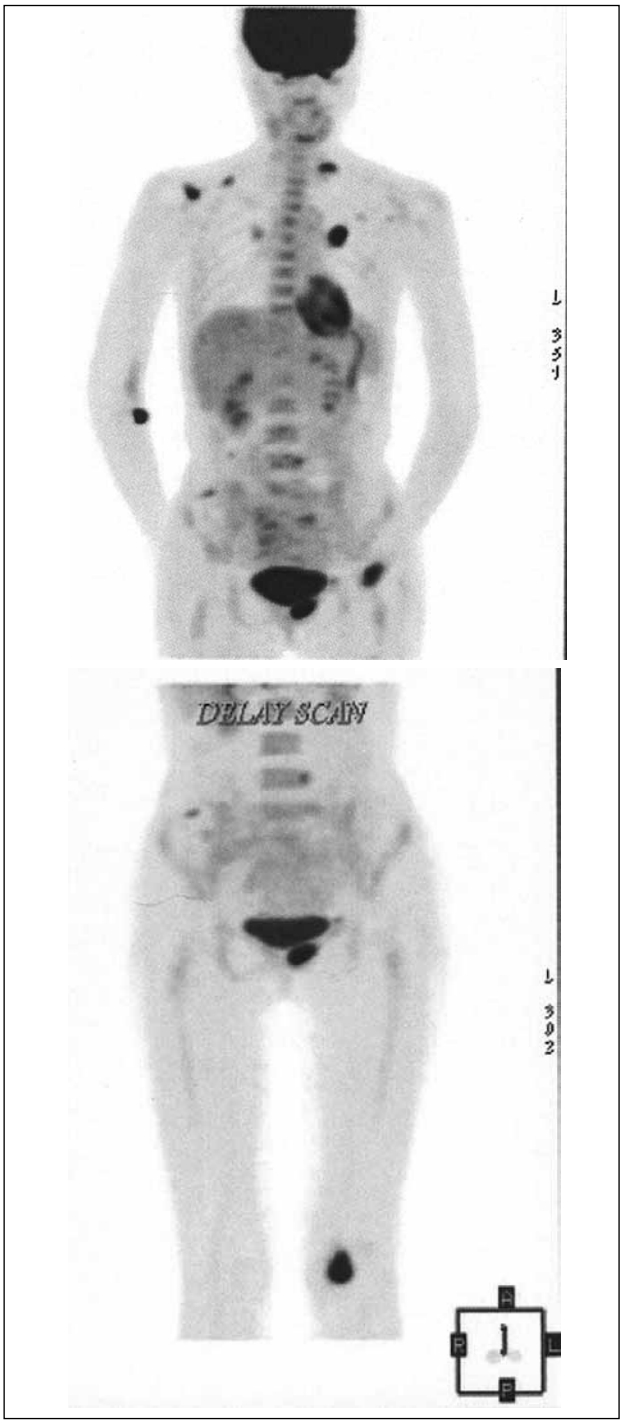

Figure 1. Positron emission tomography of the patient in January 2009.

A colonoscopy performed in search of the source for the *S. bovis* infection identified a localised area of colitis with mild stricture in the distal transverse colon, but did not look malignant. Histopathology report of the biopsy from that site showed submucosal invasion by an adenocarcinoma with tall columnar malignant cells. Immunohistochemistry of these cells was positive for cytokeratin 7 (CK7) and CK20, but negative for CDX2. The lack of surface involvement and the immunostaining profile were not supportive of a colonic primary, but suggested a non-colorectal metastasis invading the colon. Possible primary sites included pancreas, biliary tract or stomach.

The patient's fever subsided after two weeks of penicillin G and gentamicin treatment, and subsequent blood culture yielded no growth. Her pain control was satisfactory with non-steroidal anti-inflammatory drugs and weak opioids. Multiple investigations were performed to ascertain the primary lesion, as the patient was not known to have had a recurrence from her pancreatic carcinoma over the last 15 years. Breast and lung primaries were suspected in view of the PET scan findings. Stereotactic-guided biopsies of a suspicious lesions found on mammography provided no evidence of malignancy. The CT-guided fine-needle aspiration for cytology of the left upper lobe lung lesion yielded adenocarcinoma cells immunoreactive for CK7 and CK20, but non-immunoreactive for thyroid transcription factor–1 (TTF-1), CA125 and gross cystic disease fluid protein (GCDFP). Again, the

