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Erythema Nodosum
Clinical Presentation. An acute form and a chronic form of erythema nodosum exist, which differ in their clinical manifestations but do not have uniformly recognized differences in their histologic characteristics.

In the acute form of erythema nodosum, there is a sudden appearance of tender, bright red or dusky red-purple nodules to plaques that only last a few days before resolving.
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The chronic form of erythema nodosum is also known as erythema nodosum migrans or subacute nodular migratory panniculitis of Vilanova and Pinol. There are one or several red, subcutaneous nodules that are found, usually unilaterally, on the lower leg. Vilanova and Pinol described this form as characterized by peripheral extension into plaques, often with central clearing. The duration may be from a few months to a few years.

Histopathology. The histologic changes are present mainly in and near the septa of the subcutaneous tissue. The overlying dermis often has only a minimal to moderate, superficial and deep perivascular lymphocytic infiltrate.
In the early lesions of acute erythema nodosum, there is edema of the septa with a lymphohistiocytic infiltrate, having a slight admixture of neutrophils and eosinophils. Focal fibrin deposition and extravasation of erythrocytes occur frequently and can be revealed by spectral microscopy. Often, the inflammation is most intense at the periphery of the edematous septa and extends into the periphery of the fat lobules between the individual fat cells in a lacelike fashion. Necrosis of the fat is not...
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Erythema nodosum that is secondary to medications or estrogenic oral contraceptives.

Later lesions of acute erythema nodosum show widening of the septa, often with fibrosis and...
when late lesions are compared with early ones. The granulomas often are loosely formed with macrophages predominating...
In chronic erythema nodosum, histologic findings are generally similar to those of the late stages of acute erythema nodosum. However, granulomas with septa with marked capillary proliferation and massive granulomatous reaction have led some authors to consider erythema nodosum migrans as an entity separate from the late lesions of acute erythema nodosum. Other authors consider all of these histologic patterns to be included within the spectrum of chronic erythema nodosum.
Pathogenesis
Although the cause of erythema nodosum cannot always be determined in an individual patient, streptococcal infection is the most common among the known causes, especially in children, as evidenced by elevation of antistreptolysin O titers. The diseases that can be associated with erythema nodosum are numerous and have been reviewed recently. In patients with erythema nodosum, bacterial infections are the most frequent, and the most frequently associated bacterial infections include streptococcal infection, tuberculosis, Yersinia enterocolitica infection, brucellosis, leptospirosis, tularemia, Chlamydia infection, and Mycoplasma pneumoniae infection. The most frequently associated fungal infections are coccidioidomycosis, histoplasmosis, dermatophytosis, and candidiasis. Among the associated viral infections, herpes simplex, human immunodeficiency virus infection, and measles can cause erythema nodosum. 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lymphocytic vasculitis, which is predominantly lobular in distribution (3D). Erythema nodosum and Sweet's syndrome have been reported in the same patient. Among the many medications that can cause erythema nodosum, some may be capable of triggering the clinical and histopathologic changes that are classified as erythema nodosum.

Direct immunofluorescence studies have shown deposits of immunoglobulins only very rarely in the blood vessel walls in erythema nodosum.
The occurrence of erythema nodosum as a response to medications and to tuberculin skin testing in patients with sarcoidosis is well-documented. In approximately 50% of cases, there is no cause identified. The predilection for the anterior shins and for the upper arms is characteristic. Other factors such as the distribution of immunoreactive macrophages and dendritic cells need investigation as well.
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Differential Diagnosis

Differential Diagnosis
Erythema nodosum needs to be distinguished from erythema induratum and nodular vasculitis. Vasculitis and zones of fat necrosis are absent in erythema nodosum and frequent in erythema induratum. In patients suspected to have erythema nodosum but with necrotizing vasculitis, the possibility of cutaneous polyarteritis nodosa must be considered. In the latter disease, medium-sized arteries rather than veins or small-caliber blood vessels are affected, with necrosis of the walls of affected arteries. In contrast, nodular vasculitis has mainly lymphocytic infiltration with fibrous thickening and obliteration of vascular lumens. Superficial migratory thrombophlebitis, unlike erythema nodosum, has a large vein containing thrombus in the center of the lumen. Syphilitic gummas are ulcerative irregular granulomatous lesions that produce depressed scars. Subcutaneous tuberculosis can mimic erythema nodosum in lesions that are extending from underlying organs, soft tissues, or bone. Stains for Mycobacterium tuberculosis and other special stains may be helpful in making this diagnosis.
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