Pancreatic carcinoma with polyarthritis, fat necrosis, and high serum lipase and trypsin activity

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Abstract

A 46 year old white man presented with subcutaneous and intramedullary fat necrosis, destructive polyarthritis, and osteolytic bone lesions, complicating a poorly differentiated adenocarcinoma of the tail of the pancreas with metastases in the liver and omentum. There was a 100-fold increase in serum lipase and trypsin activity. His condition deteriorated rapidly, was characterised by rapid tumour growth, formation of ascites, a 20 kg weight loss, extensive subcutaneous fat necrosis, and fistula formation in the left calf. Treatment with 5-fluorouracil 300 mg/m² on days 1-5 and doxorubicin 50 mg/m² and cisplatin 100 mg/m² on day 1, every three weeks, was well tolerated and resulted in rapid clinical improvement. After three courses of treatment a partial remission was seen and after seven courses further improvement occurred with a return to normal of serum lipase and trypsin activity. One year after starting chemotherapy the tumour relapsed but responded again to chemotherapy (epirubicin 40 mg/m² and carboplatin 300 mg/m² on day 1, every three weeks).

Pancreatic tumours are usually not metabolically active. Since the first description by Berner in 1908¹ only 23 cases have been described.² The syndrome is characterised by fever, polyarthritis, subcutaneous nodular fat necrosis, increased serum lipase activity, and eosinophilia,^{3,5} and it occurs predominantly in men over 50 years of age. Serum α amylase activity is raised in only about 30% of cases.³ Osteolytic bone lesions may be present,⁴ but ascites is uncommon.⁵ The tumour is considered to be resistant to treatment,³ with a fatal course within several weeks or months.⁶

The following report is, to our knowledge, the first documented case of a poorly differentiated pancreatic adenocarcinoma with exceptionally high serum lipase and trypsin activity and a major response to combination chemotherapy.

Methods

For the various assays we used the Phadebas IsoAmylase Test (Pharmacia Diagnostics),⁷ the RIA-gnost trypsin radioimmunoassay kit (Behring-Hoechst),⁸ and the Monotest Lipase (Boehringer Mannheim Diagnostics).⁹ Serum carboxypeptidase-B activity was determined by the salmine (protamine) method.¹⁰ The mean (SD) reference value, determined for 29 healthy volunteers, was 149 (61) U/l. Serum α_1 antitrypsin activity was measured nephelometrically, using antisera prepared by Dako (Glostrup, Denmark).¹¹

Case report

A 46 year old white man presented in September 1987 with skin lesions resembling erythema nodosum. Within the next three months a severe polyarthritis developed, requiring non-steroidal anti-inflammatory drugs and morphine. Physical examination showed an ill man with normal vital signs, a temperature of 38°C, and a smooth 10×17 cm non-tender mass in the left upper abdomen. There was a florid arthritis of the right wrist, the right metatarsophalangeal joints 2-4, the left ankle, and the right knee. The circumference of the right knee increased when the atrophic upper leg or the tender, swollen inflamed calf were compressed, suggesting an open communication. The left pretibial surface showed several non-tender slightly raised erythematous nodules about 1 cm in diameter.

Laboratory tests showed the following abnormalities: erythrocyte sedimentation rate 120 mm in the 1st hour (Westergren); haemoglobin 9.6 g/dl, normochromic, normocytic; white blood count 10.2×10⁹/l with 5% eosinophils; alkaline phosphatase 245 U/l (normal <120 U/l); lactic dehydrogenase 500 U/l (normal <300 U/l), and gamma-glutamyltransferase 84 U/l (normal <40 U/l).

Aspiration of the right knee and left ankle yielded a yellow-green, creamy, purulent fluid. Many fat globules were shown by Sudan-red stain. Cytological examination showed necrotic material. All cultures were negative. Computed tomography and ultrasonography of the abdomen showed a 18×15×15 cm mass with hypo- and hyperdense areas, most probably originating from the tail of the pancreas. An exploratory laparotomy showed a large retroperitoneal tumour with several small metastases in the liver and omentum. Conventional histopathology in biopsy specimens from the primary tumour and the metastatic lesions was compatible with a poorly differentiated adenocarcinoma. No signs of pancreatitis were found in the resected specimen.

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Values of α amylase, lipase, trypsin, α_1 antitrypsin, and carboxypeptidase-B on admission

	Serum	Serum reference values	Urine	Urine reference values	Ascites	Joint fluid
Pancreas amylase (U/l)	24-26	15-183	35	-	ND	ND
Salivary amylase (U/l)	11-17	15-190	64	-	ND	ND
Total α amylase (U/l)	35-43	90-330	99	<1500	<33	42
Lipase (U/l)	17 600-19 840	10-190	<1	-	2975	533
Trypsin (μ g/l)	55 000-60 500	140-400	<1	1.0 (+3.4)*	ND	ND
α_1 Antitrypsin (g/l)	6810-7320	1800-3200	ND	-	ND	ND
Carboxypeptidase-B (U/l)	134-176	149±61	ND	-	ND	ND

ND = not done; - = unknown.

*Lake-Bakaar G, Summerfield JA. Gut 1978; 19: A960.

Figure 1: (A) Nodular necrosis is seen in the subcutaneous fat tissue with ghost cells (arrow heads) and a leucocyte infiltrate (Haematoxylin & eosin. Original magnification $\times 400$). (B) Birefringent crystals (arrow heads) are shown with polarised light in the periphery of the necrotic fat lobules (H&E. Original magnification $\times 400$).

