Acinar Pancreatic Tumor with Metastatic Fat Necrosis

Report of a Case and Review of Rheumatic Manifestations

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Fat necrosis metastasizing beyond the abdomen and thorax may occur with disease of the pancreas. When associated with a pancreatic tumor, the nodular subcutaneous lesions (panniculitis), polyarthritis, and eosinophilia are known as Schmid's triad (1). Fever, fat necrosis in bone marrow, lytic bone lesions, and elevated serum lipase are also features of the syndrome.

Twenty cases of metastatic fat necrosis (MFN) have been reported with pancreatic neoplasms (1–20), which were invariably derived from exocrine elements (1–16, 18–20). Pancreatitis ranging from severe (21) to silent (22) may be associated with an identical syndrome. This paper deals with MFN associated with a pancreatic tumor initially interpreted histologically as islet cell carcinoma or islet cell carcinoid. Ultrastructurally, however, the tumor was diagnosed as an atypical acinar carcinoma.

CASE REPORT

The patient, a 47-year-old black man, presented in October 1970 complaining of abdominal pain. Epigastric tenderness and microscopic hematuria were found, but subsequent urinalyses, arteriographic pyelography, and a gastrointestinal x-ray series were normal.

Nausea, postprandial vomiting, and weight loss prompted readmission in August 1971. A large, left upper quadrant mass was palpable. The white blood count was 11,900/mm^3, with a differential of 73% polymorphonuclear cells, 21% lymphocytes, and 6% eosinophils. The serum amylase was 48.4 Somogyi units (normal 60–160); and the serum calcium, phosphorus, and glutamic oxaloacetic transminase were normal. The prothrombin concentration was 70%, and the alkaline phosphatase, 73 units (normal up to 38). An upper-gastrointestinal x-ray series showed a retrogastric mass and hepatomegaly. Technetium-99m pertechnetate scintography showed a greatly enlarged liver with extensive "cold" areas. An arteriogram showed evidence of a highly vascular, space-occupying lesion fed by the dorsal magna and caudal pancreatic arteries, appearing to be 10 × 8 cm in size (Figure 1) and another vascular, space-occupying lesion involving the right lobe of the liver with stretching and displacement of branches of the right hepatic arteries (Figure 2).

Celiotomy on August 24, 1971, revealed numerous deposits which were visible and palpable under the capsule of the liver, and a hard 8 × 8-cm mass in the body and tail of the pancreas. A biopsy of one of the lesions in the liver showed cells characterized by eosinophilic cytoplasm and a round hyperchromatic nucleus, consistent with a metastatic, partially necrotic neoplasm.

The patient was discharged for follow-up care elsewhere. On November 8, 1971, tender edema around the ankles was noted. As this subsided, several red, painful pretibial nodules emerged. On readmission to our hospital on February 28, 1972, he complained of pain in his lower legs as well as swelling and pain about the knees. Soft, erythematous, minimally tender, 1–2-cm subcutaneous nodules resembling bland abscesses were scattered over the anterior surfaces of the lower legs (Figure 3). At the left knee there was pain on motion, increased heat, and swelling extending across the lower margin of the patella. At the lower border of the swelling were two fluctuant nodules with central scarring and eschars (Figure 4), the sites of recent spontaneous purulent drainage. Less marked articular swelling and tenderness were noted at the right knee.

Serum amylase determinations ranged from 114 to 145 units. The serum lipase was 25.8 units (Tietz–Borden, normal 0–2). Other serum laboratory values included alkaline phosphatase, 552 units (normal up to 79); uric acid, 3.7 mg; cholesterol, 218 mg; and total protein, 8.5 g/100 ml. Serum protein electrophoresis and immunoglobulins by radial immunodiffusion were normal. Eosinophilia fluctu-

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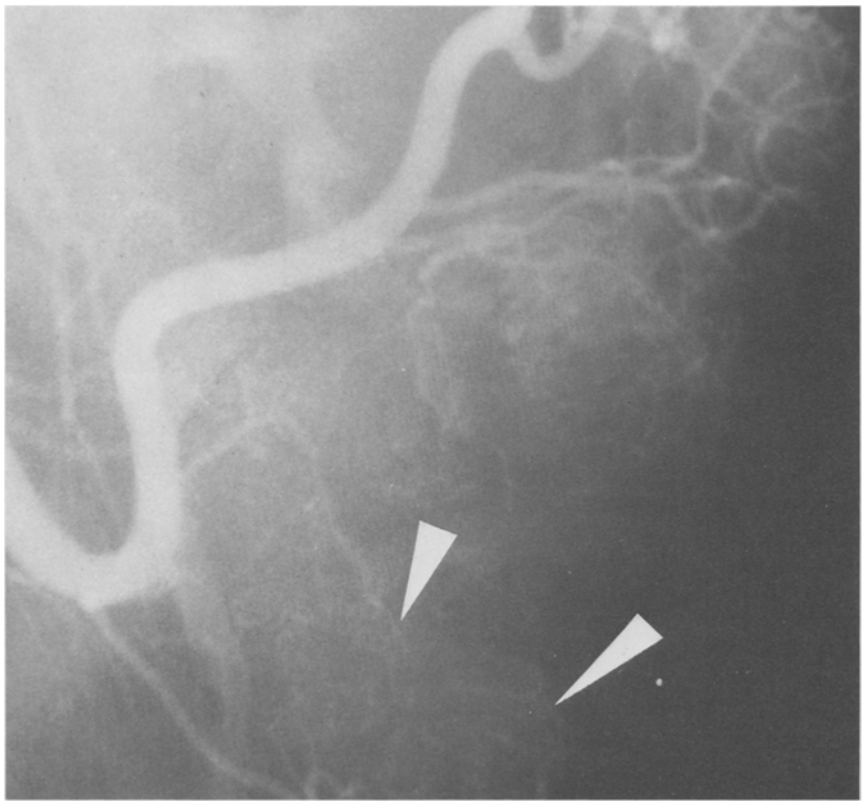

