Pancreatic Panniculitis Secondary to Acinar Cell Carcinoma of the Pancreas

Ian R. Gorovoy, MD; John McSorley, MD; Jaclyn B. Gorovoy, BS

Practice Points

- Panniculitis frequently represents a dermatologic manifestation of a systemic disease and therefore merits consideration of a systemic workup.
- Pancreatic panniculitis can occur in the setting of normal pancreatic enzyme levels.
- Pathologic features of pancreatic panniculitis include a predominantly lobular panniculitis without vasculitis, necrotic adipocytes called ghost cells, and calcium salts deposited within the adipocyte cytoplasm.
- The triad of panniculitis, recent weight loss, and new-onset depression is particularly concerning for pancreatic cancer.

We report the case of a 68-year-old white woman who presented with painful, 1- to 4-cm, erythematous nodules located bilaterally on the anterior and medial shins that had progressively developed and worsened over the last month. Workup revealed pancreatic panniculitis (PP) secondary to acinar cell carcinoma of the pancreas (ACCP). The unique clinicopathologic features, differential diagnosis, underlying causes, associated laboratory and clinical findings, pathophysiology, treatments, and appropriate workup for PP also are reviewed.

Cutis. 2013;91:186-190.

Case Report

A 68-year old white woman presented for treatment of painful, 1- to 4-cm, erythematous nodules located bilaterally on the anterior and medial shins that had progressively developed and worsened over the last month despite treatment with cephalexin prescribed by her primary care physician (Figure 1). Her medical history was remarkable for non–small cell lung cancer that currently was in remission after treatment with radiation and chemotherapy, as well as diabetes mellitus, chronic anemia, nephrolithiasis, gastroesophageal reflux disease, migraines, hyperlipidemia, and fibromyalgia.

A review of systems was positive for 10-lb unintentional weight loss in the last 6 months, increased arthralgias in the last 2 months primarily involving the knees and ankles, and new-onset depression. Besides the cutaneous findings, physical examination was unremarkable, with a benign abdominal examination. Results of laboratory tests showed a mildly increased erythrocyte sedimentation rate of 46 mm/h (reference range, 0–20 mm/h), eosinophilia of 1.5×10^9/L (reference range, 0–0.5×10^9/L), increased lipase of 234 U/L (reference range, <95 U/L), and a normal amylase level. Alanine aminotransferase and aspartate aminotransferase levels demonstrated mild transaminitis (45 U/L and 51 U/L, respectively; reference range, 8–20 U/L). The remainder of the hepatic function panel was within reference range. The patient also reported a 30 pack-year history of smoking cigarettes.

A 5-mm punch biopsy specimen revealed mixed septal and lobular panniculitis with necrotic adipocytes (Figures 2–4). The adipocytes lacked nuclei

Dr. Gorovoy is from the Department of Ophthalmology, University of California, San Francisco. Dr. McSorley is from the Department of Dermatology, University of Pittsburgh Medical Center Presbyterian Shadyside, Pennsylvania. Ms. Gorovoy is from the Nova Southeastern University College of Osteopathic Medicine, Fort Lauderdale, Florida.

The authors report no conflict of interest.

Correspondence: Ian R. Gorovoy, MD, University of California, San Francisco, 10 Koret Way, Room K203, San Francisco, CA 94143 (gorovoyi@vision.ucsf.edu).

