

Panniculitis: a diagnostic algorithm

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Abstract

Panniculitis is broadly defined as inflammation of the subcutaneous tissue. Although a number of diseases involve the panniculus, the spectrum of morphological patterns is limited, namely lobular and septal. Therefore, despite the perceived complexity of this topic, careful analysis of the pattern and the inflammatory infiltrate allows a histological diagnosis in a majority of cases. In this review we will cover the most important types of panniculitis, and will offer a diagnostic algorithm to help analyse this type of biopsy.

Keywords algorithm; histological pattern; panniculitis

Introduction

The adipose tissue is composed of lobules of adipocytes separated by fibrous septa. Within the fibrous septa run the vessels and nerves. Although it may be too simplistic a scheme, most inflammatory conditions of the panniculus are divided into septal and lobular. The former is characterized by fibrosis and widening of the septa, with relatively little inflammation involving the lobules. In contrast, lobular panniculitis shows most of the inflammatory infiltrate involving the adipocytes, with relatively normal septa. When determining the pattern, it is important to remember that most biopsies will show features of both. Therefore, the morphologist analysing such a biopsy should evaluate which one of the two is predominant, that is widening of the septa with little involvement of the lobule versus diffuse inflammation in the lobule with thin septa. Consideration is also important of the size and type (artery versus vein) of the vessels involved and the type of inflammatory infiltrate (neutrophils, eosinophils, lymphocytes, plasma cells, macrophages, multinucleated giant cells and granulomas). Obviously, the type of infiltrate will vary according to the duration of the lesions. Almost all panniculitis will start with a predominantly neutrophilic infiltrate and end with a predominantly mononuclear infiltrate.

According to most authors the main difference between the two types of panniculitis is the type of vessel involved; venous

disorders are associated with septal panniculitis while lobular panniculitis usually has alterations in the arterial supply. The relative size of the affected blood vessels is also important. Inflammation of large vessels results in involvement of the fat lobules immediately adjacent to the vessel. Since medium-sized vessels are located in the septa, damage to these vessels will result in septal inflammation and secondary ischaemic damage to the lobules. Damage to small vessels can affect septa, lobules or both. Since these small vessels have a relatively slow blood flow, there is usually a high degree of exudation and migration of inflammatory cells into the panniculus.

In addition to the standard vascular pathogenesis of panniculitis, since the upper portion of the panniculus contains eccrine and apocrine glands and hair follicles, diseases primarily involving these skin adnexa may result in secondary panniculitis.

Finally, a crucial fact in histological analysis of panniculitis is the type of biopsy. Punches should be discouraged, since most sizes (5 mm or less) will result in specimens containing very little adipose tissue (usually only a portion of one lobule), therefore impairing the capability of analysing the lobular structure. Thus, skin ellipses including adipose tissue are probably the best specimens.

Predominantly septal panniculitis (Figure 1)

Erythema nodosum

Erythema nodosum (EN) is the most common form of septal panniculitis. Most commonly, EN presents as an acute, nodular, red eruption usually limited to the anterior lower legs, in young women (9:1 M:F ratio). Lesions are usually multiple, symmetric and bilateral. Streptococcal infections, sarcoidosis, inflammatory bowel disease and pregnancy have been associated with erythema nodosum.

There are acute and chronic forms. In the acute form, there is a sudden appearance of tender, bright red or dusky red-purple nodules with slight elevation of the overlying skin. The nodules measure from 1 to 5 cm in diameter, and are usually located on the anterior surfaces of the lower legs. Less commonly they appear on the calves, thighs, forearms, hands and even the face. The lesions usually do not ulcerate and generally involute within a few weeks. As a result of the intermittent appearance of new lesions, the disease may persist for several months. There may be accompanying fever, malaise, leucocytosis and arthropathy. A number of pulmonary infections can produce both hilar adenopathy and EN.