Fig 1. Primary mass in pancreas demonstrated by selective abdominal arteriogram. Multilobular 10 × 8-cm hypervascular neoplastic mass below the splenic artery. The mass is located posteriorly in the body and tail of the pancreas. Pancreatic arteries originating at splenic artery provide vascular supply for the mass. Note abnormal small vessel vascularity in foreground (see arrows).

ated between 7% and 12% of white blood cell counts from 10,400 to 11,400/mm^3.

A clear yellow fluid (8 ml) was aspirated from the left knee. The viscosity was normal, amylase, 73; and white count, 1900/mm^3 with 74% polymorphonuclear cells and 25% lymphocytes. Bacterial and fungal cultures were negative. Polarized microscopy disclosed no crystals, birefringent fat globules, or lipophages. Repeated needle aspiration of fluctuant nodular areas distal to the left knee yielded only a few drops of opaque material. On one occasion the aspirate contained a few diphtheroids and on another a few colonies of *Staphylococcus epidermidis*. Biopsy of a pretibial nodule showed necrosis of adipose cells and a superficial chronic inflammatory infiltrate sparing the epidermis.

The patient continued to complain of painful nodules and swelling of his lower legs, which varied from day to day. He developed pain and heat in the ankle and metatarsophalangeal joints. Two weeks after admission, several soft areas were evident on the bony anterior tibial surface near the left knee, the largest of which measured 2 × 1½ cm, palpable as a nontender crater with sharp edges covered by a membrane barrier. x-Rays showed lytic lesions and periosteal new bone in both tibias (Figures 5 and 6). The remaining skeletal structures were normal.

On March 7, 1972, weekly injections of 5-fluorouracil, 15 mg/kg intravenously, were started, with temporary improvement of abdominal distention and pain. The nodules over his lower legs and the pain in his joints resolved gradually, and new lesions did not occur after July 12, 1972.

He was admitted for the last time on August 25, 1972, after 2 weeks of multiple watery stools, his sole experience with diarrhea during the illness. Nodular subcutaneous lesions and joint swelling were no longer present. The serum sodium and carbon dioxide were normal; potassium was 2.9 mEq/liter; amylase, 104 units; and lipase, 24.9 units. Diarrhea was easily controlled by tincture of belladonna and by withholding 5-fluorouracil. x-Ray showed minimal progression of the lytic tibial lesions since March 1972. On September 19, 1972, he abruptly became obtunded and died.

Necropsy

Gross Findings. The peritoneum and omentum showed no signs of fat necrosis. The pancreas was normal except

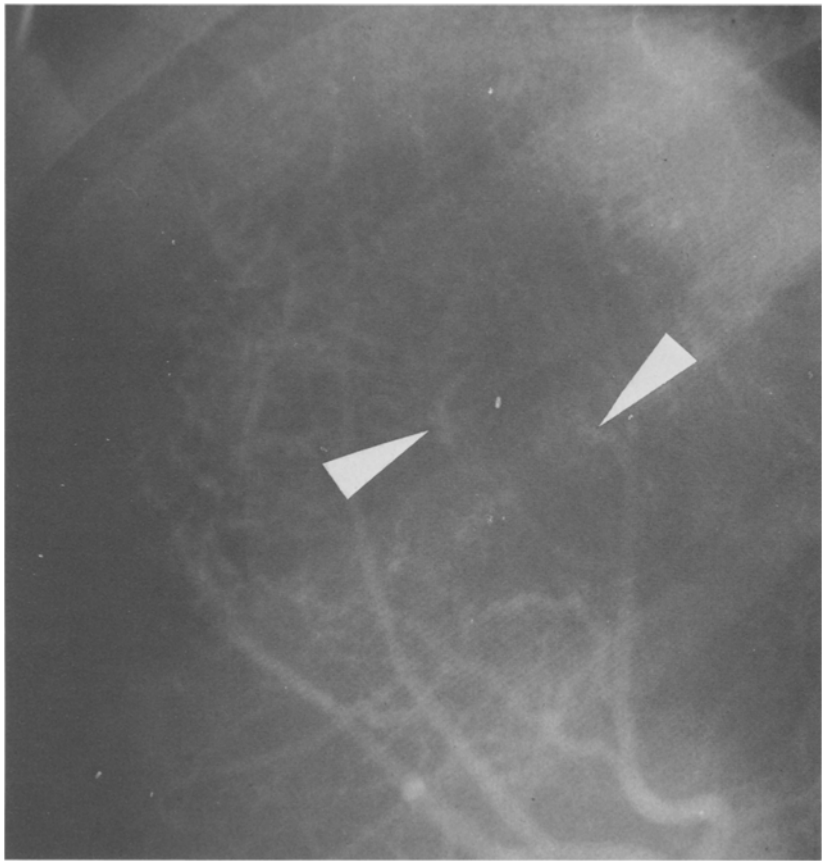

Fig 2. Metastatic infiltration in liver. Right upper quadrant detail of hypervascular metastatic lesion in liver. Note neoplastic tortuous irregular small vessels in metastasis (see arrows).

for a firm neoplasm measuring 10 × 5 cm in the body and tail. The tumor overlay the upper half of the left kidney but was not adherent to it. The liver weighed 6000 g; most of the parenchyma was replaced by tumor nodules, some showing central necrosis. Metastatic neoplasm was found in several periaortic lymph nodes, in the wall of the jejunum, and around the splenic artery and vein. Several cortical defects were noted in the upper part of the tibias. The marrow of the proximal left tibia was replaced by greenish, necrotic, putty-like material. The cartilage and synovium of the left knee were normal.

