Pancreatic disease, Panniculitis and Polyarthritis (PPP) Syndrome: a case report and review of the literature

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In rare cases, pancreatic disease is preceded by tender nodular skin lesions (= panniculitis) combined with painful swelling of peripheral joints (= polyarthritis). Documentation of this potentially fatal triad is scarce, where early recognition is critical for the reduction of the high mortality rate (24%) due to underlying pancreatic disease. The Pancreatic disease-Panniculitis-Polyarthritis (PPP) syndrome was first described in 1908 by Berner.[2] Approximately up to 3% of patients with pancreatic disease also present themselves with panniculitis. However, manifestation of the full PPP triad remains extremely rare and less than 30 cases are reported in the literature. We present a man with painful skin nodules and polyarthritis in the lower extremities, giving rise to the discovery of a cystic mass in the pancreatic head and diffuse liver metastases.

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Introduction

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The Pancreatic disease-Panniculitis-Polyarthritis (PPP) syndrome was first described in 1908 by Berner.[2] Approximately up to 3% of patients with pancreatic disease also present themselves with panniculitis.[3] Manifestation of the full PPP triad however, remains extremely rare and less than 30 cases are reported in the literature.[4] We report a man with painful skin nodules and polyarthritis in the lower extremities, giving rise to the discovery of a cystic mass in the pancreatic head and diffuse liver metastases.

Report

A 62-year old Caucasian male presented himself at our department with an inflammatory skin le-

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Key words: pancreatic mass with diffuse liver metastases, panniculitis, polyarthritis, polychemotherapy.

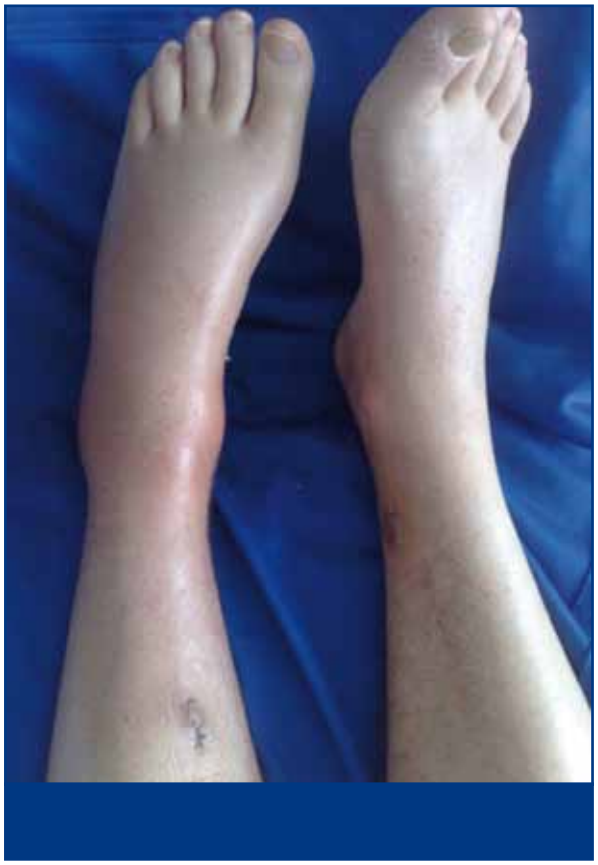

Figure 1. Inflammation of the left ankle, nodular skin lesion on the right lower limb.

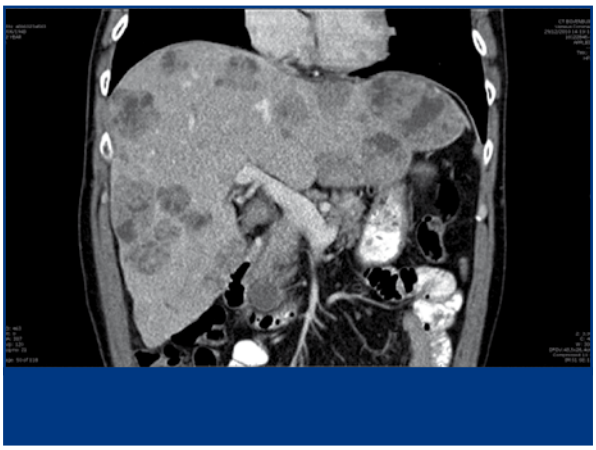

Figure 2. Abdominal CT: cystic mass in the pancreatic head - diffuse liver metastases.

