# Pancreatic Panniculitis Associated With Acinic Cell Adenocarcinoma: A Case Report and Review of the Literature

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GOAL

To understand pancreatic panniculitis to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the clinical and histopathologic features of pancreatic panniculitis.
2. Discuss the treatment of pancreatic panniculitis.
3. Identify panniculitides involved in the differential diagnosis of pancreatic panniculitis.

CME Test on page 296.

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*Pancreatic panniculitis represents a rare skin manifestation of underlying pancreatic pathology. The clinical presentation of the condition is remarkably consistent and privy to several unique clinical and histopathologic findings. We report a case of a 50-year-old white woman with pancreatic panniculitis and newly diagnosed pancreatic acinic cell adenocarcinoma. The clinical and histopathologic features, underlying causes, and treatments are reviewed.*

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## Case Report

In June 2005, a 50-year-old white woman presented to the emergency department with a 6-month history of nausea, vomiting, abdominal pain, and weight loss, and a 3-week history of painful leg nodules that had been increasing in size and number in the days

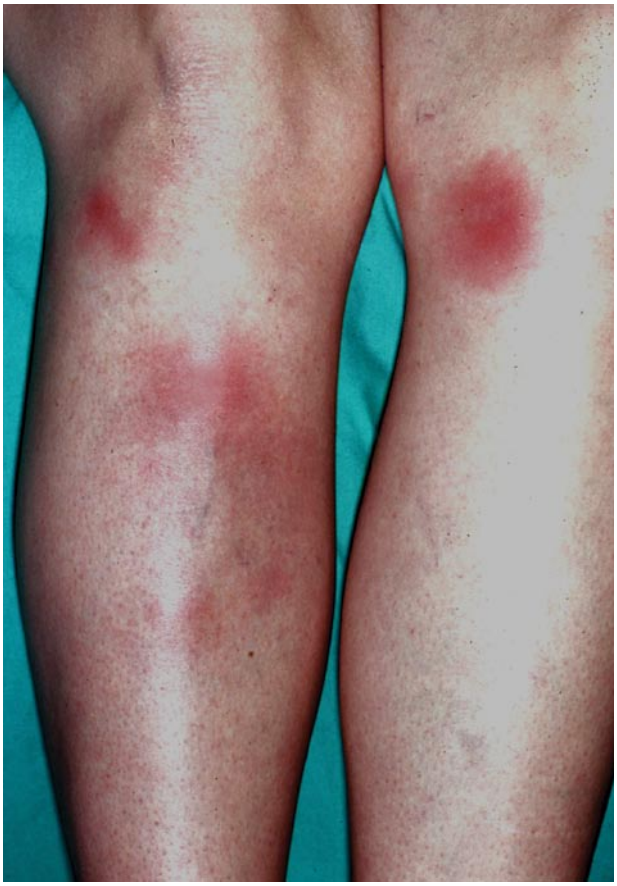

**Figure 1.** Erythematous nodules on the anterior and anteromedial shins bilaterally.

prior to admission. She currently was not taking any medications and was allergic to clindamycin and cefuroxime axetil. She smoked half a pack of cigarettes a day for the past 15 years and denied alcohol use. Her family history was notable for breast and colon cancer in her maternal grandmother and cervical cancer in her sister.

Physical examination revealed multiple 2- to 4-cm, firm, tender, erythematous nodules on the anterior and anteromedial shins bilaterally (Figure 1). There also was mild tenderness on palpation of the abdomen in the epigastric region. The remainder of the physical examination was unremarkable. Pertinent laboratory findings included an elevated lipase level of 4000 U/L (reference range, 31–186 U/L) and a slightly elevated amylase level of 114 U/L (reference range, 27–131 U/L). A complete blood count and liver function panel were within reference range.

A 5-mm punch biopsy specimen obtained from one of the nodules revealed a predominantly septal panniculitis with some lacelike lobular infiltration of inflammatory cells (Figure 2). Lymphocytes and neutrophils were observed, and eosinophils were particularly prominent. In addition, there were small foci of lipocyte degeneration and calcification, with formation of ghost cells (Figure 3). Aggregates of granular basophilic material also were identified, particularly near the base of the specimen. Gram, Gomori methenamine-silver, and acid-fast bacilli stains were negative for organisms. A diagnosis of pancreatic panniculitis was made.

