Erythema Nodosum
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Clinical Presentation. An acute form and a chronic form of erythema nodosum exist, which differ in their clinical manifestations. 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 for a few days. Erythema nodosum occurs in 10% to 20% of patients with sarcoidosis and is thought to portend a good prognosis.
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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 noted that the nodules may coalesce and form plaques. They may subsequently develop perifocal fibrosis. The nodules may undergo central clearing 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 common. Clusters of macrophages around small blood vessels, or a slitlike space, occur in early lesions and are known as Miescher’s radial nodules. Some authors have failed to find central vessels and have considered Miescher’s nodules to be characteristic of erythema nodosum, stating that they can be found in all...
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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.
In chronic erythema nodosum, histologic findings are generally similar to those of the late stages of acute erythema nodosum. However, granulomas lacking a central zone of caseation, with fibrous septa and marked capillary proliferation and massive granulomatous reaction have led several 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 addition to streptococcal infection, the most frequently associated bacterial infections are tuberculosis, Yersinia enterocolitica infection, brucellosis, leptospirosis, tularemia, Chlamydia infection, and Mycoplasma pneumoniae infection. The most frequently associated fungal infections are coccidioidomycosis, histoplasmosis, dermatophytosis, and Torulopsis glabrata infection. Protozoal infections such as toxoplasmosis, amoebiasis, and Giardia infection can cause erythema nodosum. Among the associated viral and rickettsial infections are herpes simplex, varicella-zoster virus, and rickettsiosis. When erythema nodosum is associated with a specific disease, it may occur either early in the course of the illness or at the time of relapse. The sarcoidal granulomas that can occur in erythema nodosum are less frequent, are septal in location, and are associated with the collagen vascular diseases. Likewise, Crohn's disease can be associated with erythema nodosum (1D), and the two diseases can be difficult to distinguish from each other histologically in the skin involvement unless there is evidence of the intestinal disease. In patients with sarcoidosis, erythema nodosum can occur due to the granulomatous inflammation. In these cases, the skin lesions are often bilateral, symmetrical, and recur on the lower legs. Erythema nodosum may be a forme fruste of Crohn's disease, and the two diseases can be difficult to distinguish from each other histologically in the skin involvement unless there is evidence of the intestinal disease.
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Lymphocytic vasculitis, which is predominantly lobular in distribution (3D), is not the exclusive feature of Erythema nodosum and Sweet's syndrome have been reported in the same patient. Among the many medications that can cause this syndrome, antibiotics and nonsteroidal anti-inflammatory drugs are common causes. Other mechanisms 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, but lymphocytic infiltration and nonspecific vascular changes consisting of damage to endothelial cells and lymphocytic infiltration have been described.
The occurrence of erythema nodosum as a response to medications and to tuberculin skin testing in patients with sarcoidosis and circulating immune complexes and rheumatoid factors have been detected in some patients. In approximately 50% of cases, there is no cause identified. The predilection for the anterior shins and for other factors such as the distribution of immunoreactive macrophages and dendritic cells need investigation as well.
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 can be used to confirm the diagnosis. Other causes of nodules include lupus erythematosus, subcutaneous necrobiosis lipoidica, ruptured follicular cysts, and factitial traumatic panniculitis.
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