Several diseases are associated with EN. The most frequent bacteria are *Streptococcus*, *Mycobacterium*, *Yersinia*, *Brucella*, *Leptospira* and *Chlamydia*. Among the fungi are *Coccidioides*, *Histoplasma*, dermatophytes and blastomycosis. Patients with toxoplasmosis, herpes simplex, infectious mononucleosis, lymphogranuloma venereum, ornithosis and psittacosis can also develop EN. Regarding neoplasms, EN may occur in association with leukaemia and Hodgkin disease, as well as with some carcinomas, particularly after adjuvant therapy. Crohn disease and sarcoidosis may also be associated with EN. EN occurs in 10–20% of patients with sarcoidosis and is thought to portend a good prognosis.

The chronic form of EN is also known as EN migrans or sub-acute nodular migratory panniculitis of Vilanova and Piñol. It

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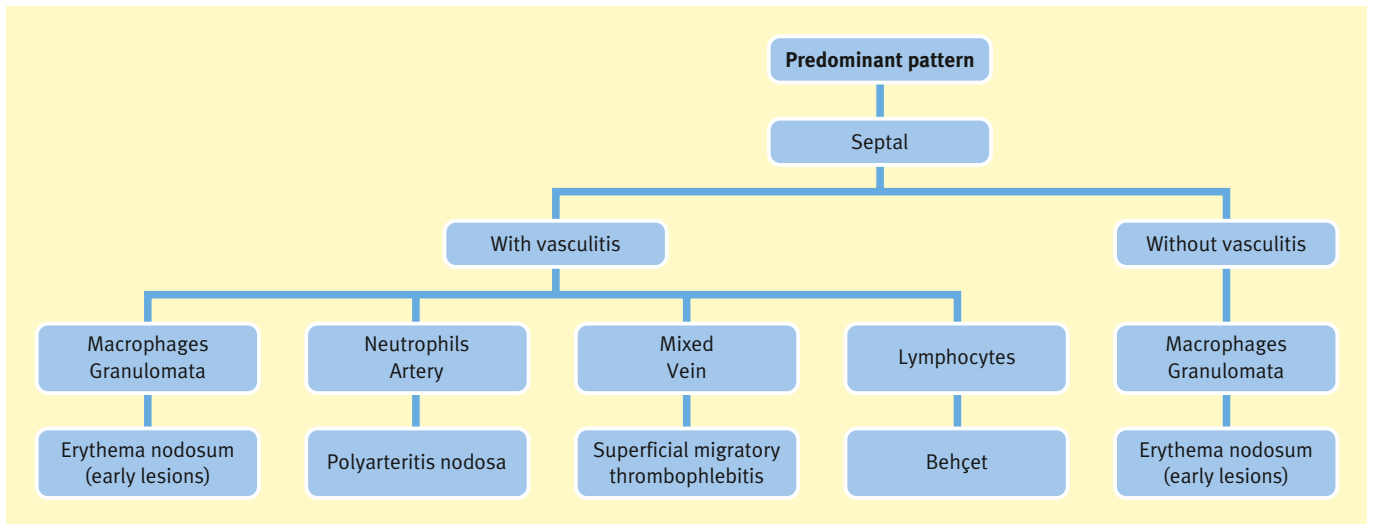


Figure 1 Diagnostic algorithm for predominantly septal panniculitis.

usually presents as a solitary (rarely several) red, subcutaneous nodule on the lower leg. Almost all patients are women with a solitary lesion and a recent history of sore throat and arthralgia. Tenderness is slight or absent. The nodules enlarge by peripheral extension into plaques, often with central clearing. The duration may be from a few months to a few years.