Further workup of the patient revealed a 5-cm ill-defined mass in the pancreatic head as well as a 2-cm liver mass. Biopsy specimens of the pancreatic and liver masses revealed pancreatic acinic cell adenocarcinoma with metastasis. The patient initially was started on octreotide acetate, gemcitabine hydrochloride, and nonsteroidal anti-inflammatory drugs. After 3 months of therapy, the tumor remained stable in size, but the leg nodules had begun to regress due to the octreotide acetate. Additional chemotherapeutic agents were added to her treatment, including streptozocin and doxorubicin

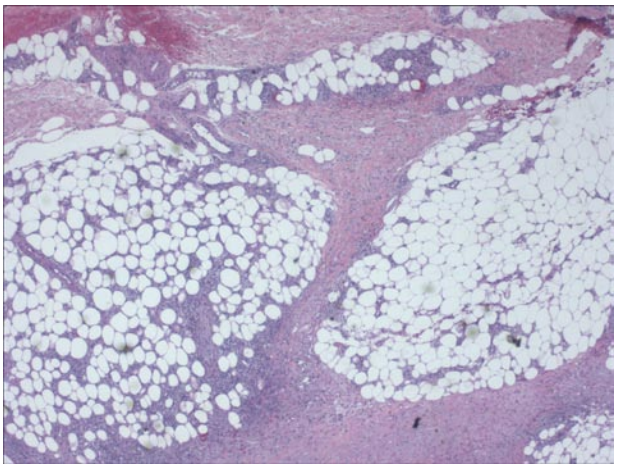

**Figure 2.** Septal panniculitis (H&E, original magnification ×40).

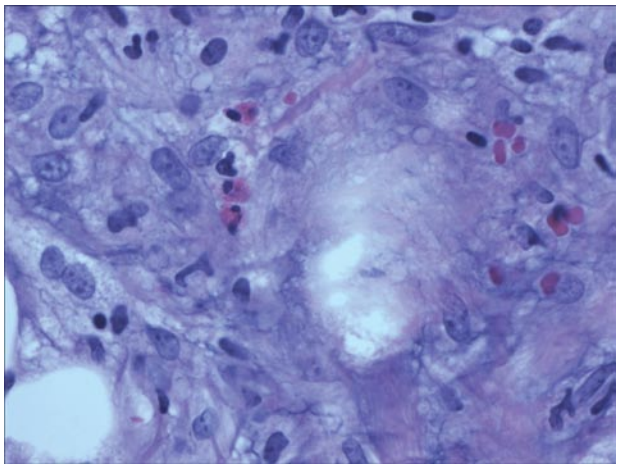

**Figure 3.** Eosinophils near a small focus of lipocyte degeneration (H&E, original magnification ×400).

Table 1.

**Clinical Features of Pancreatic Panniculitis**

| |
|---|
| Multiple subcutaneous tender nodules |
| Located on the lower legs and possibly the thighs, buttocks, trunk, and upper extremities |
| Ulceration with discharge of degenerated lipocytes |
| Resolution with lipoatrophy and scarring |
| Association with arthritis in 54%–88% of cases |
| Elevated sedimentation rates and lipase and trypsin levels are common |

hydrochloride liposome. In August 2005, the pancreatic carcinoma and liver metastasis had dramatically decreased in size and the panniculitis had resolved. The patient requested that the octreotide acetate and chemotherapy be discontinued. She presented again in December 2005 with the return of her panniculitis, this time involving her shins, arms, and hands. A few of the nodules on the shins were noted to express a brown-green oily fluid. Workup revealed an increase in size of her primary tumor and multiple liver masses. Octreotide acetate and chemotherapy were restarted. Two months later (February 2006), the patient's panniculitis had again regressed and her tumors slowly were decreasing in size.