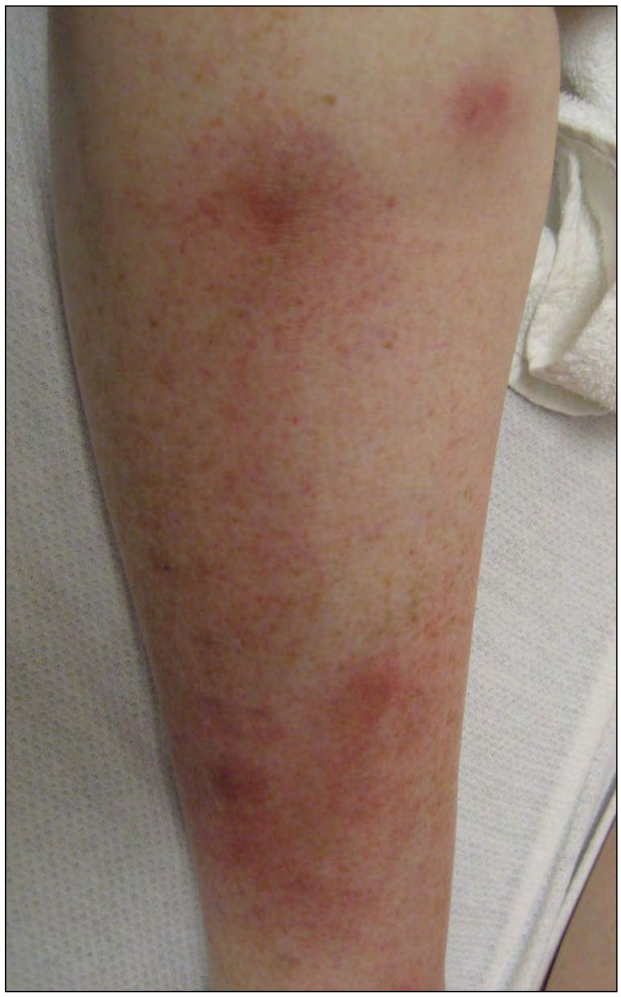

Figure 1. Tender erythematous subcutaneous nodules measuring 1 to 4 cm on the anterior and medial shin.

and demonstrated intact and thickened eosinophilic cell walls. The periphery of necrotic adipocytes showed deposition of granular basophilic material that was consistent with calcium. Histology was not consistent with vasculitis, and Gram, acid-fast, and Gomori methenamine-silver stains all were negative. Given the patient's extensive smoking history and unintentional weight loss, computed tomography of the abdomen was performed, which revealed a mass in the head of the pancreas and liver metastasis. Thus, a diagnosis of pancreatic panniculitis (PP) was made.

The patient underwent an endoscopic biopsy that revealed an acinar cell carcinoma of the pancreas (ACCP). Because of the liver metastasis, the patient was not a surgical candidate but was offered palliative chemotherapy, which she accepted. The patient died 5 months after the diagnosis of pancreatic cancer.

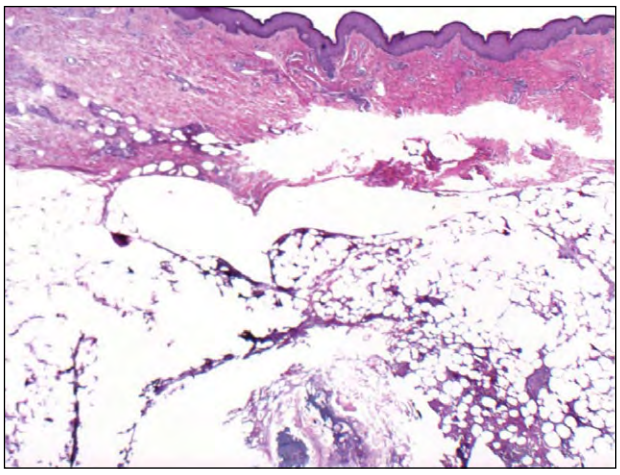

Figure 2. Low-power view demonstrates largely lobular panniculitis without vasculitis (H&E, original magnification ×2.5).

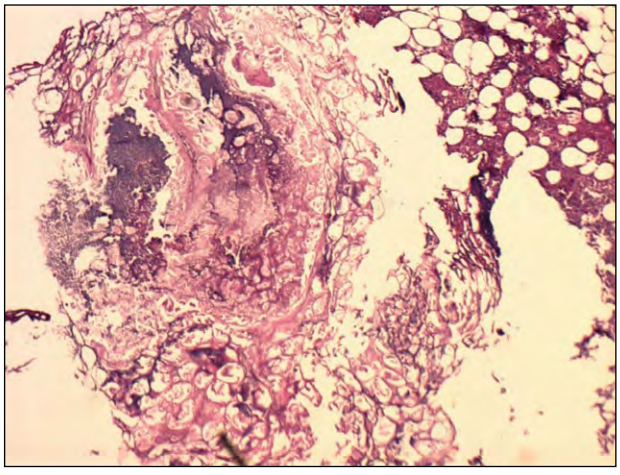

Figure 3. Coagulative fat necrosis with some ghost cells inferiorly (H&E, original magnification ×40).