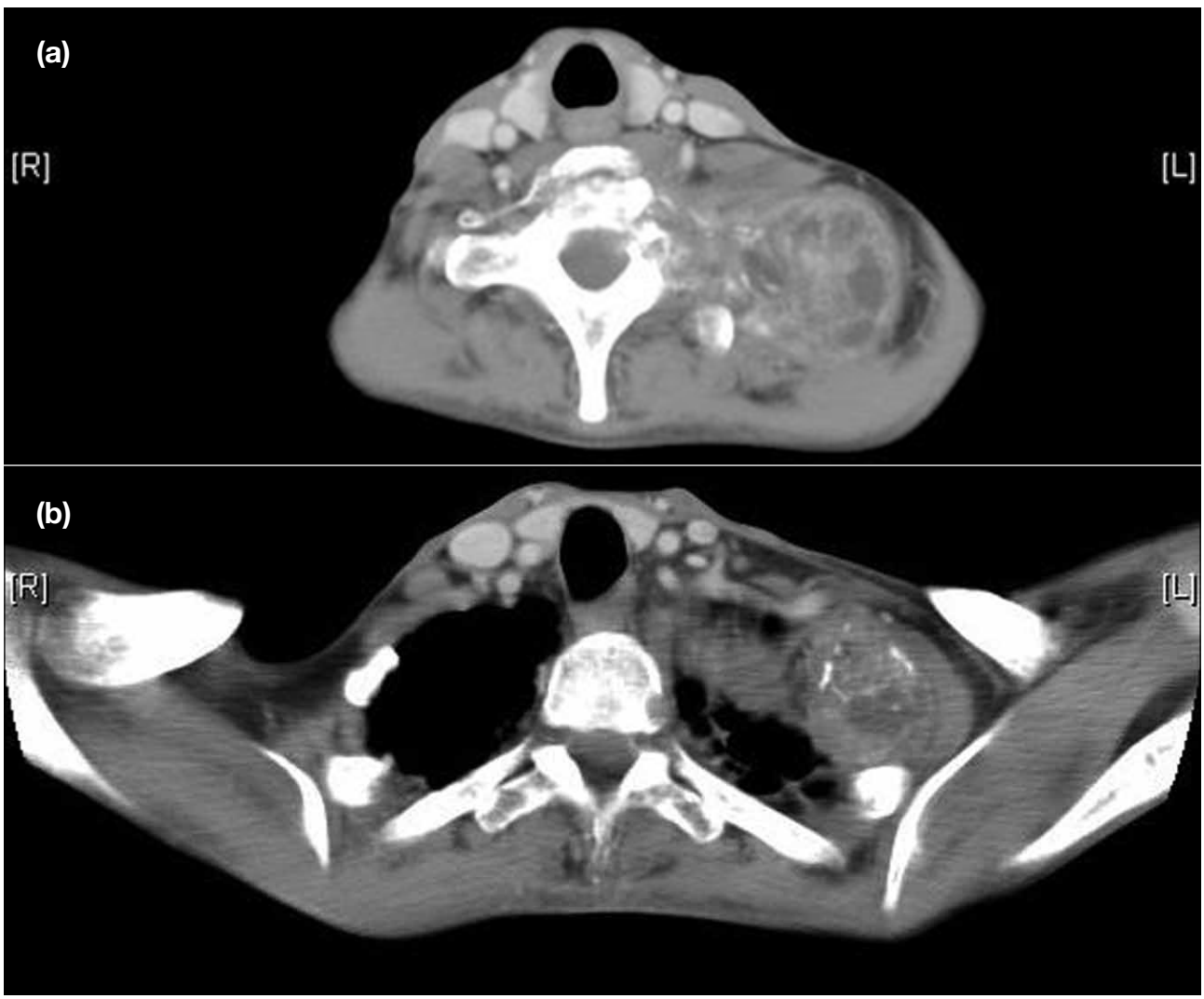

Figure 2. Contrast-enhanced computed tomograms of the patient in June 2009, showing a large left apical chest wall mass invading adjacent vertebra with extension into (a) spinal canal and (b) ribs.

likely primary sites were reported as compatible with a pancreaticobiliary or stomach lesion.

In view of the immunostaining findings of the specimens, an oesophagogastroduodenoscopy was also performed in March 2009, but no abnormality was detected. Biopsies from the gastric stoma and body only showed mild active chronic gastritis.

In view of these findings, it was decided that the patient should be treated as a case of metastatic pancreatic carcinoma. The patient's condition deteriorated before initiation of palliative chemotherapy. In May 2009, worsening bone pain was treated with palliative radiotherapy to the left hip (28 Gy in seven fractions over 1.5 weeks) and in June 2009 to the right hip (20 Gy in five fractions over one week). She had also developed a large mass over the left lower neck and supraclavicular region, and there was neck pain radiating down into the upper limbs. Contrast CT revealed a large left apical chest wall mass with invasion of adjacent vertebra and rib, and extension into spinal canal (Figure 2). Biopsy of the mass yielded a metastatic adenocarcinoma. When stained for specific markers, it was positive for CK7, CK20 and CK19, and negative for CDX-2, estrogen receptor, GCDFP, TTF-1 and CA125, which was compatible with a pancreaticobiliary origin. Palliative radiotherapy to the left supraclavicular fossa / apical chest wall region (covering C5 to T4 vertebrae) was completed in June 2009. In the same month, the patient suffered a left neck of femur fracture that was treated by excisional arthroplasty with the femoral head retrieved and neck trimmed. Pathology of the femoral head showed clusters of metastatic adenocarcinoma in the marrow.