## Comment

Pancreatic panniculitis is a cutaneous finding marked by multiple subcutaneous, raised, firm, tender, edematous nodules varying from erythematous to violaceous to red-brown. These nodules most commonly present on the lower legs but also can involve the thighs, buttocks, trunk, and upper extremities.[1-10] Individual nodules sometimes ulcerate and discharge a creamy, tan-brown, sterile, viscous substance made up of degenerated lipocytes. Lesions usually resolve with lipoatrophy and hypopigmented and/or hyperpigmented scars.[1,2] Additional clinical findings can accompany the skin lesions and relate to lipocyte degeneration in other organs. Periarticular lipocyte degeneration results in a secondary acute arthritis that most frequently involves the ankles and may be migratory, intermittent, or persistent. Other joints subsequently or concurrently may be involved, including the knees, metacarpals, wrists, and elbows. Arthritis has been reported in 54% to 88% of cases.[1,3] More rarely, submucosal lipocyte degeneration resulting in gastrointestinal tract bleeding can occur.[1] Common laboratory abnormalities associated with pancreatic panniculitis include elevated sedimentation rates and lipase and trypsin levels (Table 1). Some cases are associated with eosinophilia and increased amylase.[1-8] A differential diagnosis of panniculitides that may resemble pancreatic panniculitis could include erythema nodosum; sclerosing panniculitis (lipodermatosclerosis); $\alpha_1$-antitrypsin deficiency panniculitis; cutaneous polyarteritis nodosa; nodular vasculitis (erythema induratum); lupus panniculitis; and infective, traumatic, and factitial panniculitis (Table 2).[2,5,11,12]

The landmark article that first linked pancreatic disease with pancreatic panniculitis was published in 1883 by Chiari.[13] Disease processes that resulted in pancreatic panniculitis included acute pancreatitis, chronic pancreatitis, pancreatic pseudocysts, pancreatic duct stenosis, abdominal trauma, and pancreatic carcinoma. A case of panniculitis associated with lupus pancreatitis also has been reported.[14] Only 0.3% to 3.0% of patients with pancreatic disease develop associated panniculitis.[2] Pancreatic carcinoma and pancreatitis are most intimately associated with pancreatic panniculitis.[1] Specifically, acinic cell adenocarcinoma is responsible for more than 50% of all cases,[4] though only 16% of acinic cell adenocarcinomas present with panniculitis.[15] A small number of neuroendocrine carcinomas have been reported in the literature, as well as an isolated case of an intraductal carcinoid tumor in a pancreas divisum.[2,9,10] Pancreatitis plays a role in the development of most of the remaining cases.[1] Although pancreatic panniculitis only manifests in a small percentage of cases of pancreatic disease, its importance as a clinical sign should be recognized. As in our case, when panniculitis is observed, it is the presenting sign in 40% of cases of underlying pancreatic disease.[16] The panniculitis usually precedes the diagnosis of pancreatic disease by an average of 13 weeks, with a reported range between 2 and 28 weeks.[1]

Table 2.

## Panniculitides in the Differential Diagnosis of Pancreatic Panniculitis*[2,5,11,12]

| Diagnosis | Clinical Features | Histology | Additional Findings | Treatment |
|---|---|---|---|---|
| Erythema nodosum | Bilateral, tender, subcutaneous nodules most commonly on the pretibial area of young women | Septal panniculitis with granulomas | Edema of the legs, malaise, fever, arthralgia, gastrointestinal tract illness | Rest, elevation of the legs, NSAIDs, SSKI |
| Sclerosing panniculitis (lipodermatosclerosis) | Induration, erythema, and hyperpigmentation of the lower legs in a stocking distribution, "inverted champagne bottle" appearance | Lobular panniculitis with fibrosis, pale lipocytes, or ghost cells; hemosiderin deposition | Venous insufficiency | Elevation of the legs, compression stockings, stanozolol |
| $\alpha_1$-Antitrypsin deficiency panniculitis | Subcutaneous nodules on the legs with ulceration and exudation of oily material | Focal necrosis of lipocytes with neutrophils and histiocytes | Emphysema, cirrhosis, angioedema | Dapsone, infusion of human $\alpha_1$-proteinase inhibitor, liver transplantation |
| Cutaneous polyarteritis nodosa | Bilateral tender nodules on the legs that may ulcerate | Vasculitis of medium-sized arteries and arterioles in the fat septa | Livedo reticularis, myalgia, fatigue, low-grade fever | NSAIDs, prednisone |
| Nodular vasculitis (erythema induratum) | Erythematous tender plaques on the posterior lower legs that may ulcerate | Lobular panniculitis with neutrophils, vasculitis, necrosis | Tuberculosis may be associated with some cases | Antituberculous medications, if indicated |
| Lupus panniculitis | Nodules and plaques on the upper body that resolve with atrophy | Lobular panniculitis with lymphoid follicles, characteristic changes of discoid lupus in the epidermis and dermis | Features of systemic lupus erythematosus | Potent topical steroids, prednisone, dapsone, hydroxychloroquine |