Microscopic Findings. The tibial marrow revealed necrosis of bone spicules and fat. Histologically, the neoplasm of the pancreas had several different patterns (Figure 7): cells packed into nests separated by a finely vascularized stroma, a trabecular pattern, and cells forming rosette-like structures around small blood vessels. In most areas, the cells were quite uniform in size and shape, the cell boundaries of the finely granular cytoplasm were indistinct, and nuclei were round or oval, varying little in size and shape. In some areas, however, there was a moderate amount of nuclear pleomorphism, and nucleoli were noted in some nuclei. Mitotic figures were not observed, and definite evidence of vascular invasion was not seen. The histologic features of the neoplasm in the pancreas and in the metastatic sites were identical. Fontana silver stains for identification of granules seen in some carcinoids were negative.

The ultrastructural findings (Figure 8) showed three types of neoplastic cells: dark cells mimicking acinar cells, granular cells, and agranular pale cells. The dark cells contained abundant round granules, ribosomes, and the rough-surfaced endoplasmic reticulum. The granules were of moderate electron density and were surrounded by a unit membrane without any clear space or halo beneath. They measured between 500 and 930 nm in diameter (average 680 nm).

DISCUSSION

Features of MFN

Tumor-associated MFN is characteristically a disease of men (17 of 20 reported cases) over 50 years of age (mean age 68, range 50–83). All but four (2, 3, 10, 13) had liver metastases, usually mas-

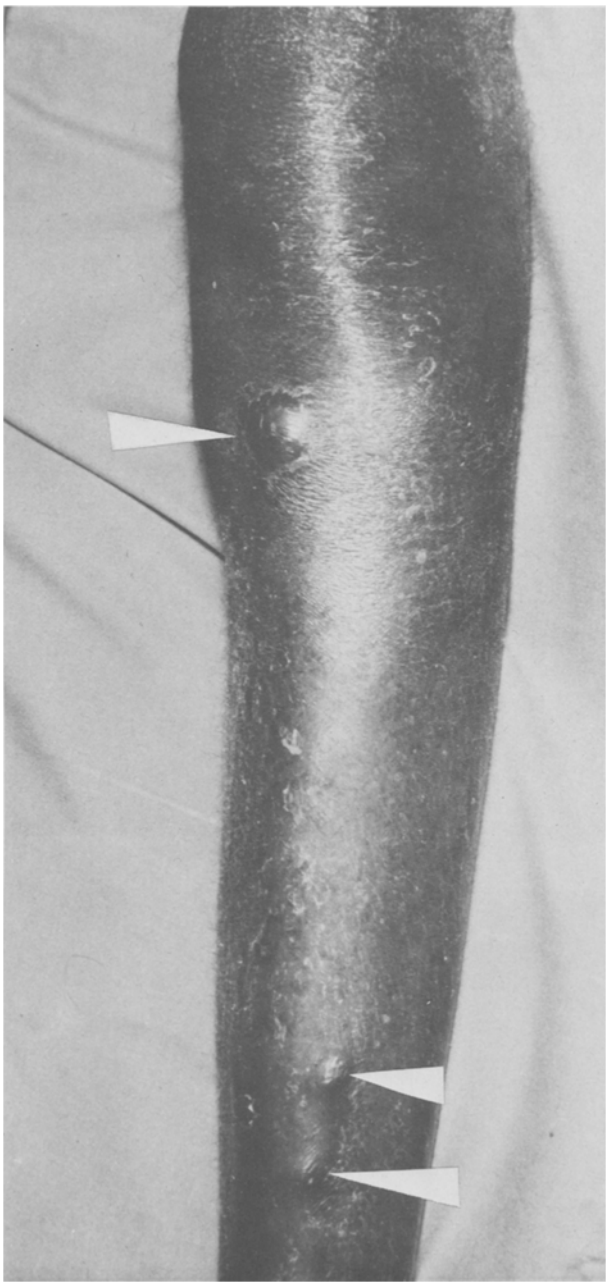

Fig 3. (3/6/72) Anterior left lower leg, extended, showing nodules (see arrows) and swelling near knee.

sive. The prognosis is poor, mean survival from appearance of subcutaneous lesions to death in 17 documented cases being only 5.9 months (range 2–12 months). However, fat necrosis *per se* has little or no role in mortality. There are numerous instances of recovery from widespread MFN associated with pancreatitis (23). Our patient is the youngest reported with tumor.

Joint involvement associated with MFN, reviewed in 1968 by Mullen and coworkers (23), may mimic the arthritis of gout, rheumatic fever, erythema nodosum, and the connective tissue diseases.

Although the joint disease is not primarily a synovitis, the end result can be dramatic. Within a month, a patient beginning with periarticular swelling progressed to "flail joints" in all the digits of the hands due to necrosis of periarticular structures (8). Necrotic material may enter the joint cavity. Necropsy of a recent case showed "shoulder, elbow, and knee joints . . . filled with copious amounts of green purulent fluid which seems to drain into the joints from the surrounding subcutaneous tissue." No synovial membrane was identified (18). In other recent cases, sinus tracts were found penetrating joint spaces at the knees and elbows (19), and wrists (15), communicating with necrotic periarticular and subcutaneous lesions (19).

