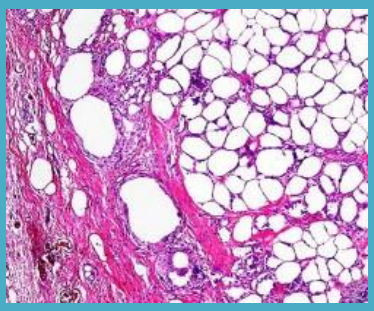
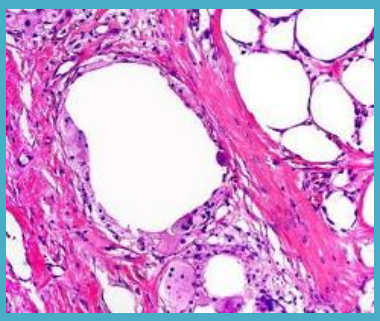
Dermatopathology

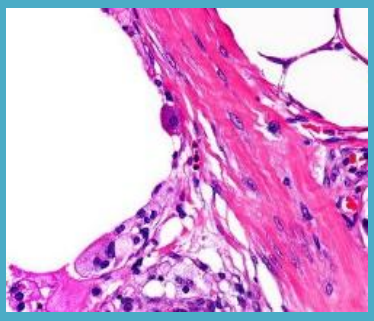
Weill Cornell Medical College

Case Presentation 4

Pancreatic Panniculitis as an Initial Presentation of Acinar Cell Carcinoma of the Pancreas







This educational series for physicians is presented by the Weill Cornell Comprehensive Dermatopathology Service

Case author: Cynthia M. Magro, MD
Case contributors: Hari Nadimanti, MD, Summit Dermatology Group, New Jersey & Ikjot Bhutani, MD, University of Cincinnati

Panniculitis is defined as inflammation of subcutaneous adipose tissue. The skin lesion in panniculitis appear as small, erythematous, painful nodules that appear alone or in clusters. They can be nonspecific and may be confused as being lesions caused by other diseases. Therefore a biopsy is required to make a definitive diagnosis. Differential diagnostic considerations include: pancreatic disease, lupus profundus, erythema nodosum, periarteritis nodusa, Weber-Christian disease, drug eruption, vasculitis, lymphoma, Whipple disease, Wegener granulomatosis, metastatic carcinoma, and gout. A correlation between skin lesions resembling erythema nodosum and pancreatic disease was first recognized by Chiari in 1883, but due to the uncommon relationship, only approximately 100 cases of pancreatic panniculitis (PP) have been reported to date. It is noted that panniculitis occurs in about 2-3% of patients with pancreatic disease. The most common cause of PP is pancreatitis, either acute or chronic, due to excessive alcohol consumption, trauma, or cholelithiasis. Less commonly PP can be caused by malignancy in the pancreas most commonly with acinar cell carcinoma or less frequently by cystadenocarcinoma. Of note, PP may be a precursor of pancreatic disease and could manifest itself before any other symptoms appear.

Clinical History

The patient was a 71 year old male who presented to the emergency room with a recent positive PPD with a 2 to 3 week history of painful erythematous nodules on the lower extremities (figure 1). Some of the lesions were draining. The clinical impression was erythema induratum. A biopsy was performed for diagnostic confirmation.

Pathological Findings

The Biopsy was taken from the skin of the left thigh. It shows a very striking neutrophilic lobular panniculitis (figure 2a, 2b,2c). There was a distinctive pattern of fat necrosis characterized by retention of the cytoplasmic membrane of the adipocyte with internal basophilic granular degeneration of the fat compatible with enzymatic fat necrosis. A diagnosis was made of pancreatic panniculitis. Subsequent investigations disclosed an elevated amylase. PET scans disclosed a mass in the heads of the pancreas. A biopsy was performed and was diagnostic of acinar cell carcinoma of the pancreas.

Discussion

Acinar cell carcinoma is a relatively uncommon cancer of the pancreas, accounting for less than two percent of malignancies of pancreatic origin (7). PP will only occur in 10 percent of patients with acinar cell carcinoma (7). Other forms of pancreatic carcinoma are not associated pancreatic panniculitis.

The exact mechanism by which this rare form of pancreatic carcinoma causes panniculitis is unclear although theories have been postulated. The most likely explanation is the elaboration of pancreatic enzymes from the tumor specifically with respect to trypsin and lipase. Pancreatic acinar cell carcinoma is highly distinctive in its clinical presentation due to significant paraneoplastic effects associated with the elaboration by the tumor of pancreatic exocrine enzymes into the pancreatic duct and large blood vessels. . One of the most characteristic manifestations is in the context of pancreatic panniculitis. The enzymes are released into the blood localizing to the subcutaneous fat of the lower extremities likely reflective of the hydrostatic effects of trypsin on the subcutaneous vasculature of the lower extremity. The effect is one of enhanced vascular permeability allowing other exocrine enzymes such as lipase to hydrolyze the fat. Indeed immunohistochemically positive reactions between anti-lipase monoclonal antibodies and pancreatic lipase in necrotic adipocytes have been observed . In addition, experiments have shown fat necrosis in rats by injection of pancreatic extract. Further supporting the theory is the fact that greater than half of all patients with a pancreatic portal fistulization develop panniculitis (8). The definitive role of lipase is not without it's limits though as there have been cases of PP occurring in patients with normal serum pancreatic enzyme levels, including lipase. Also, panniculitis does not develop when normal human subcutaneous tissue is incubated with serum containing pancreatic enzymes in vitro. Other features of pancreatic panniculitis include peripheral blood eosinophilia.

