Acrometastasis from a Pancreatic Primary Adenocarcinoma: A First Report in the Literature
O'Grady J*, Collins D, O'Reilly S and Power DG
Department of Medical Oncology, Cork University Hospital, Wilton, Cork, Ireland
*Corresponding author: O'Grady J, Department of Medical Oncology, Cork University Hospital, Wilton, Cork, Ireland, Tel: 00353861672725, E-mail: jogrady@live.ie


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Abstract
A seventy five year male presented with acute onset right foot pain and swelling. Plain imaging revealed a lytic area in the medial and middle cuneiform bones of the right foot. Background history of resected pancreatic cancer and current presentation were consistent early diffuse disease recurrence of a pancreatic primary tumour. The presenting feature in this case was of symptomatic acrometastases, that is, metastases to the feet. Acrometastases have been described in association with multiple primary tumours, but not pancreatic cancer. Our case highlights rare sites of metastatic disease secondary to pancreatic cancer, and we review the literature.

Case report
A seventy five year old retired business man presented with acute onset right foot pain and swelling. He was unable to weight bear due to the severity of symptoms. There was no history of trauma or rheumatologic disorder. Following initial review, he underwent plain imaging of his right foot. This revealed a lytic area in the medial and middle cuneiform bones of the right foot (Figure 1).

Background history was significant for pancreatic adenocarcinoma. He had undergone surgical resection of the pancreatic tumour (Whipple's procedure) ten weeks prior to this current presentation which also included excision of a solitary liver metastasis, which had been an unexpected intraoperative finding. He was due to receive gemcitabine chemotherapy following multidisciplinary team discussion postoperatively, but presented acutely prior to this with his current complaint. Tumour marker analysis on this admission revealed a CA 19-9 level of 1489 kU/L (normal range 0-37 kU/L). Preoperative CA 19-9 was 934 kU/L three months prior to this.

A Technetium- 99 Isotope bone scan revealed significantly increased tracer uptake in the right tarsal bones and the right first tarsometatarsal joint (Figure 2), consistent with the acute presenting feature. Increased tracer uptake, with less avidity, was also noted near the proximal right tibia, left tarsal joints and left ankle joint. The areas of most avid activity corresponded with the patient's symptom site as well as the lytic lesions described on plain imaging. All findings were consistent with bone metastases.
Further cross sectional computed tomography imaging of the thorax, abdomen and pelvis revealed multiple new pulmonary nodules and a soft tissue mediastinal mass, partially encasing the descending thoracic aorta (Figure 3). Within the abdomen, multiple new hepatic lesions, throughout both lobes, were visualized. All findings were consistent with metastatic disease. Multiple intramuscular and subcutaneous metastases were also uncovered by computed tomography, with some readily palpable on clinical examination. These included deposits within the anterior abdominal wall, right gluteus muscles (4.5cm lesion) and right paraspinal muscle (1.5cm lesion) (Figure 4). Histology from an accessible abdominal wall deposit confirmed a metastatic carcinoma, in keeping with cutaneous involvement by the patient’s previous pancreatic adenocarcinoma.
Concurrent multidisciplinary care was instigated for relief of pain and to improve mobility. Input was received from the palliative care team, physiotherapy and occupational therapy departments as well as radiation oncology review. This clinical scenario was consistent with early diffuse disease recurrence of a pancreatic primary tumour following recent surgical resection of apparent radiologic localized disease. The presenting feature in this case was of symptomatic acrometastases. Initial therapy was with gemcitabine single agent chemotherapy. The presence of acrometastases, together with intramuscular and subcutaneous metastases, is an unusual presentation of pancreatic cancer recurrence and forms the basis for this discussion.

Discussion

Of all gastrointestinal malignancies, pancreatic is the most common after colorectal [1]. The incidence of pancreatic cancer is estimated at eleven per hundred thousand population in the United States [1]. In Ireland, incidence is similar at about ten per hundred thousand of the population [2]. Pancreatic cancer is difficult to treat and associated with high mortality rates. It is often diagnosed at advanced stages due to a lack of early warning symptoms and signs, and more common in older patients [3,4]. The five year survival for pancreatic cancer ranges from 1.3-8% and has changed little over years [4-8]. Those patients who are amenable to surgical resection have longer survival rates [7], however recurrence is commonplace.