The combination of these findings suggested a functional exocrine pancreatic tumour with fat necrosis. This was confirmed by the serum lipase and trypsin activities, which appeared to be increased 100-fold. In contrast, serum α amylase and carboxypeptidase-B activities were normal (Table). In unconcentrated urine neither trypsin nor lipase was detected. The serum α_1 anti-trypsin concentration was raised and serum cholesterol and triglyceride concentrations were within normal limits.

Chest x rays were normal. Films of the long bones showed sharply delineated osteolytic lesions.

An arthrotomy of the right knee was performed and 200 ml of creamy debris was evacuated. The synovium was covered with a yellow 'fibrin like' deposit. The osseous parts of the joint showed severe destruction. Histopathology showed a chronic, partly active synovitis. Fat necrosis was seen in the periarticular fatty tissue, in the bone biopsy of the tibia, and in the subcutaneous tissue.

Occasionally, characteristic 'ghost cells' (Fig 1A) with thickened cell walls containing negative birefringent material and von Kossa's negative staining particles were observed (Fig 1B). Extensive immunohistochemical examination was negative. Electron microscopic examination on formalin fixed, paraffin embedded material showed compact cell nests or a tubular pattern with a central lumen lined with apical microvilli. The rough endoplasmic reticulum was remarkably well developed (Fig 2). Neither zymogen nor neuroendocrine granules were detected. Therefore the tumour was classified as a poorly differentiated pancreatic adenocarcinoma.

About four months after the first symptoms the patient deteriorated rapidly. His weight fell by 20 kg, the subcutaneous nodules extended over the whole body, the tumour occupied the whole left part of the abdomen, and ascites appeared. The left calf was drained of 100–200 ml debris daily via a spontaneously formed fistula.

We decided to start treatment with a chemotherapeutic combination of 5-fluorouracil 300

Figure 2: Three tumour cells are partly visible in this electronmicrograph. They are characterised by a well developed, concentrically arranged rough endoplasmic reticulum (arrow heads). Neither zymogen nor endocrine granules were observed (Original magnification $\times 5200$).

mg/m² intravenous bolus on days 1 to 5 and doxorubicin 50 mg/m² bolus and cisplatin 100 mg/m² in 4 hours intravenously on day 1 every three weeks. After three courses with only minimal early side effects a major clinical response was achieved. Dose reduction to 75% was needed because of myelosuppression. Evaluation after seven courses showed only a 4 cm residual tumour mass in the region of the tail of the pancreas, a low grade inflammation of both knees and the left calf, and radiologically unchanged osteolytic bone lesions. Serum lipase and trypsin activity had become normal (Fig 3). Further treatment with combination chemotherapy was impossible because of a progressive polyneuropathy. One year after the start of

Figure 3: Serum trypsin and lipase activity during chemotherapy. Vertical bars: 5-fluorouracil 300 mg/m² on days 1–5; doxorubicin 50 mg/m² and cisplatin 100 mg/m² on day 1. Vertical lines: epirubicin 40 mg/m² and carboplatin 300 mg/m² on day 1.

chemotherapy and five months after the last course a relapse was discovered by a rapid increase in serum lipase and trypsin activity (Fig 3). A new liver metastasis was detected. After four courses of epirubicin 40 mg/m² and carboplatin 300 mg/m², both on day 1 every three weeks, serum lipase and trypsin activity returned to normal (Fig 3), and the liver metastasis almost completely disappeared.

Discussion

De Graciansky *et al*¹² were the first to show trypsin activity in the discharge of skin nodules in a patient with subcutaneous fat necrosis. Whether trypsin plays an important part in the pathogenesis of fat necrosis remains unclear. Since we measured the sum of trypsin, trypsinogen, and trypsin I bound to antiproteases, the biologically active free trypsin fraction is unknown, and might even be absent, because the antiproteases α_1 antitrypsin and α_2 macroglobulin are present in great excess in blood. The α_1 antitrypsin concentration can even double under various types of stress.¹³ This might account for the absence of trypsin in the urine, and the increase (instead of a decrease) in the serum α_1 antitrypsin concentration in our patient.

Although we were technically unable to show lipase or trypsin activity in the paraffin embedded tumour tissue, we assume that the tumour produced the enzymes. First of all, trypsin synthesis is attributed exclusively to the pancreas.^{14,15} Pancreatitis or pancreatic duct obstruction causes a temporary increase of all exocrine enzymes.^{14,15} We measured a persistent 100-fold increase in serum lipase and trypsin activity, without a rise in α amylase or carboxypeptidase-B. Finally, there was a positive correlation between tumour size and serum lipase and trypsin activity.

The good response to chemotherapy in our patient was remarkable. In the past, corticosteroids, colchicine, and various chemotherapeutic agents were used, but were ineffective.^{3,16-18} First, we treated our patient according to the phase II study regimen of 5-fluorouracil, doxorubicin, and cisplatin, which is used for inoperable locally advanced pancreatic carcinomas.¹⁹ After three courses we achieved a partial remission and after seven courses a further regression, approaching a 90% reduction in total, with normal enzymes and a major palliative result. Five months after the last course of combination chemotherapy the tumour relapsed, but then responded as successfully as the first time to chemotherapy consisting of epirubicin and carboplatin.

Further investigation is needed to establish the value of chemotherapy in the treatment of functional exocrine pancreatic carcinomas. It is clear, however, that the tumour behaves completely differently from the more common non-functional pancreatic carcinomas and might therefore be more susceptible to chemotherapy.

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