Histologically, early lesions are characterized by extravasated red blood cells, neutrophils, lymphocytes, histiocytes and eosinophils, within oedematous septa (Figure 2). Often the inflammatory infiltrate is most intense at the periphery of the oedematous septa and extends into the periphery of the fat lobules between individual fat cells in a lace-like fashion. Necrosis of the fat is not prominent. Later lesions show lymphocytes, macrophages and giant cells. Macrophages at the edges of the fat lobules phagocytize lipid from damaged adipocytes and the small droplets of lipid in their cytoplasm give them a foamy appearance. Granulomas formed by macrophages, without lipid deposition, are more frequent in late lesions. Those granulomas are often loosely formed with macrophages predominating in a focus with multinucleated giant cells. Occasionally, well-formed, discrete sarcoidal granulomas occur in small numbers in the septa. Resolving lesions contain septal fibrosis and lipogranulomas with a minimal inflammatory infiltrate. Miescher granuloma, a septal aggregate of macrophages around a vessel or a slit-like space, is very characteristic of EN, but can also be seen in Sweet syndrome and in necrobiosis lipoidica.

In contrast to bacterial and fungal infections, EN usually lacks necrotizing granulomas, neutrophilic abscesses or frank leucocytoclastic vasculitis. The exception is some cases of drug-associated EN (e.g. steroid oral contraceptives, which may have vasculitis).

Regarding EN pathogenesis, direct immunofluorescence studies have shown deposits of immunoglobulins only very rarely in the blood vessel walls and these patients usually lack circulating immune complexes. Thus, a type IV-delayed hypersensitivity reaction may play an important role. Furthermore, the predilection for the anterior shins and for dependent parts of the body suggests that trauma or sluggish blood flow are important in the pathophysiology of this disease.

Regarding the differential diagnosis, vasculitis, zones of fat necrosis and prominent granulomatous reaction are more commonly seen in erythema induratum (see also below). Polyarteritis nodosa shows damage of medium-sized arteries rather than veins or small-calibre blood vessels. Superficial migratory thrombophlebitis has a large vein containing thrombus in the centre of

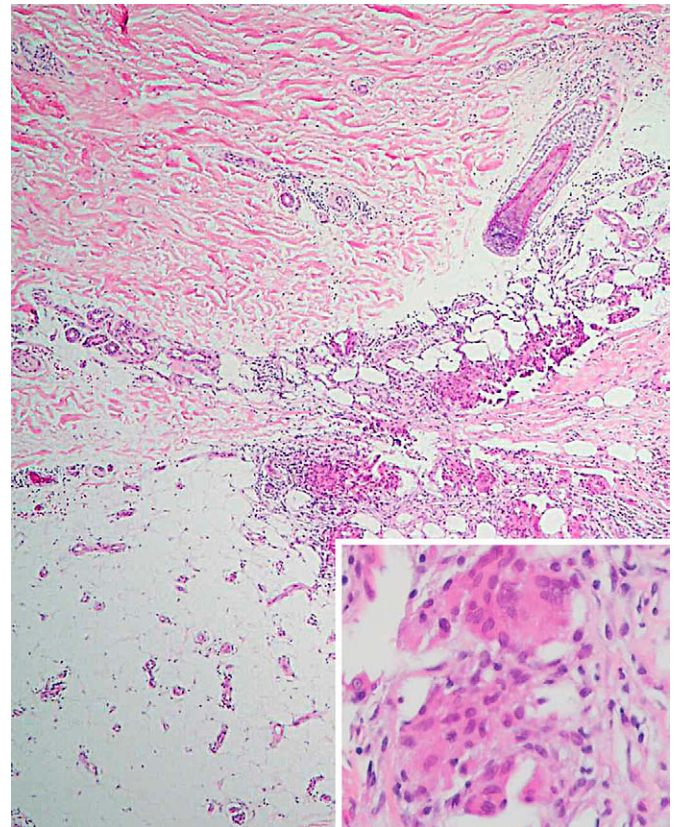


Figure 2 Erythema nodosum. Note the wide septa with only focal involvement of adipose lobules, lymphocytes and characteristic multinucleated giant cells (inset).

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