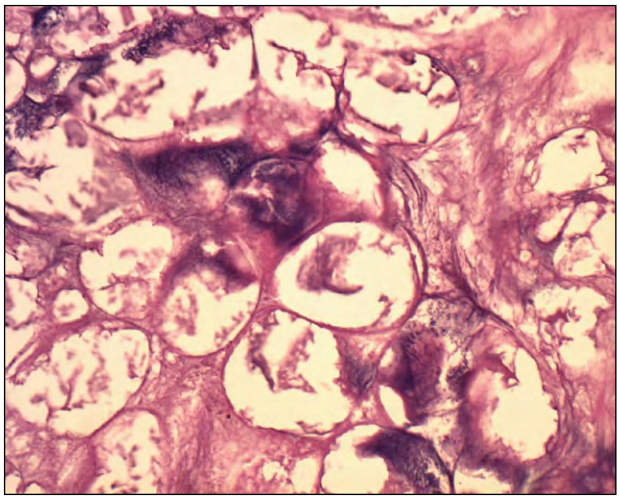

Figure 4. High magnification of ghost cells, which are characterized as anucleated adipocytes with a partially digested, shadowy cell membrane and basophilic granular calcium deposits (H&E, original magnification ×80).

Comment

Pancreatic panniculitis, also known as nodular subcutaneous fat necrosis, is a rare complication of pancreatic disease in which fat necrosis occurs in the subcutaneous tissue and throughout the body. It has an incidence of approximately 0.3% to 3% in patients with pancreatic disease.[1] First described by Chiari[2] in 1883, there now are approximately 100 reported cases in the literature. Pancreatic panniculitis is marked by multiple erythematous subcutaneous nodules that most commonly occur on the lower legs but also can involve the thighs, breasts, trunk, upper extremities, and even the scalp. Occasionally the nodules can ulcerate and discharge a sterile oily material comprised of degenerated lipocytes. Lesions usually heal with lipoatrophy and hypopigmented or hyperpigmented scars.[3]

Pancreatic panniculitis most frequently is associated with an acute or chronic pancreatitis, though it can occur in the setting of any pancreatic disease process (Table 1). Among the pancreatic cancers, ACCP has the highest incidence of causing panniculitis.[4] Panniculitis typically precedes the diagnosis of pancreatic disease in 2 to 28 weeks with an average of 13 weeks.[5] Therefore, diagnosis of the preceding skin manifestation is critical to patient care.

Differential Diagnosis—The differential diagnosis for tender subcutaneous nodules is extensive, including other forms of panniculitis and processes unassociated with panniculitis. The panniculitides include erythema nodosum, sclerosing panniculitis, α-1 antitrypsin deficiency panniculitis, erythema induratum, lupus panniculitis, Weber-Christian disease (idiopathic panniculitis), cutaneous polyarteritis nodosa, lipodystrophy, infectious panniculitis, traumatic panniculitis, cold panniculitis, malignancy-related panniculitis, and factitial panniculitis.[6] Other causes not associated with panniculitis include drug eruptions, subacute bacterial endocarditis, lymphoma, Whipple disease, gout, and carcinomas metastasizing to the dermis.[1] Therefore, it is crucial for the diagnostician to take a careful history and order appropriate laboratory studies.