In our patient, swelling at the knees was mainly due to involvement of periarticular fat. At the time of necropsy, penetration of necrotic material into the left knee had not occurred and the synovium was grossly normal.

Articular fluid has been obtained in 11 patients with MFN (4, 8, 12, 18–22, 24–26). Most of these aspirates probably represented liquefied material from juxtaarticular lesions that may or may not have entered the joint space (8, 18, 19, 22, 25). The fluids have been described variously as grayish with yellow flakes of tissue (4, 8), watery (25), or grossly pussy (18), and creamy (20) to yellow-brown (19). Two fluids were found infected, by *Staphylococcus aureus* (24) and *S. epidermidis* (21), respectively. Elevated synovial lipase has been noted (12). Questionable urate crystals were reported once (21), and possible pyrophosphate crystals in another instance (19), perhaps comprising mixed lipid crystals. Fat globules were demonstrated in 2 recent cases by Sudan stain (20, 26). In our patient, fluctuant juxtaarticular lesions near the patella were separable from a true synovial effusion.

The subcutaneous nodules may be either painful (3, 7, 10, 20, 22, 23, 25, 27) or painless (8, 9, 23, 25). They may occur anywhere but are most common over the lower legs, either posteriorly (10) or over the shins (19, 20, 22, 25), and they are especially frequent over pressure points (7, 25). They have been characterized as hot or erythematous (19, 22), flesh colored to purplish brown (10), usually unrelated to blood vessels (10), although in one case

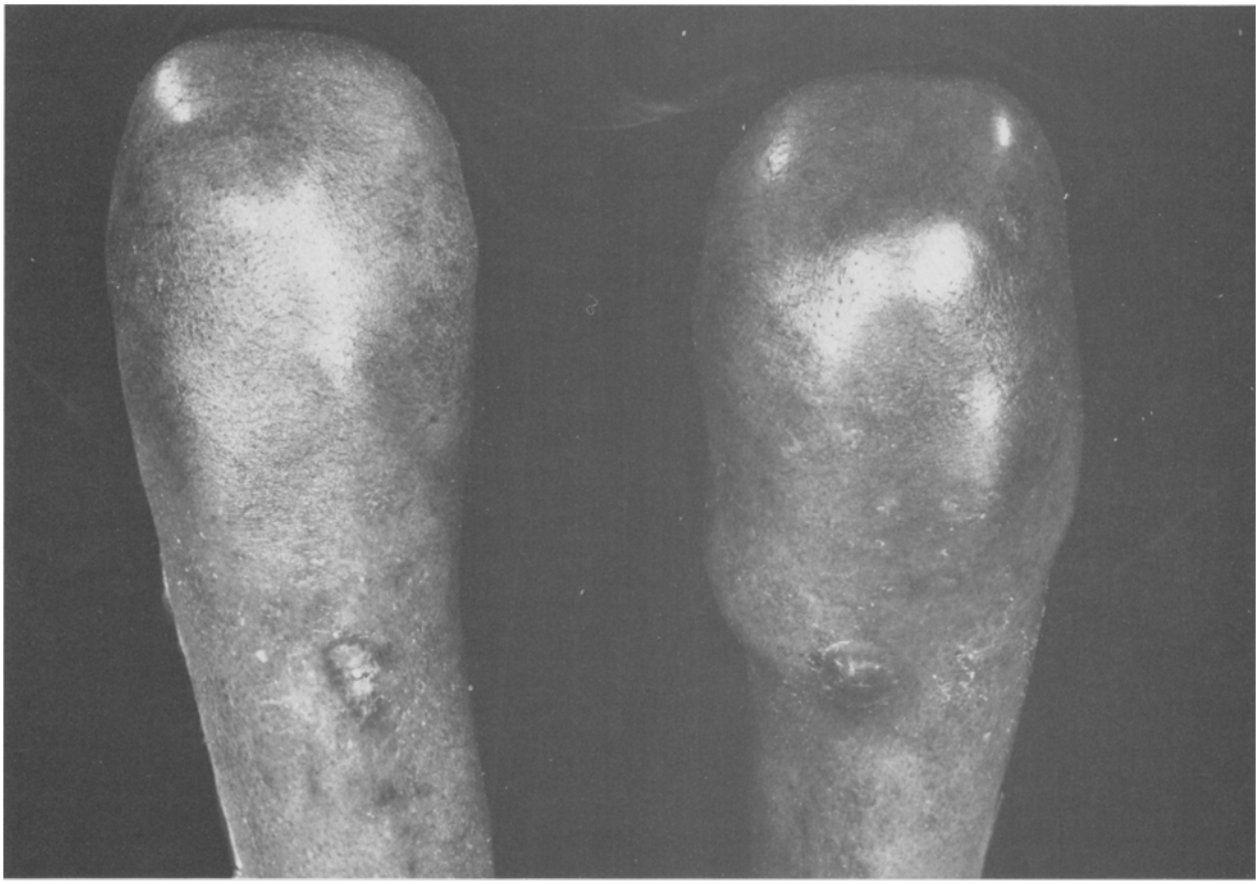

Fig 4. (3/8/72) Frontal view of both knees, flexed to 90°, showing appearance of localized fluctuant swellings distal to left patella. Swelling at right knee is not as extensive or apparent.

adjacent palpable cords suggested involvement of veins of lymphatics (3) and in another case the nodules followed the course of the superficial saphenous vein (16). The nodules occasionally break down and drain creamy oily material (11) that may show fat globules and lipophages microscopically (20, 23).

