

Update on Panniculitis

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Abstract

There is considerable confusion regarding the pathogenesis, nosology and treatment of panniculitis. This paper examines newer concepts in five types of panniculitis: i.e., histiocytic cytophagic panniculitis, erythema induratum, lipodermatosclerosis, pancreatic panniculitis and alpha-1-antitrypsin deficiency panniculitis. Recent developments in etiology, pathogenesis, molecular techniques, and therapy are discussed.

Key Words: Panniculitis, lymphoma, cytophagic, alpha-1-antitrypsin, pancreatitis.

PANNICULITIS HAS BEEN OBSERVED in a number of clinical entities. These include erythema nodosum, erythema induratum, Weber-Christian panniculitis, pancreatic fat necrosis, lupus panniculitis, as well as others. Histologically, inflammation may predominate in the septae of the panniculus or within fat lobules, and the pattern of inflammation can often be useful in distinguishing these entities. On the other hand, the precise pathology of many so-called "well-defined" panniculitides can be confusing, since the histology depends on the stage of the lesion, which may evolve from day to day. The general pathology of panniculitis has previously been reviewed (1, 2). We will present material on five uncommon types of panniculitis in which significant advances have been made in the past ten years.

Histiocytic Cytophagic Panniculitis

Originally, histiocytic cytophagic panniculitis (HCP) was classified as a systemic histiocytosis. HCP, first described by Winklemann and associates (3, 4), has a characteristic clinical presentation. Patients develop large, ecchymotic, subcutaneous nodules that frequently become ulcerated. Systemic manifestations such as fever and malaise are common, as are anemia, leukopenia, thrombocytopenia, elevated hepatocellular enzymes, and a severe coagulopathy; often there is disseminated intravascular coagulation. While many patients with HCP

suffer from relatively indolent variants of the disease, many others die as the result of massive visceral hemorrhage or organ system failure (5). Pettersson et al. reported that chemotherapy usually has only limited efficacy (6). However, a recent report by Ito et al. suggests that CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) therapy combined with cyclosporin A may be useful (7).

The pathology of HCP is quite distinctive (3, 4). Characteristically, there is prominent infiltration by histiocytes within the subcutis. These histiocytes, which phagocytize erythrocytes and other cells, have been referred to as "beanbag" cells. Peripherally, there are small lymphocytes that are cytologically benign. Similar infiltration affects other areas as well, including bone marrow, lymph nodes and other tissue of the reticuloendothelial system.

Three recent developments have changed our understanding of this entity. The first was the realization that certain cases of so-called systemic Weber-Christian panniculitis with visceral involvement actually represent HCP.

Weber-Christian panniculitis was originally described in the 1920s as a poorly defined, local, non-suppurative condition involving the subcutaneous fat. Other cases of Weber-Christian panniculitis were reported in which there was suppuration and/or visceral involvement. Ultimately, the condition was considered to progress through three stages: the first was characterized by suppuration; "foam cells" are prominent in the second; and fibrosis develops in the third. The second stage of Weber-Christian panniculitis was alleged to be the most diagnostic. It is now clear that: (a) the histology of Weber-Christian disease is not as specific as was previously thought and (b) many cases of "systemic" Weber-Christian disease, upon sub-

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sequent review, have been proven to represent other types of panniculitis. It is now also apparent that those cases with bone marrow and serosal involvement demonstrate cytophagocytosis and therefore should be reclassified as cytophagic panniculitis (8, 9).

The second development that changed our understanding of HCP was the realization that there is a clinical and histologic overlap of some cases of HCP with subcutaneous panniculitic T-cell lymphoma. In panniculitic T-cell lymphoma, cytologically atypical lymphocytes are found adjacent to benign-appearing histiocytes which have engulfed a variety of other cell types (10). This condition has a clinical course and prognosis similar to that of cytophagic panniculitis (11). We and others have demonstrated that cytophagic panniculitis often shows a concomitant lymphoma or molecular genetic evidence of a clonal process (12), and has an adjacent infiltrate of T cells. The histiocytes in both conditions seem to have a normal immunohistochemical profile and appear cytologically benign. It is tempting to speculate that cytophagic panniculitis and subcutaneous T-cell lymphoma represent variants of the same disease process, one in which the lymphocytes are atypical and clearly malignant, the other in which lymphocytes are also most likely malignant but cytologically benign appearing. In both variants, these lymphocytes presumably produce cytokines that induce benign-appearing histiocytes to engulf surrounding inflammatory cells (12).