| Diagnosis | Clinical Features | Histology | Additional Findings | Treatment |
|---|---|---|---|---|
| Infective panniculitis | Erythematous nodules | Lobular panniculitis with neutrophils, microorganisms may be identified with special stains | Immuno-suppression | Antimicrobial medications |
| Traumatic panniculitis | Indurated erythematous nodules on the breasts or shins | Confluent lipocyte degeneration resulting in cystic spaces with hemorrhage and fibrosis | History of trauma, resolution with lipoatrophy | None |
| Factitial panniculitis | Nodules occur at sites of injection of foreign material | Lobular panniculitis, foreign material identified with polarization | Psychiatric disease | Removal of foreign material, if feasible; psychiatric treatment |

*NSAIDs indicates nonsteroidal anti-inflammatory drugs; SSKI, saturated solution of potassium iodide.

The characteristic histopathologic features of pancreatic panniculitis were first described by Szymanski and Bluefarb[17] in 1961. Early lesions are nonspecific, marked by perivascular lymphocytic infiltrates that lack necrosis and may resemble erythema nodosum.[4] In fact, Ball and colleagues[18] have suggested that pancreatic panniculitis may begin as a septal panniculitis and only later develop lobular involvement. Biopsies performed on specimens from the nonulcerated, fully developed erythematous nodules reveal both lobular and septal panniculitis highlighted by focal areas of lipocyte degeneration populated by anucleate necrotic adipocytes surrounded by thickened acidophilic cell membranes, termed *ghost cells*. A unique feature, when present, is the deposition of granular or homogenous basophilic material resulting from the saponification of fat by calcium salts.[12] A dense infiltration of lymphocytes, macrophages, neutrophils, and variable numbers of eosinophils exists at the periphery of the necrotic areas along with evidence of calcification. Resolution of the nodules is characterized by a granulomatous infiltrate that replaces the areas of necrotic tissue.[1] The presence of numerous eosinophils was a striking feature in our case and has not been emphasized previously in the literature in this form of panniculitis.

Although there is no universally accepted mechanism for the development of the skin lesions, a popular hypothesis states that a synergism exists between the elevated serum levels of lipase and trypsin. Trypsin alters the permeability of the tissue blood vessels, which allows lipase to hydrolyze lipids in the adipocyte cell membranes and interior, which leads to lipocyte degeneration of the tissue.[16,19] Support for this hypothesis is garnered by the observations that more than 50% of patients with pancreatic portal fistulization develop panniculitis, and immunohistochemical analysis of the areas of lipocyte degeneration demonstrate pancreatic lipase.[6,20] Potts and colleagues[21] suggested a possible immunologic mechanism in a patient with pancreatic carcinoma and pancreatic panniculitis who was noted to have decreased complement levels and deposition of immunoglobulin G in the pleura.

Successful treatment of pancreatic panniculitis usually requires diagnosis and treatment of the underlying pancreatic pathology. As the pancreatic enzyme levels decrease, the skin lesions usually tend to regress.[3] There has been some success

reported with the administration of octreotide acetate, a synthetic polypeptide that inhibits pancreatic enzyme production.[1,2,4,6] In addition, general supportive measures, including rest, elevation of the legs, compression stockings, and nonsteroidal anti-inflammatory drugs, may be helpful.

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