Bone involvement in MFN has been reviewed by Achord (24). Acute lesions present as medullary necrosis and multiple small osteolytic lesions, sometimes with periostosis. Bone lesions are frequently found underneath draining subcutaneous lesions (18). Although bone involvement has been described as painful (7, 27), it is more often painless (22, 24, 27, 28), as with our patient. Rapid progression with destruction of a phalanx within a short period has occurred (23). Our patient developed painless, palpable cortical defects in his tibias.

Immelman (27) as well as Gerle and co-workers (28) have pointed out that intramedullary calcific deposits and aseptic necrosis of bone may be sequellae of pancreatic bone disease. There is indeed evidence that bone lesions are far less rare than subcutaneous fat necrosis. At autopsy, necrotic marrow lesions were found in 7 of 67 patients with fatal pancreatitis, none of whom had subcutaneous lesions (29). Radiographs of the bones evidently may fail to divulge the presence or extent of marrow fat lesions. In the distal femur, extensive marrow necrosis found at necropsy was not visible in premortem films (7, 27).

Pathogenesis of MFN

In their patient with MFN, Heggler and Wohlvill (3) found a few nests of metastatic tumor cells in a necrotic marrow lesion and theorized that functional embolized tumor cells produce "ferments" that finally envelop the metastasis within a necrotic

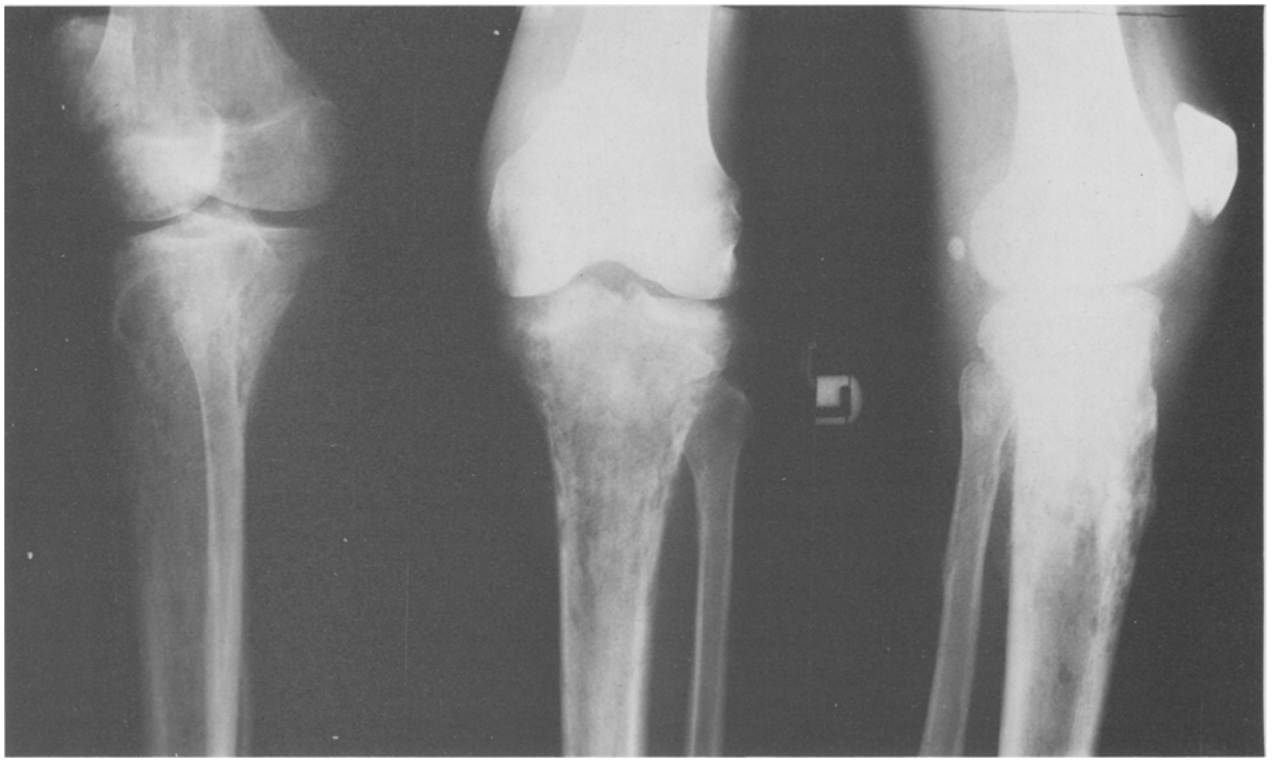

Fig 5. Oblique x-ray view of right knee as well as frontal and lateral view of left knee showing focal osteolytic cortical defects particularly evident in proximal tibia. Note bilateral symmetry of the defects and complete penetration of the cortex posteriorly in the left tibia.

reaction (''the cells dig their own graves''). Schmid (1) also found nests of tumor cells in bone marrow and in subcutaneous and paraarticular necrotic areas as well. However, others have not been able to find tumor metastases associated with focal necrotic lesions in marrow or subcutaneous fat.