The third important recent development that has affected the concept of HCP is evidence of the presence of concomitant Epstein-Barr Virus (EBV) infection. EBV-encoded RNAs have been found in infiltrating T cells in both HCP and panniculitic T-cell lymphoma (13–16). For unknown reasons, EBV involvement seems to occur more commonly in cases in Asia than in the United States. American cases have mostly been EBV negative, except for those in which there were angiodestructive foci in which medium-sized blood vessels were infiltrated and destroyed by atypical lymphocytes.

The implication of these three developments is clear. If a patient presents with a panniculitis with prominent skin involvement and systemic signs and symptoms, a comprehensive diagnostic work-up is mandatory. It is important that the initial skin biopsy be step-sectioned to look for evidence of cytophagocytosis, because this feature, which is often focal and minimal, can easily be missed. Second, if

there is evidence of extracutaneous (e.g., lymph node or bone marrow) involvement, tissue biopsies should be obtained from these sites. Tissue biopsies can detect cytophagic changes that may not have been detected on skin biopsy. Third, if there is a suggestion of recent viral or infectious illness, the patient should be evaluated for EBV infection. Once the diagnosis of HCP is established with complete certainty by the histological exclusion of other types of panniculitis, systemic chemotherapy is advisable.

Erythema Induratum

Erythema induratum is a type of panniculitis that has, in a sense, come full circle. When first described by Bazin in 1861 as “*erythème indure des scrofuleux*” (17), it was thought to be a tuberculid, i.e., a skin eruption occurring in patients as a hypersensitivity reaction to concomitant tuberculosis. At that time, the concept of hypersensitivity to tuberculosis seemed reasonable, given the high prevalence of tuberculosis in the population and the presence on pathologic section of features typical of tuberculosis, e.g., “caseous” necrosis of fat (18). Moreover, there were cases, albeit very rare, in which the organism was isolated from involved tissue.

However, there are many patients with identical dermatologic presentations and similar pathologic findings in whom tuberculous infection cannot be identified. This occurs most often in women who have no concurrent systemic infection and in whom the circulation in the legs is “sluggish.” The pathology is similar, though not identical. This variant of erythema induratum, allegedly due to vascular disturbance, was first described by Galloway and later by Whitfield (19), and has been referred to as nodular vasculitis. As tuberculosis became less common, its association with erythema induratum became less tenable (1).

Recently, however, two events have turned back the clock on the concept of erythema induratum: (a) the re-emergence of tuberculosis with the HIV pandemic and the occurrence of multi-drug-resistant strains (20) and (b) the development of polymerase chain reaction (PCR) technology (21–23). The resurgence of tuberculosis has been accompanied by an increased incidence of erythema induratum. We have recently reported two cases in which the clinical diagnosis of erythema induratum was essential to the diagnosis of tuberculosis infection, which had not been suspected clinically (20). In one

case, a 21-year-old woman with vague constitutional symptoms developed an ulcerating panniculitis. Repeated pathologic examinations failed to disclose an etiology for the panniculitis but suggested erythema induratum. Eventually, mediastinal lymph node biopsy was performed and unequivocally established the diagnosis of tuberculosis. The second patient, who presented with lower extremity ulcers diagnosed as erythema induratum (18), was found to have pulmonary tuberculosis.

PCR technology, which allows the amplification of trace quantities of DNA in tissue, has revolutionized the study of disease entities thought to be related to infectious organisms. In most cases of erythema induratum, even though no mycobacteria can be demonstrated by culture, special stains, or animal inoculation experiments, the clinical association with tuberculosis is undeniable. The PCR technique is able to detect DNA from *Mycobacterium tuberculosis* in fresh clinical specimens and even in paraffin-embedded tissue that has been stored for long periods of time. Penneys et al. (24), using a probe for mycobacteria, looked at five specimens from lesions known to be tuberculids and detected DNA from tuberculosis in virtually all of the lesions. Baselga et al. (22), using probes for mycobacteria in a nested PCR assay, looked at cases of erythema induratum and found that DNA from *M. tuberculosis* was present in 75% of the cases.

These data suggest that tuberculosis might be the cause of many cases of erythema induratum and that antituberculosis therapy ought to be helpful. Paradoxically, some studies have failed to show any correlation between response to antituberculosis drugs and positive PCR results, whereas other treatments, e.g., systemic steroids, have been effective. This is especially significant, since corticosteroids can cause reactivation of tuberculosis and are usually avoided unless the patient is on antituberculosis therapy.