Clinical Associations—The same processes that produce PP in the subcutaneous tissue affect the entire body; consequently, there is a high incidence of systemic manifestations of the disease. The most common clinical association is arthritis, affecting more than half of patients with PP.[5] Arthritis most commonly is symmetric and oligoarticular with involvement of the ankles, but any joints can be affected.[7] Joint aspiration typically produces a sterile, sometimes creamy fluid with few leukocytes and occasionally liquid lipid crystals containing triglycerides and pancreatic enzymes.[8]

Table 1.

Characteristics of Pancreatic Panniculitis

Clinical Associations
Acute/chronic pancreatitis (secondary to alcohol, trauma, biliary disease, infection, autoimmune disorders)
Pancreatic carcinoma
Pancreatic divisum
Pancreatic duct stenosis
Pancreatic pseudocysts
Pathologic Hallmarks
Ghost cells (lipocytes lose nuclei but have thick eosinophilic cell walls)
Saponification by calcium salts with deposition of granular or homogeneous basophilic material
Predominantly lobular panniculitis without vasculitis

Additional clinical signs of PP include fever, abdominal pain, osteolytic bone lesions, mesenteric or bone marrow thrombosis, gastrointestinal bleeding from submucosal adipose breakdown, and polyserositis (eg, pleural effusions)(Table 2). Radiographically, a characteristic moth-eaten appearance of the bone with periostitis from bone marrow fat necrosis and trabecular bone destruction is sometimes seen.[9]

Laboratory Abnormalities—Laboratory abnormalities in PP usually include elevated erythrocyte sedimentation rates as well as trypsin and lipase levels. Less commonly, eosinophilia, a high white blood cell count, and elevated amylase levels also are seen (Table 2).[5-7,10] As in our patient, amylase elevation is not commonly seen and patients may have increased levels of none or only 1 of the pancreatic enzymes.[10]

The triad of panniculitis, polyarthritis, and eosinophilia in a patient with a pancreatic tumor (known as Schmid triad) portends a poor prognosis.[11] If there is clinical suspicion of PP, we recommend checking the pancreatic enzyme levels, liver function, and erythrocyte sedimentation rate, in addition to a complete blood cell count and punch biopsy. It also is reasonable to conduct a carcinoembryonic antigen or cancer antigen 19-9 test, especially in patients with a history of smoking; unexplained weight loss; or pancreatic laboratory values within reference

Table 2.

Signs of Pancreatic Panniculitis

Clinical Findings
Subcutaneous nodules that may have an oily, ulcerative discharge with scarring and lipoatrophy on resolution
Arthritis associated with 50%–80% of cases, most commonly in the ankles
Fever
Abdominal pain
Ascites
Pleural effusion
Osteolytic bone lesions
Mesenteric or bone marrow fat thrombosis
Laboratory Findings
Elevated ESR, lipase, and trypsin levels, though they may be within reference range
Occasional eosinophilia, a leukemoid reaction, and elevated amylase level

Abbreviation: ESR, erythrocyte sedimentation rate.

range, which usually are elevated in the setting of acute pancreatitis.

Pathology—Although the histology of PP is truly diagnostic when the pancreatic disease has manifested itself, certain histopathologic characteristics are suggestive of PP before symptoms of pancreatic disease are present. Pathognomonic features of PP include a predominantly lobular panniculitis without vasculitis, necrotic adipocytes called ghost cells, and calcium salts deposited within the adipocyte cytoplasm from fat saponification secondary to pancreatic enzyme activation (Table 1).[1,10] Despite this triad of pathologic features, there is a characteristic evolution of the lesions through the disease course, which must be kept in mind when making the pathologic diagnosis.[12]

Early findings in cases of PP are nonspecific and marked by perivascular lymphocytic infiltrates, which lack necrosis and often are confused with erythema nodosum.[10] In the initial course of the disease, PP actually shows septal panniculitis prior to the development of lobular involvement.[12] Mechanistically, Ball et al[12] suggested that involvement of the septa occurs prior to the fat lobules because pancreatic enzymes first attack the endothelial lining of the septal vasculature. As the lesions progress, lobular panniculitis with characteristic coagulative necrosis consisting of focal areas of ghost cells and a neutrophilic infiltrate appear.