According to prevailing opinion, simple reflux of lipolytic enzymes into the systemic circulation from necrotic pancreatitis or from functional acinar tumor cells provides the basis for distant fat necrosis. Years ago, prompt elevation of serum lipase was demonstrated following experimental ligation of the pancreatic duct (30). Intraperitoneal injection of lipase has reproduced distant fat necrosis (31). Assays of acinar tumor tissue from patients with MFN have shown high lipase activity (1, 7, 11, 12, 19).

In addition to primary pancreatitis and tumors, an assortment of pancreatic diseases have been associated with this curious syndrome, including trauma (27), a gumma (32), tuberculosis (32), ductile calculi (25), rupture of pseudocyst into the portal vein (33), and adenocarcinoma combined with chronic pancreatitis (8). From histologic descriptions available in 19 cases of tumor-associated MFN, it has been estimated that acinous carcinoma, which accounts for only 10% of pancreatic carcinomas, may have occurred in as many as 16 (84%) (18–20).

Although pancreatitis is well established as one cause of MFN, it appears that unknown synergistic factors are necessary for emergence of lesions in the subcutaneum, bones, and joints. Authors dealing with large numbers of patients with pancreatitis have not recognized a single case of subcutaneous fat necrosis (34, 35). In a trenchant experiment of nature, when a fistula developed between a pancreatic pseudocyst (into which the pancreatic duct drained) and the portal vein, subcutaneous necrotic lesions appeared acutely all over the body; however, no bone or joint involvement became apparent during the patient's remaining 6 weeks of life (33). The possibility of an immune-mediated component in MFN has been studied in two patients. In a case with a pancreatic tumor, no immunoglobulin or complement deposits were found in a dermal lesion, and serum complement com-

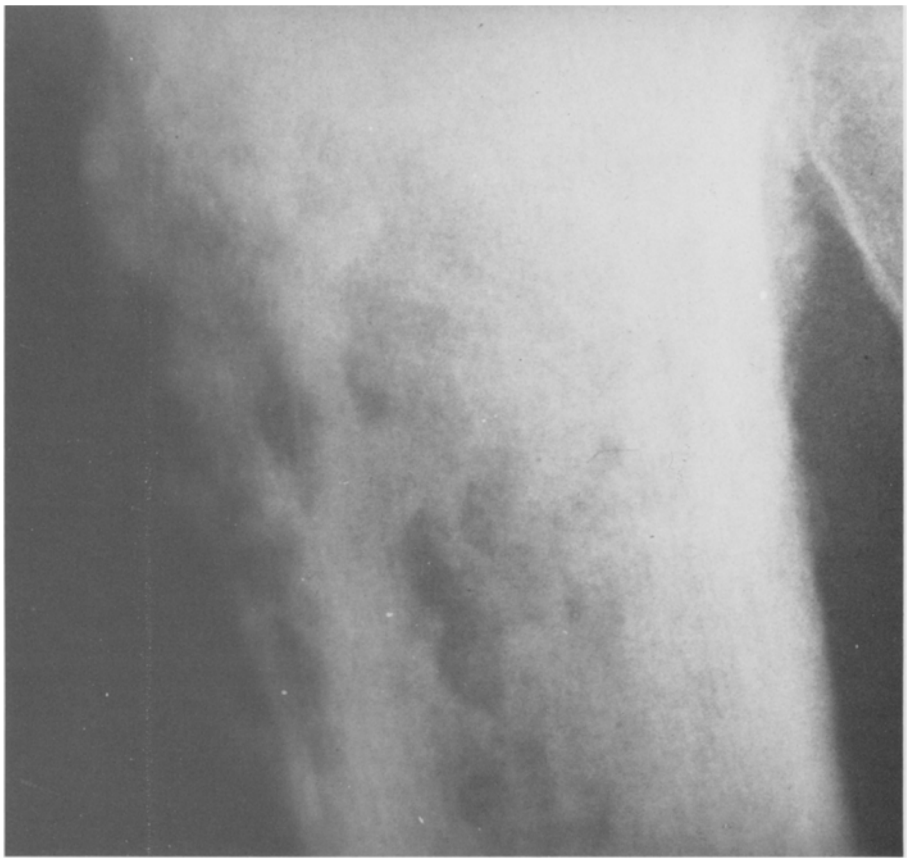

Fig 6. Close-up lateral x-ray view of right proximal tibia. Focal osteolysis is moderately well defined with distinct margins. In addition periosteal reaction is present posteriorly. The defects are scalloped. Similar local areas of periostosis were present in other areas of the proximal tibia. The osteolysis is not characteristic of permeation associated with neoplasm.

ponents were normal (20). In a case of pancreatitis associated with MFN and pleuropericarditis, immunoglobulin and C3 deposits were found in the pleura, as well as reduced serum total hemolytic complement (36).

Hyperlipasemia is a valuable diagnostic clue for MFN. Serum lipase was elevated in our patient during and after the period when active lesions of MFN were evident. A review of enzyme determinations reported in published cases of MFN with tumor, including our own (Table 1), shows an elevated lipase in all 9 patients tested for this enzyme; hyperamylasemia was found 4 times among 12 tested for amylase. Including our case, elevated lipase has been found 6 times in patients never showing hyperamylasemia. Conversely a normal lipase has never been reported in patients with elevated amylase.

Comments

In spite of the resemblance of the tumor by light microscopy to an islet cell tumor or a carcinoid, we prefer to accept the ultrastructural interpretation of the tumor, namely, an acinar cell carcinoma. Favoring this interpretation was the finding of the larger, homogeneous, moderately electron-dense granules (mean diameter 680 nm) which resemble the ultrastructural appearance of zymogen granules of acinar cells. Granules of islet cell tumors or carcinoids are smaller, having a mean diameter of 185–400 nm, and they may vary in electron density and in shape (37, 38).