Lipodermatosclerosis

For many years it has been apparent that patients with stasis dermatitis, an ostensibly epidermal and superficial dermal process, often develop changes in the deeper dermis and subcutis. Damage to superficial capillaries occurs early on in this condition. And the vascular fragility causes repeated hemorrhage into the dermis, which manifests clinically as reddish-brown discoloration of the legs from hemo-

siderin deposition. There is persistent edema, superficial and then deep fibrosis, and ultimately, in some cases, ulceration. The deep fibrosis results in a constricting panniculitis.

The clinical appearance of this disease process is quite remarkable. The legs above the ankles start to taper suddenly, forming a constricting band resembling an inverted coke bottle. In addition, there is brownish-red pigmentation and induration. This combination of lesions in the dermis and subcutis is called lipodermatosclerosis.

The pathology of this condition is quite variable (25, 26). In the superficial portions of the biopsy, the changes are typical of venous stasis. Thick-walled capillaries, surrounded by fibrin, often extend deeply. Siderophages (macrophages that have ingested iron) are present around capillaries, and fibrosis is noted.

The changes may extend into the fat. Early on, there is lobular as well as septal panniculitis, both mediated by lymphocytes. Later on, ischemic necrosis of fat becomes evident. Multiple small and large cystic spaces form and coalesce. These cystic spaces are frequently lined with thick, eosinophilic, PAS-positive material that is believed to represent condensation of lipocyte membranes. The membranes are arrayed in complex arabesque patterns that give this panniculitis its characteristic appearance (Fig. 1) (27, 28). Because of this pattern, lipodermatosclerosis has had many names, including membranous lipodystrophy and lipomembranous fat necrosis.

Although these changes are alleged to be very characteristic, many have called their

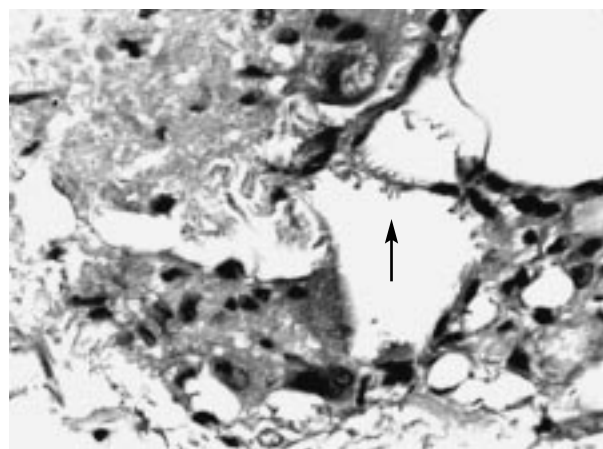


Fig. 1. Characteristic membranocystic change seen in lipodermatosclerosis. A multinucleated giant cell surrounds a convoluted cell membrane showing the so-called "arabesque" pattern (arrow) (hematoxylin and eosin, 100x).

specificity into question. The same change previously had been described in a genetic disease, membranous lipodystrophy, and Snow et al. (29) described almost identical changes in cases with classic clinical and histologic features of morphea. However, in that study there was microcystic change in the fat.

Therapy for lipodermatosclerosis focuses on the usual treatments for venous stasis, including bed rest, leg elevation, and stocking compression. In view of the intimate association with fibrin cuffs and capillary leakage, some have advocated fibrinolytic agents such as the anabolic steroid, stanozolol (30).

Pancreatic Panniculitis

Pancreatic panniculitis is a rare condition in which necrosis of fat occurs in subcutaneous tissue and elsewhere in the setting of pancreatic disease (31–35). The distinctive clinical presentation and pathognomonic histopathologic findings may be the presenting features of underlying pancreatic pathology.

Pancreatic panniculitis usually occurs in association with pancreatitis or pancreatic carcinoma, both of which have a male predominance (3.5:1). Interestingly, pancreatic acinar carcinoma, which accounts for only 10% of all pancreatic carcinoma, is associated with 84% of pancreatic panniculitis cases (34). Patients present with tender, erythematous, fluctuant nodules that may drain an oily substance. An associated arthritis and/or polyserositis (32) may be present as well. Because of the tenderness and arthritis, pancreatic panniculitis is often mistaken for erythema nodosum.