sion on the 5th toe of his left foot. The lesion was presumed to be erysipelas and was being treated with antibiotics. However, 2 weeks later, other skin lesions with an erythema nodosum-like appearance appeared on both his lower legs. The patient reported alternating painful episodes in both legs with migration of pain and swelling between ankles, knees and smaller joints of the feet. The patient had no cancer in the family history, no nicotine abuse and average alcohol consumption. Before his retirement he had worked in the metal industry.

Physical examination showed a man in good overall health without fever. Heart and lung auscultation were normal and so was evaluation of the abdomen. Abnormalities were found on both lower legs where 2 painful red nodules were seen on the medial sides. In addition we report marked swelling of the knees, the left ankle and the first toe of his right foot (*Figure 1*).

Investigation of a first blood sample revealed a hemoglobin of 10.2 g/dl, white cell-count of 11,200, thrombocytes of 433,000, a normal creatinin value, GOT of 56 U/l (normal 7-27 U/l), GPT of 285 U/l (normal 50-160 U/l), lactate dehydrogenase of 822 U/l (normal 50-150 U/l) and a gamma-glutamyl transpeptidase of 597 U/l (normal 8-78 U/l). Pancreatic enzymes were exceedingly high with lipase 98,680 U/l (normal 7-60 U/l) and amylase 5,000 U/l (normal 0-110 U/l); C-reactive protein was 5.93 mg/dl (normal 0-1 mg/dl) and tumour markers PSA, CEA and CA19,9 were all normal. On joint aspiration, a thick yellow-brown fluid could be yielded with negative cultures.

Radiographic imaging of the knees showed no signs of arthritis except for soft tissue swelling. Feet and thorax imaging showed no abnormalities. Computed tomography (CT) of the superior abdomen revealed diffuse metastases in the liver and an irregularly confined cystic mass in the pancreatic head suspect for malignant transformation (*Figure 2*). Next, a positron emission tomography-CT (PET-CT) was conducted to detect other metastatic lesions and to determine the nature of the cystic mass in the pancreas more accurately. Surprisingly, the result demonstrated absolutely no tracer uptake by the cystic mass in the pancreas, while the liver metastases clearly showed increased uptake. No clearly defined primary tumour could be recognised on basis of thorough radiographic evaluation. A percutaneous cylinder biopsy of a liver metastasis illuminated a poorly differentiated adenocarcinoma not clearly defined to an organ. Skin biopsy of a

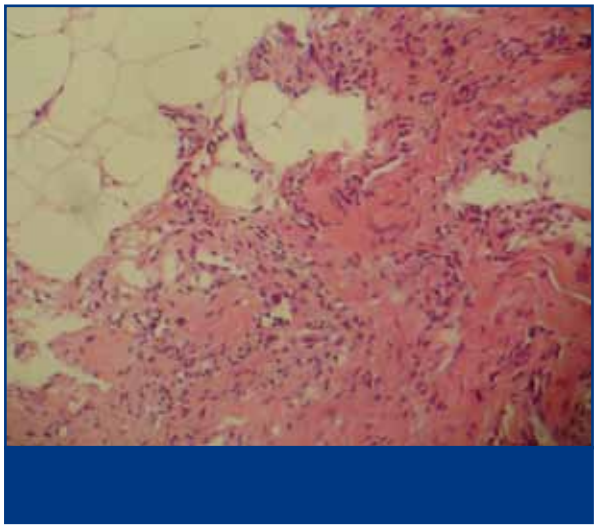

Figure 3. Subcutaneous biopsy: fat necrosis.