Ghost cells lack nuclei, have thickened but partially digested cell walls, and contain granular or homogeneous basophilic deposits made of calcium within the periphery of the cytoplasm.[13] As the lesions further evolve, the ghost cells become less evident, and a mixed granulomatous infiltrate of foamy histiocytes and foreign body giant cells surround the resolving coagulative fat necrosis and subsequent fibrosis. Clinically, healing of the nodules and lipoatrophy correlate with this last burnt-out stage.[14]

Pathophysiology—The exact mechanism of PP is still unclear, but the increased production and release of pancreatic enzymes likely is involved.[15] Some authors speculate that pancreatic trypsin may increase the permeability of the microcirculation within the lymphatic vasculature, allowing pancreatic enzymes to more easily enter into the fat lobules, causing fat necrosis and inflammation.[16] The mechanism by which pancreatic enzyme precursors are activated currently is not understood; however, it is possible that immunologic processes initiate subcutaneous fat necrosis and activate pancreatic enzymes locally.[17]

Immunohistochemical staining with antilipase monoclonal antibodies demonstrates pancreatic lipase within the necrotic adipocytes, which supports the pathogenic role of pancreatic lipase by at least placing the enzyme at the scene of the crime.[18] However, the majority of patients with pancreatitis or pancreatic carcinomas with increased serum levels of lipase do not develop panniculitis. Also, PP has been described in cases with serum levels within reference range for all pancreatic enzymes.[19] In vitro studies have failed to reproduce PP when normal human subcutaneous fat was incubated with serum of a patient with elevated levels of pancreatic enzymes.[1]

The mechanism of the arthritis likely involves the same lipolytic process seen in the panniculus affecting the periarticular and intramedullary fat. Free fatty acids often are found on synovial fluid analysis and illustrate the systemic effects of these pancreatic enzymes.[19] Other clinical signs may indicate fat necrosis in other organs. In addition to fat necrosis, Potts et al[20] suggested an immunologic component to the serosal involvement. They described a patient with pancreatic carcinoma and PP who had decreased serum complement levels and IgG deposited within the pleura. It is possible that this immunologic mechanism also may cause synovitis, which compounds the joint disease in these patients.

Natural Course and Supportive Treatment—In general, PP is more aggressive and widespread and more

likely to be ulcerative when the underlying cause is pancreatic carcinoma rather than pancreatitis.[10] Systemically, skin lesions tend to regress with the treatment of the underlying disease and the subsequent fall in pancreatic enzyme levels.[21] However, considering that the average 5-year survival rate for ACCP is 5%, this regression unfortunately does not occur when the underlying cause is malignancy.[22] The most successful treatment known to date is the use of the somatostatin analogue octreotide, which provides symptomatic relief by inhibiting the production of pancreatic enzymes.[21] A few reports in the literature have described improvement of lesions with surgical resection of the malignancy, which also may work by lowering pancreatic enzyme levels.[9,21] Additionally, supportive therapies including treatment with nonsteroidal anti-inflammatory drugs, dexamethasone, compression stockings, and leg elevation may help to a degree,[17] but there has been some debate about their effectiveness.[9]

Conclusion

The cutaneous manifestations of internal malignancies vary in their presentations and can be challenging for primary care physicians and dermatologists, especially when patients present with no other findings associated with malignancy. Interestingly, our patient presented with new-onset depression, which has been documented as an early symptom of pancreatic cancer.[23] Pancreatic panniculitis should be included in the differential diagnosis of painful erythematous nodules, particularly when they are progressive and unrelenting. Clinicians should be aware of this uncommon symptom, as early intervention can provide the patient with the best hope for treatment.