The histopathology of pancreatic panniculitis in early stages characteristically includes lobular fat necrosis with ghost-like fat cells and a surrounding polymorphous infiltrate of neutrophils, lymphocytes, macrophages, and foreign-body giant cells (Fig. 2). There may be foci of calcification and focal hemorrhage. A report of a biopsy of a 2-day-old lesion purporting to show septal panniculitis, a feature more characteristic of erythema nodosum (36), raised the possibility that pancreatic panniculitis may evolve from an early septal reaction to a fully developed lobular panniculitis. In older lesions, the histopathology can show a nonspecific fibrosing reaction with foamy macrophages and hemosiderin deposition. Birefringent, saponified, fatty-acid crystalline structures have been found in pancreatic fat necrosis from the mesentery (37) and in the

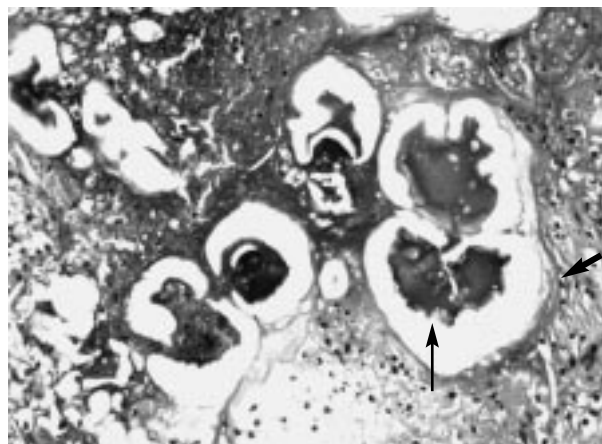


Fig. 2. Necrotic lipocytes (thin arrow) surrounded by a thin rim of calcium (wide arrow) seen in pancreatic panniculitis (hematoxylin and eosin, 100x).

associated arthritis (38), but not in cutaneous lesions.

Pancreatic panniculitis is caused primarily by lipase, phospholipase, trypsin, and amylase. The mechanism of activation of precursor pancreatic enzymes into activated forms is not clear. It is tempting to speculate that vascular damage from increased levels of circulating pancreatic enzymes might increase vascular permeability, thereby allowing the enzymes to enter fat lobules and cause necrosis. Therapy should be directed to the primary disease, though symptomatic treatment with support hose and leg elevation may be helpful.

Alpha-1-Antitrypsin Deficiency Panniculitis

Alpha-1-antitrypsin (alpha-1 AT) is a proteinase inhibitor (pi) that is produced in the liver and accounts for much of the proteolytic inhibitory activity in the blood. It inhibits many other serine proteinases in addition to trypsin. Its serum concentration is determined by the inheritance of autosomal co-dominant alleles, with M, S, and Z the most abundant. PiZ homozygotes have only 10–20% of the normal serum concentration of the proteinase inhibitor and have an increased risk for the development of pulmonary emphysema. Some 10–20% of the Z homozygotes develop neonatal hepatitis, with or without cirrhosis. SZ heterozygotes have one-third of the normal inhibitor level and a relatively low risk of developing emphysema, while MZ heterozygotes have a moderate risk (39). In addition to the well-recognized association of pulmonary emphysema, neonatal hepatitis and cirrhosis with alpha-1 AT deficiency,

distinctive ulcerating lobular panniculitis may also occur. Since the original description by Warter et al. (40), numerous cases of ulcerative lobular panniculitis have been reported (41–44).

Alpha-1 AT deficiency panniculitis is characterized clinically by recurrent, tender, erythematous, subcutaneous ulcerating nodules usually seen on the trunk and extremities. It is occasionally associated with a history of previous trauma. The serum alpha-1 AT level is significantly decreased. Most cases are of the PiZZ phenotype (45–49), although other types have been reported (50, 51).

Biopsy of well-formed lesions shows a lobular panniculitis with mixed infiltrate of neutrophils and histiocytes. Secondary leukocytoclastic vasculitis may be seen in areas of necrosis. A direct immunofluorescence study reported complement (C3) and/or IgM in blood vessels of the panniculus or dermis (52). In early-stage disease, a sprinkling of neutrophils between collagen bundles in the reticular dermis may be the only finding (53). Therapies that appear to be of greatest benefit include dapsone as well as alpha-1-proteinase inhibitor replacement (54).

Summary

We have discussed recent advances in the diagnosis, pathogenesis and treatment of five different types of panniculitis. It is clear, even from this limited review, that many of the entities are difficult to diagnose. Yet appropriate diagnostic tests, along with an adequate biopsy, notwithstanding the histologic overlap, should provide some help in treating these conditions.

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