The ‘seed and soil’ concept of metastases suggests that bone offers a more suitable environment to promote growth of certain metastases [9]. Primary tumours that metastasise most frequently to bone include prostate, breast and lung [9]. The most common sites for bone metastases, in all patients, are the vertebrae, pelvis, ribs, sternum and skull [10]. Bony metastases below the elbow and the knee are rare. Moreover, metastases to the hand or foot, acrometastasis, are rarer still with an estimated incidence 0.007-0.3% [10-14]. Hands are more usually involved than feet [10]. Acrometastases have been described in association multiple primary tumours but not pancreatic cancer. A review of metastatic foot lesions revealed genitourinary tumours as the most frequently associated primary [15]. Lung [10,16,17], breast [18,19], renal [11,20], colonic [12,21,22] and, rarely, hepatocellular [23] tumours in association with acrometastatic disease have also been reported.

Pancreatic adenocarcinoma metastases to bone have an overall estimated incidence of between five and twenty percent [24]. Metastatic bone sites include the spine [25], mandible [26] and lower limb [27]. Pancreatic bony metastases have been associated with both osteolytic and osteoblastic lesion formation [28]. To our knowledge there have been no cases of pancreatic tumours in association with distal hand or foot metastatic deposits, as was the presenting feature in our case. The reason why skeletal metastases from pancreatic cancer are uncommon is not clear. It has been postulated that parathyroid hormone-related protein (PTHrP), interleukin 6 (IL-6), vascular endothelial growth factor (VEGF) may play a role as well as other factors such as interleukin 11 (IL-11) and matrix metalloproteinase (MMP).

A further interesting finding in our case is the evidence of multiple intramuscular and subcutaneous metastatic deposits. Gastrointestinal cancers, such as pancreatic, are rarely associated with bone or muscle metastases. Muscular metastases as a feature of pancreatic cancer have been reported in association with other metastatic disease sites [27,29-31], in a similar manner to that of our patient. It has been reported previously that tumour invasion into muscular tissue predicts a relatively worse prognosis and plays an important role in disease progression [32]. There does not appear to be any association between histologic subtype and site or timing of metastatic disease.

Symptoms from bone metastases are rare unless late in the disease course [28]. Treatment options include systemic chemotherapy, radiotherapy and even amputation [33,34]. Gemcitabine and fluorouracil chemotherapy remain the backbone of oncological therapeutics and have modest benefits [5]. There is ongoing research into the most effective ways to utilise these and other cytotoxic agents most effectively [35].

The frequent manifestation of early metastatic disease is testament to the fact that pancreatic cancer, even when localised on scans, is a systemic disease. Occult micrometastases in bone marrow are common and likely explain the poor survival [36,37]. Given that metastatic disease, usually in the peritoneal cavity or liver, is associated with a poor outcome in pancreatic cancer, it may be that life expectancy is not long enough for the micrometastatic disease in bone to manifest itself. The early development of metastatic disease, even in unusual sites, should always be suspected, even in cases of surgery with curative intent.

The use of bisphosphonates or RANK ligand antibodies may provide some benefit in the early treatment of pancreatic cancer given the reported incidence of micrometastatic bone disease. The use of RANK ligand antibodies may prevent chemotaxis between circulating tumour cells and the bone microenvironment [38].

In summary, we describe a first reported case of extensive pancreatic adenocarcinoma with acrometastatic disease. Our patient also developed metastatic deposits in subcutaneous and muscular tissue, both rarely reported with pancreatic cancer. Our case highlights rare sites of metastatic disease secondary to pancreatic cancer and emphasises that pancreas cancer is a systemic disease at diagnosis even when ‘localized’ on cross sectional imaging.
References

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