MFN has never been a feature of islet cell carcinoid tumors, although there are reports of non-B islet cell adenomas associated with a red, sore tongue and migratory skin eruption characterized by annu-

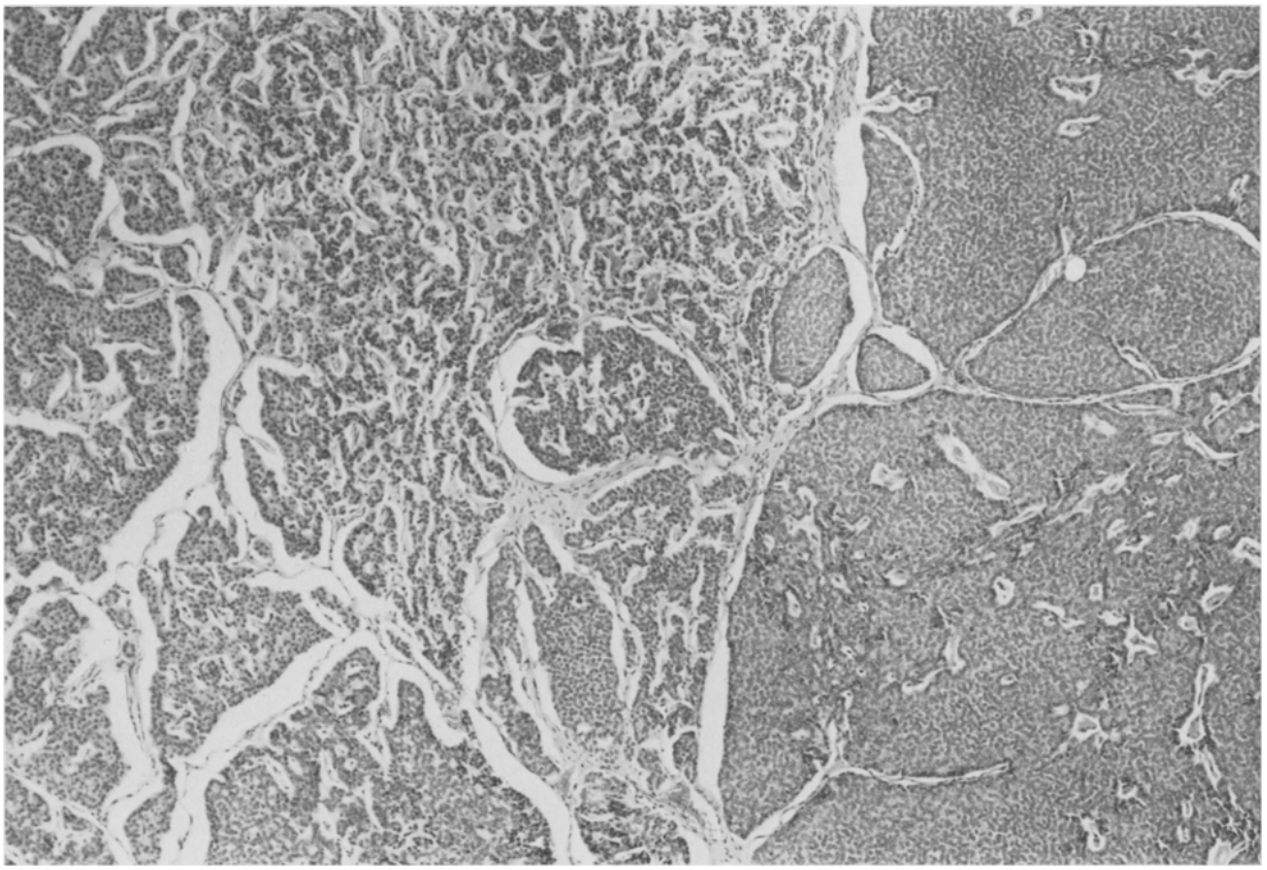

Fig 7. Tumor of the pancreas showing a trabecular pattern (left and center) and tumor arranged in sheets (right).

lar erythema and necrosis resembling a superficial chemical burn (39, 40). As several of these tumors have been glucagon secretors, it has been proposed that a lesion in the superficial epidermis is specific for hyperglucagonemia (41). In these patients, there are no reports of hyperlipemia or hyperamylasemia to lend support to the earlier suggestion (42) that circulating pancreatic enzymes were responsible for the dermal pathology. Such a dermatitis has not been described in patients with MFN, where the superficial portion of the skin is spared.

Therapy

Treatment of MFN has been ineffective. Subcutaneous nodules and joint pain have been unresponsive to colchicine, salicylates, phenylbutazone, corticosteroids, indomethacin, zymofren, iniprol, and ϵ-aminocaproic acid. In patients with tumors, lesions involving the subcutaneum and joints characteristically continue to appear to the time of death. In a recent patient (20), panniculitis resolved during the final 6 weeks of life after initiation of chemotherapy with bleomycin, adriamycin, cyclophosphamide, oncovin, and prednisone. In our patient, joint pain and subcutaneous nodules also abated during the final months of life, possibly an effect of 5-fluorouracil therapy.