Continued

The lesions of PP are erythematous subcutaneous nodules which may discharge an oily brown material. This substance emanates from liquefaction necrosis of adipocytes . The parts of the body where the lesions are most likely to be found are: the distal parts of the lower extremities, although they can occur anywhere else (10). In the case herein, the patient reported nodules on his lower extremities for 2-3 weeks prior to coming to the ER, some of which were draining. paraneoplastic PP caused may exhibit a more chronic course rather than those cases attributable to acute pancreatitis .

A definitive diagnosis of pancreatic panniculitis usually requires biopsy assessment. It can be challenging to diagnose PP clinically due to the monotony of the lesions caused by differing etiologies and also microscopically due to the dynamic changes in the subcutaneous tissue in regard to inflammatory cell composition and distribution over time (9). Of utmost importance is recognizing specific tell tale histopathological clues as to the cause of the lesions. While neutrophilic lobular panniculitis can be seen in various settings including nodular vasculitis, the infection id panniculitis including erythema induratum, subcutaneous Sweet's syndrome and alpha 1 antitryspin deficiency, the distinctive nature of the fat necrosis in PP is virtually diagnostic of this entity. The characteristic hallmarks are adipocytes exhibiting internal degeneration with basophilic granular degeneration of the cytoplasmic contents. The cytoplasmic membranes acquire a thick, residual, shadowy wall. The nucleus is not discernible. The effects are attributable to hydrolysis of fat followed by the subsequent reaction of fat with calcium which imparts the granular basophilic quality to the cells. This process is consistent with saponification. In later stages there is granulomatous inflammation with foamy histiocytes, multinucleate giant cells and hemosiderin deposition . While the positive history of tuberculosis lead the medical team to consider erythema induratum which can also exhibit a neutrophilic and granulomatous lobular panniculitis, the distinctive adipocyte alteration as alluded to above is truly pathognomonic for PP.

Treatment of PP will ultimately involve resolving the primary pancreatic disease causing the release of enzymes into the bloodstream. In cases of pancreatic carcinoma, surgical removal of the tumor might alleviate the symptoms. Given the morbidity of pancreatic cancer, this is not always possibl. Interestingly, there has been a report of a case of PP relieved by the use of octreotide; octreotide inhibits pancreatic enzyme production). Supportive care is utilized for the management of the skin lesions while the primary pancreatic pathology is treated .

Conclusion

Pancreatic Panniculitis may represent a subcutaneous paraneoplastic presentation of one of the rarest but most distinct forms of pancreatic carcinoma. Recognition of this association may lead to earlier diagnosis offering the potential for cure of an otherwise uniformly lethal form of malignancy.

Case References

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Figure Legend

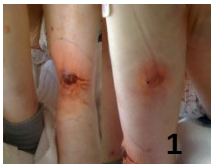

Figure 1 : Painful erythematous nodules developed on the lower extremity. Ulceration was observed.

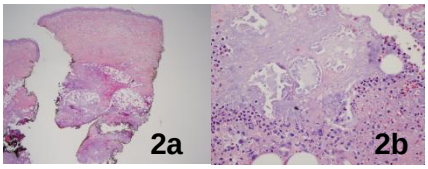

Figure 2a and 2b: The biopsy showed a lobular panniculitis with striking permeation of the interstitial spaces of the fat lobule by neutrophils.

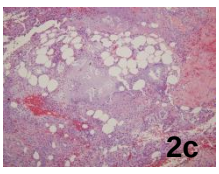

Figure 2c: The pattern of fat necrosis is one diagnostic of enzymatic fat degeneration. The hypereosinophilia of the cytoplasmic membranes in concert with the internal granular basophilia is diagnostic of enzymatic fat necrosis reflecting the affinity of hydrolyzed fat with calcium The adipocyte cytoplasmic membranes typically retain their integrity.

Under the direction of Dr. Cynthia M. Magro, the Weill Cornell Comprehensive Dermatopathology Service is a leading edge consultation service and CAP-accredited laboratory for dermatologists, plastic and general surgeons and other dermatopathologists. Dr. Magro is an internationally renowned dermatopathologist, educator and author. She is a Professor of Pathology and Laboratory Medicine at the Weill Cornell Medical College in Manhattan, and is board certified in anatomic pathology, dermatopathology and cytopathology. Dr. Magro is an expert in the diagnosis of complex inflammatory skin diseases. Her areas of expertise include cutaneous manifestations of auto-immune disease, systemic viral disease and vasculitis, atypical drug reactions, benign, atypical and overtly malignant lymphocytic infiltrates of the skin, and diagnostically difficult melanocytic proliferations.The award-winning author of *The Melanocytic Proliferation: A Comprehensive Textbook of Pigmented Lesions*, Dr. Magro has recently completed her second book, *The Cutaneous Lymphoid Proliferation, a comprehensive textbook on benign and malignant lymphocytic infiltrates*. She has co-authored over 250 peer reviewed papers and several textbook chapters. Dr. Magro frequently presents courses on inflammatory skin pathology and difficult melanocytic proliferations to the American Academy of Dermatology, the United States and Canadian Academy of Pathology, and the American Society of Clinical Pathology. Dr Magro has consistently been recognized in Who's Who in America®, Castle Connolly's renowned America's Top Doctors – New York Metro Area® edition and in the Super Doctors® list published in The New York Times Magazine.

For more information, consultation, or patient referral please contact:

Cynthia M. Magro, MD, Director
Weill Cornell Comprehensive Dermatopathology Service
Tel. 212-746-6434
Toll-free 1-800-551-0670 ext. 66434
Fax. 212-746-8570
www.weillcornelldermpath.com