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 for weeks.
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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 the lesion to spread peripherally and coalesce, forming plaques that often clear centrally. 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 fat. 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 ... . 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 labeled Miescher's nodules as 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 predominating in the cytoplasm. The oldest lesions have septal widening and fibrosis with a decrease in all of the inflammatory cells.
In chronic erythema nodosum, histologic findings are generally similar to those of the acute form, but with the development of granulomas and fibrous septa with marked capillary proliferation and massive granulomatous reaction. Several authors 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, 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. Infections, both bacterial and fungal, and miscellaneous conditions. The most frequent bacterial infections are 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, candidiasis, and blastomycosis. 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, and rickettsial diseases such as Rocky Mountain spotted fever, Q fever, and trench fever. The sarcoidal granulomas that can occur in erythema nodosum are less frequent, are septal in location, and are associated with a diffuse infiltrate that is usually located around the small arteries and mostly in the lobules of the subcutaneous fat. Likewise, Crohn's disease can be associated with erythema nodosum (1). In such cases, the disease may resemble erythema nodosum clinically but often is different histologically in having neutrophilic and lymphocytic infiltrates, along with slight hilar adenopathy, fever, arthralgias, and occasionally acute iritis, uveitis, and parotid swelling (uveoparotid fever).
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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 these syndromes, certain drugs have been shown to 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. 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 has been documented. Circulating immune complexes and rheumatoid factors have been detected in some patients with sarcoidosis and erythema nodosum. In approximately 50% of cases, there is no cause identified. The predilection for the anterior shins and for the anterior aspects of the ankles needs further investigation.
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 mycobacteria are positive in cases of subcutaneous tuberculosis.
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