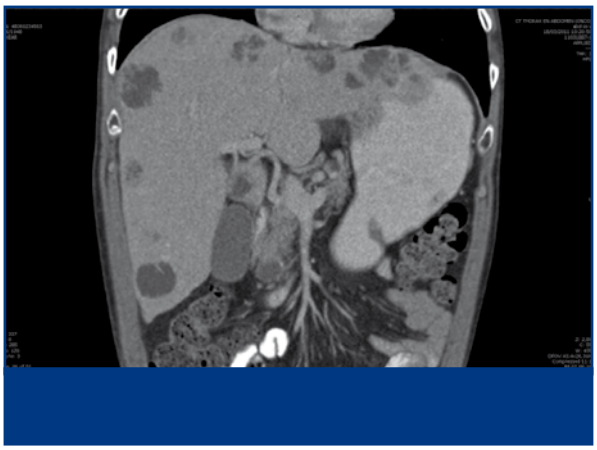

Figure 4. Abdominal CT after 3 courses of chemotherapy: reduction in size of the pancreas mass; necrosis of liver metastases.

pretibial nodule indicated manifest steatonecrosis with signs of tissue recovery. However, the pathognomonic ghost cells (= poorly outlined necrotic fat cells without a nucleus produced by enzymatic degradation) seemed to be absent (*Figure 3*).

In the meantime, increasing doses of pain medication (paracetamol, ibuprofen and fentanyl) were started in association with corticosteroids, with incomplete and unsatisfactory control of disease symptoms. In our multidisciplinary oncological consultation (MOC) we decided, after inserting a port-a-cath into the subclavian vein, to start polychemotherapy immediately, based on the scheme that we use as a standard for PTU (= primary tumour unknown/uncertain): the cyclophosphamide-adriamycin-cisplatin (CAP) regimen. Chemotherapy was started in an attempt to diminish the volume of the cystic mass in the pancreatic head (= differential diagnosis between a real pancreatic cancer and an inflammatory or non-inflammatory benign cystic mass in the pancreatic head) as well as the diffuse liver metastases. Supportive therapy was continued during chemotherapy.

Evolution

After the first course of CAP, we observed that his renal function became moderately compromised, so in the second chemotherapy course we changed the nephrotoxic cisplatin to the safer carboplatin at an AUC of 4.

After 3 courses of chemotherapy we observed a good clinical and laboratory response in our patient. Clinically, the patient was completely symptom-free: the subcutaneous noduli turned into hyperpigmented flat spots, the painful arthritis disappeared in every joint and he could resume his daily activities, free of pain symptoms. The C-reactive protein, GOT and GPT values normalised and a marked reduction was observed in lactate dehydrogenase, gamma-glutamyl transpeptidase and the pancreatic enzymes lipase (98,680 à 43,000 U/l) and amylase (5,000 à 3,500 U/l).

Overall, the chemotherapy was well-tolerated. Before starting the third cycle of chemotherapy, our patient was admitted because of profound anorexia and subsequent weight loss; therefore we administered parenteral nutrition only during 1 week, with recovery of his weight loss. At this moment (end of March 2011) the patient is gradually reducing his pain medication and methylprednisolone dose since pain and signs of inflammation are no longer present.

Discussion

In this case report we describe the rare situation where pancreatic disease is preceded by a clinically overt panniculitis and polyarthritis. The PPP triad is mostly reported in patients with acute or chronic pancreatitis. When it occurs in patients with pancreatic malignancy, it usually features cancer of the

acinar cell type.[5,6] Pancreatic panniculitis can also be present as a first sign of liver carcinoma, as reported by Corazza et al.[7]

In addition, we noted that our patient's lipase values (98.680 U/l) were approximately 10 times as high as mean values described in the literature, and amylase values were raised to a spectacular level as well. This might indicate specific changes of the cells within the cystic mass of the pancreas head. Where lipase is a prognostic factor in the follow-up of pancreatic disease, no linear relationship with bone and skin damaging appears to exist.