As the patient's condition progressively deteriorated, she was considered unsuitable for palliative chemotherapy and supportive care was opted for by the patient and her relatives. After transferring to a hospice for terminal care, she died in August 2009, which was eight months after her admission for FUO.

Retrospectively, we traced the pancreatic tumour specimens obtained in 1993 for immunostaining. We also performed further immunostaining on the biopsy specimen from the left apical chest wall mass. The immunophenotypes of the two specimens were compared (Table) and found to be almost the same, apart from being negative for the CK20 marker in the pancreatic tumour obtained in 1993. It is uncertain whether this represents a genuine difference between the origins of the two tumours or the immunophenotype had changed in the metastatic tumour.

DISCUSSION

According to one definition, classical FUO is defined as a temperature of >38.0° C for more than three weeks with more than two physician visits or three days in hospital.[5] Infection accounts for 30 to 50% of the causes of FUO and malignancy for 15 to 20%.[5] In the present case, blood culture yielded *S. bovis* (part of the normal intestinal flora),[6] of which bacteraemia is significantly associated with colonic pathology.[6] Colonoscopy was therefore performed and the suspected metastatic tumour with extrinsic invasion into the colon identified. *S. bovis* is also a known causative agent that infects heart valves,[6] and so prompted cardiac investigations to rule out endocarditis.

In this case, the diagnostic challenge was to identify the primary site responsible for the disseminated metastasis. It is uncommon for a patient to present with disseminated metastases from a pancreatic carcinoma diagnosed 15 years earlier; whilst secondary spread to lung and bone was also distinctly unusual for a pancreatic primary. Moreover, minimal disease was apparent in the abdomen according to the PET scan findings, though intra-abdominal recurrence was likely in view of the colonoscopic findings.

The suspicion of disseminated metastases from previous pancreatic carcinoma was based on immunostaining, and the fact that no other primary tumour could be identified and assuming that none of the multiple lesions we had located were primaries. The immunohistochemical

Table. Comparison of immunophenotypes of the pancreatic tumour resected in 1993 and that of the biopsy specimen from the left apical chest wall mass in 2009 for the patient.

Markers	Pancreatic tumour 1993	Left apical chest wall mass biopsy 2009
CK7	+	+
CK20	-	+
CK19	+	+
CDX2	-	-
TTF-1	-	-
ER	-	-
CA125	-	-
GCDFP	-	-

Abbreviations: CK = cytokeratin; TTF-1 = thyroid transcription factor–1; ER = estrogen receptor; GCDFP = gross cystic disease fluid protein.

profile for both CK7 and CK20 being positive, was compatible with a pancreatic primary, as occurs in 62 to 65% of cases.[7] Given the presence of lung lesions, a lung primary cannot be definitely excluded, as 10 to 11% of lung adenocarcinoma can show the same immunohistochemical profile.[7] Moreover, TTF-1 staining is positive in 75 to 80% of lung adenocarcinomas.[8] Thus, though the patient in this case could have suffered from a rare instance of disseminated metastases 15 years after the initial diagnosis of pancreatic carcinoma, a lung primary with an unusual immunohistochemistry profile cannot be definitively excluded as the cause of disseminated metastases at this presentation. The clinical finding against this argument was the absence of mediastinal lymph node metastases as shown by PET; in most instances regional lymph node metastases precede systemic dissemination of lung cancer.[9] Given the unusual presentation and disease pattern arguably, the patient could also be labelled as having metastatic adenocarcinoma of unknown origin.

The inherent difficulty of immunohistochemistry is that it does not have 100% sensitivity and 100% specificity. It is only one of the pieces of important information to direct doctors to the possible primaries. Histology, clinical and radiological findings are also important. If no definitive conclusion can be drawn after adequate investigation, treatment must be based on the most likely primary. We therefore opted to treat the patient as having a pancreatic primary with disseminated metastases.

Treatment of metastatic pancreatic adenocarcinoma usually entails gemcitabine in combination with erlotinib, which may result in a modest survival gain.[10] Both of these agents are also used to treat metastatic adenocarcinoma of the lung, and so there was a chance the patient might have responded irrespective of whether she had a pancreatic or lung primary. However, given the widespread metastatic disease at presentation and the relatively rapid disease tempo since diagnosis, the patient's prognosis was poor irrespective of the site of the primary.

CONCLUSION

This is a report of a patient with disseminated metastases, suspected to have originated from a previous pancreatic carcinoma based on immunohistochemistry profiling and clinical history. The unusual feature of this case was that the pancreatic carcinoma appeared to have recurred 15 years after the initial diagnosis, and it was also uncommon for such disseminated metastases to occur without local recurrence or liver metastases. This case also serves to illustrate the possible diagnostic approach to searching for unknown primaries in patients with disseminated metastases, as they could be candidates for palliative chemotherapy.

DECLARATION

Part of this material was published in abstract format and presented in poster format at the 18th Annual Scientific Meeting of Hong Kong College of Radiologists, Hong Kong Special Administrative Region, China, on 30-31 October 2010.

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