SUMMARY

This report deals with a pancreatic tumor associated with metastatic fat necrosis. Our patient displayed the full gamut of nodular panniculitis, polyarthritis, fever, eosinophilia, hyperlipasemia, lytic bones lesions, and marrow fat necrosis. The rheumatologic features are reviewed. Elevated serum lipase is a most helpful laboratory confirmation. The tumor in our patient presented a difficult problem in classification. Although the appearance under light microscopy was most compatible with islet cell carcinoma or islet cell carcinoid, the ultrastructural characteristics were those of acinar carcinoma.

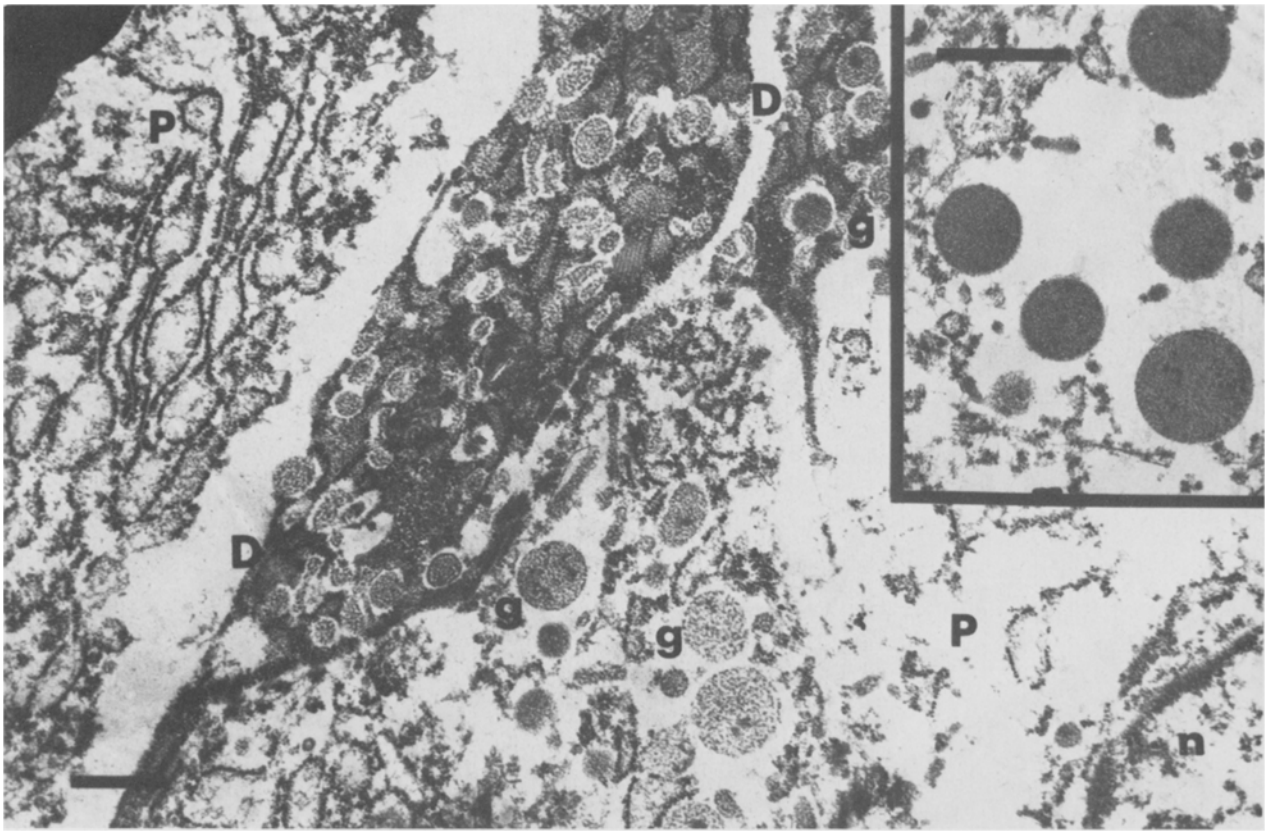

Fig 8. Electron micrograph showing parts of three pancreatic tumor cells. Two are pale cells (P), one granular, the other agranular. The third is a dark cell (D) containing dense granules (g), many ribosomes, and rough-surfaced endoplasmic reticulum. Inset: Higher magnification of the intracytoplasmic granules which have a mean diameter of 680 nm and a homogeneous content. (Formaldehyde fixation. The solid bars measure 1 μm; n = nucleus).

TABLE 1. SERUM ENZYME VALUES REPORTED IN METASTATIC FAT NECROSIS ASSOCIATED WITH TUMOR

Reference	*Year*	*Highest amylase (Somogyi units, normal 60–180/100 ml)*	*Lipase (units)*
Belsky and Cornell (8)	1955	367*	ND
Schmid (1)	1957	"normal"	ND
Alcantara (10)	1962	45	ND
Wuketich and Pavlik (11)	1963	"normal"	"high"
Lievre et al (12)	1964	65	4.5 (Cherry–Crandall, normal 0–0.5)
DeGraciansky et al (14)	1965	90	1.75* (normal 0–1.5)
Robertson and Eeles (16)	1970	"normal"	"elevated 4 times normal"
Bayle et al (17)	1971	300* (normal 50–100)	29* (normal 0–10)
Virshup and Sliwinski (18)	1973	300	26.9, 25.2 (Tietz–Borden, normal 0–2)
Burns et al (19)	1974	750	19–25 (Tietz–Borden, normal 0–2)
Tannenbaum et al (20)	1975	100	11.9–12.3 (Cherry–Crandall, normal 0–1.5)
Good et al	This report	145	25.8, 24.9 (Tietz–Borden, normal 0–2)

*Method not stated.

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