The pathogenesis of the remote symptoms in PPP syndrome is still unclear, but the presumed hypothesis states that massive release of pancreatic enzymes into the systemic circulation leads to subcutaneous fat necrosis and intramedullary lipolysis. Massive hypersecretion of lipase leading to panniculitis is reported in association with a wide range of pathologies including acute and chronic pancreatitis, pancreatic carcinoma, liver carcinoma, pancreas divisum and pancreatic vascular fistulas.[8] Correlation with past or present alcohol abuse is suspected, as a literature review of 25 cases with acute or chronic pancreatitis revealed that 64% of the subjects had a history of heavy drinking.[1] The average patient age in the study was 51 years (range 16-76) with a male/female ratio of 2/1. In contrast to what is usually observed in patients with pancreatic disease, abdominal symptoms are mild or absent in two thirds of the patients, often leading to postponed diagnosis or misdiagnosis.[1] However, physicians need to be alert to this PPP triad, not only because it has a mortality ratio of approximately 1/4, but also because joint involvement further deteriorates as long as pancreatic disease is not treated promptly.[1]

The non-suppurative panniculitis in PPP syndrome must be differentiated from erythema nodosum, lupus profundus and polyarteritis nodosa.[9] Typically, the skin lesions are small, erythematous nodules, 1–2 cm in size with central softening, and preferentially involving the lower limbs.[10,11] Proximal migration over the arms and trunk is reported and the nodules may ulcerate spontaneously, exuding an oily, brown, viscous substance as a result of liquefaction necrosis.[1,3] The damaged cells attract inflammatory cells, activate platelets and the complement system, leading to production of cytokines, free radicals and other vasoactive substances. Free radicals are suspected to be the culprits responsible for arthritis.[12] Biopsy of skin lesions shows inflammatory cells, steatonecrosis and sometimes pathognomonic ghost cells: adipocytes that underwent coagulative necrosis and thereby lost their nuclei.[8]

MRI is the most sensitive imaging method for detection of typical intramedullary fat abnormalities, which can precede necrosis.[13] It can also help in the differentiation from osteolytic skeletal metastasis as seen in pancreatic carcinoma.[14] Bone lesions have an evolution independent of pancreatic disease and respond poorly to non-steroidal anti-inflammatory drugs.[1]

In our case, we performed a PET-CT-scan and unexpectedly there was an increased uptake of FDG in the liver metastases, but not in the at that moment presumed pancreatic cancerous mass. We therefore assumed that in our patient we were not dealing with a malignant pancreatic mass, but with a benign, non-inflammatory, secretory cystic process; an inflammatory mass seems less likely because in that case, we would expect to find FDG-uptake. We did not organise an echo-endoscopic biopsy of the pancreatic mass because we had easily obtained more biopsy material from a malignant liver lesion, and also, because the assessment of the pancreatic lesion would not have any therapeutic consequences. So in the end, we progressed to the following diagnosis: primary tumour unknown/uncertain (PTU) with diffuse liver metastases and a non-inflammatory pancreatic cystic lesion secreting a massive amount of lipase and amylase.

Conclusion

It is important to suspect underlying pancreatic disease when a patient is presented with polyarthritis and migrating erythematous nodules on the lower limbs, because early recognition and initiation of therapy seem to be the only factors determining the outcome of both pancreatic and joint disease.

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Key messages for clinical practice

1. Think of pancreatic disease when a patient is presented with erythematous nodules and arthritis on the lower limbs and rule out malignant disease in pancreas or liver.
2. Immediately start treatment for pancreatic disease, as delay worsens prognosis for both pancreatic and joint disease.
3. In case of malignant disease, chemotherapy is the cornerstone of treatment with mostly a fatal outcome in case of metastases.
4. Pain medication, non-steroidal anti-inflammatory drugs and corticosteroids are frequently used in treating the symptoms of the PPP syndrome, with incomplete and unsatisfactory control of disease symptoms if the underlying cause is not successfully treated.

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