REFERENCES

1. Johnson MA, Kannan DG, Balachandar TG, et al. Acute septal panniculitis. a cutaneous marker of a very early stage of pancreatic panniculitis indicating acute pancreatitis. *JOP.* 2005;6:334-338.
2. Chiari H. Über die sogenannte Fettnekrose. *Prag Med Wochenschr.* 1883;8:255-256.
3. Sibrack LA, Gouterman IH. Cutaneous manifestations of pancreatic diseases. *Cutis.* 1978;21:763-768.
4. Berkovic D, Hallermann C. Carcinoma of the pancreas with neuroendocrine differentiation and nodular panniculitis. *Onkologie.* 2003;26:473-476.
5. Bogart MM, Milliken MC, Patterson JW, et al. Pancreatic panniculitis associated with acinic cell adenocarcinoma: a case report and review of the literature. *Cutis.* 2007;80:289-294.
6. Phillips RM Jr, Sulser RE, Songcharoen S. Inflammatory arthritis and subcutaneous fat necrosis associated with acute and chronic pancreatitis. *Arthritis Rheum.* 1980;23:355-360.
7. Francombe J, Kingsnorth AN, Tunn E. Panniculitis, arthritis and pancreatitis. *Br J Rheumatol.* 1995;34:680-683.
8. Chi ZC, Ma SZ. Rheumatologic manifestations of hepatic diseases. *Hepatobiliary Pancreat Dis Int.* 2003;2:32-37.
9. Price-Forbes AN, Filer A, Udeshi UL, et al. Progression of imaging in pancreatitis panniculitis polyarthritis (PPP) syndrome. *Scand J Rheumatol.* 2006;35:72-74.
10. García-Romero D, Vanaclocha F. Pancreatic panniculitis. *Dermatol Clin.* 2008;26:465-470.
11. Solcia E, Capella C, Klöppel G. Tumors of the pancreas. In: *Atlas of Tumor Pathology.* Series 3. Washington, DC: Armed Forces Institute of Pathology; 1997:103-114.
12. Ball NJ, Adams SP, Marx LH, et al. Possible origin of pancreatic fat necrosis as septal panniculitis. *J Am Acad Dermatol.* 1996;34(2, pt 2):362-364.
13. Barnhill RL, Sewall L. Panniculitis. In: Barnhill RL, Crowson AN, eds. *Textbook of Dermatopathology.* 2nd ed. New York, NY: McGraw-Hill; 2004:267-298.
14. Durden FM, Variyam E, Chren MM. Fat necrosis with features of erythema nodosum in a patient with metastatic pancreatic carcinoma. *Int J Dermatol.* 1996;35:39-41.
15. Dhawan SS, Jimenez-Acosta F, Poppiti RJ Jr, et al. Subcutaneous fat necrosis associated with pancreatitis: histochemical and electron microscopic findings. *Am J Gastroenterol.* 1990;85:1025-1028.
16. Cutlan RT, Wesche WA, Jenkins JJ 3rd, et al. A fatal case of pancreatic panniculitis presenting in a young patient with systemic lupus. *J Cutan Pathol.* 2000;27:466-471.
17. Phelps RG, Shoji T. Update on panniculitis. *Mt Sinai J Med.* 2001;68:262-267.
18. di Sant'Agnese PA. Acinar cell carcinoma of the pancreas. *Ultrastruct Pathol.* 1991;15:573-577.
19. Preiss JC, Faiss S, Loddenkemper C, et al. Pancreatic panniculitis in an 88-year-old man with neuroendocrine carcinoma. *Digestion.* 2002;66:193-196.
20. Potts DE, Mass MF, Iseman MD. Syndrome of pancreatic disease, subcutaneous fat necrosis and polyserositis. case report and review of literature. *Am J Med.* 1975;58:417-423.
21. Beltraminelli HS, Buechner SA, Häuserman P. Pancreatic panniculitis in a patient with acinar cell cystadenocarcinoma of the pancreas. *Dermatology.* 2004;208:265-267.
22. Gold EB, Goldin SB. Epidemiology of and risk factors for pancreatic cancer. *Surg Oncol Clin N Am.* 1998;7:67-91.
23. Mayr M, Schmid RM. Depression in pancreatic cancer: sense of impending doom [published online ahead of print February 9, 2010]. *Digestion.* 2010;82:1-3.