Anatomy and Histology of Normal Subcutaneous Fat, Necrosis of Adipocytes, and Classification of the Panniculitides

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KEYWORDS

• Panniculitis • Subcutaneous fat • Adipocytes
• Necrosis of the adipocytes

The panniculitides comprise a heterogeneous group of inflammatory diseases involving the subcutaneous fat. These disorders have been classically considered diagnostically challenging, both for dermatologists and dermatopathologists, for several reasons. First, from a clinical point of view, dermatologists are used to evaluating different morphologic aspects of the altered skin to render a diagnosis, but subcutaneous tissue is not visible to examining eye. Instead, the lesions usually show a disappointing monotony, and entirely disparate diseases involving the subcutaneous fat appear with the same morphology, which consists of erythematous nodules, mostly located on the lower limbs. Second, the lesions are situated deep in subcutaneous tissue and large excision biopsies through subcutaneous fat must be performed for diagnosis to evaluate correctly the pattern of the inflammatory cell infiltrate and the involvement of blood vessels. Third, from a histopathologic point of view, the subcutaneous fat responds to a variety of insults in a limited number of forms, and pathologic differences between some of the conditions are sometimes subtle. Moreover, the panniculitides, like other inflammatory diseases of the skin, are dynamic processes in which both the composition and the distribution of the inflammatory infiltrate cells change within the course of a few days, and often biopsies are taken from late-stage lesions because of inadequate clinicopathologic correlation and they show nonspecific findings. Some authorities believe that "the histologic septal-lobular dichotomy is sometimes diagnostically useful, but more often there is a mixed picture that adds to interpretative difficulties."[1]

Despite these pitfalls, the authors believe that with an adequate biopsy and performing serial sections through the specimen, dermatopathologists may classify the panniculitic process as a mostly septal or a mostly lobular panniculitis, and this classification system is very helpful for initial diagnostic purposes. This is just the first step in the diagnostic process, however, and it should be followed by the search of additional histopathologic findings that allow a more specific final diagnosis in the language of clinical dermatology. The second step in the histopathologic diagnosis deals with the assessment of whether vasculitis is or is not present, and when it is present the nature of the involved blood vessel should be determined. Finally, the third diagnostic step is the identification of the nature of the cells that compose the inflammatory infiltrate and the search for additional

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histopathologic features that allow a specific diagnosis. **Box 1** provides a working classification of the panniculitides using this approach for diagnosis.[2,3]

ANATOMY AND HISTOLOGY OF THE SUBCUTANEOUS TISSUE

Subcutaneous tissue is widely scattered throughout the body, forming a true organ as regards both structure and function.[4] This tissue is crucial for thermal regulation, insulation, provision of energy, and protection from mechanical injuries. In a normal individual, subcutaneous fat constitutes about 10% of body weight. According to Ackerman,[5] the basic unit of the subcutaneous fat is the primary microlobule, which measures approximately 1 mm in diameter and is composed of a microscopic collection of adipocytes or lipocytes. Primary microlobules aggregate to form secondary lobules that measure approximately 1 cm in diameter and are surrounded by thin septa of connective tissue. The septa provide stability to the subcutaneous tissue by compartmentalization. The thickness of the subcutaneous fat varies from one part of the body to another, with a thinner subcutis in areas of lax skin, such as the eyelids and scrotum, and a thicker hypodermis in the hips and buttocks. There are also gender differences in the distribution of subcutaneous fat, and an increased thickness of the subcutis results in the rounded contours of the female torso, hips, pubis, and thighs. Underlying the morphologic heterogeneity of the subcutaneous fat is the demonstration that adipocytes from different sites of the same individual show differences in metabolic activity.[6]

The adipocytes derive from mesenchymal stem cells and represent a specialized component of the connective tissue capable of fat synthesis and fat storage. Considered as individual cells, the adipocytes are large, with a diameter up to 100 μm, and with hematoxylin-eosin stain appearing as empty cells with signet-ring morphology. This is because the lipid content dissolves in routinely processed specimens and the flat spindle nucleus is displaced at the periphery of the cell by a single, large intracytoplasmic vacuole, which contains fat. Frozen sections or other techniques must be used to demonstrate the adipocytes in their full monotonous splendor because of their cytoplasmic contents of essentially neutral lipids and triglycerides. Each adipocyte is separated from their neighbors by an inconspicuous matrix and they express S-100 protein and vimentin in immunohistochemical stains.[7]

The septa that divide the subcutaneous fat into lobules are thin and are composed of collagen and reticulin fibers that are extensions of the dermis. This close relationship between dermal structures and subcutis may explain why some dermal inflammatory conditions may secondarily affect the septa of panniculus giving rise to septal panniculitis, such as necrobiosis lipoidica, deep morphea, subcutaneous granuloma annulare, rheumatoid nodule, and necrobiotic xanthogranuloma.

These septa house the blood and lymphatic vessels and the nerves. Arteries and veins of the subcutis run along the septa. Each individual secondary lobule is supplied by a small muscular artery (250–500 μm diameter) branching from the septa to form arterioles (100–300 μm in diameter) that supply every individual primary microlobule. The arteriole branches to form capillaries into the microlobule, and a capillary network surrounds each individual adipocyte. Probably, adipocytes are the individual cells of the human body with a better vascular supply. Postcapillary venules meet in veins, which also run along the septa. In each microlobule, the arteriole occupies a central position, whereas the venule runs along the periphery.[5] As a consequence, interference with the arterial supply results in diffuse changes within the lobule (mostly lobular panniculitis), whereas venous disorders are manifested by alterations in the septal and paraseptal areas (mostly septal panniculitis).[8] This peculiar structure of the blood supply in subcutaneous fat explains why large-vessel vasculitis involving the septal vessels is usually accompanied by little inflammation of the fat lobules, whereas when the vasculitis involves small blood vessels, there is extensive necrosis of the adipocytes with centrilobular infarct and dense inflammatory infiltrate within the lobule. In contrast with the dermal vascularization, the blood supply of each subcutaneous microlobule is terminal, implying there are no capillary connections between adjacent microlobules or between dermis and subcutaneous fat. The septa of the subcutaneous fat also contain a rich lymphatic plexus, which comes from the dermis and transverses the subcutis, first parallel to the surface of the skin and then vertically penetrating the deep fascia and draining into the regional lymph nodes.

A crucial histopathologic point in the study of panniculitis with large-vessel vasculitis is to differentiate whether the involved vessel is artery or vein. A peculiarity of the veins in the subcutaneous fat of the lower limbs is that they often have an arterial appearance because they have a thick muscular layer.[9] With hematoxylin-eosin stain, however, the venous nature of these vessels may be determined because the middle layer of the subcutaneous veins is composed of