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REVIEW

ERYTHEMA NODOSUM LEPROSUM

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Leprosy is a chronic, slowly progressive granulomatous infectious disease, supposedly caused by the bacillus *Mycobacterium leprae*, which has a predilection for skin and nerves. The two main forms are tuberculoid and lepromatous. Two other types are indeterminate and borderline. Indeterminate lesions may progress to either tuberculoid or lepromatous. Borderline lesions have clinical and histologic features of both main forms. Borderline disease is unstable and tends to "downgrade" towards lepromatous, especially if untreated, or "upgrade" towards tuberculoid. The progression of the disease is usually slow and indolent, but sometimes a change in the immunologic status of the patient develops suddenly and a reactional state occurs. Lepra reactions are divided into type I reactions that occur in borderline disease and are associated with "upgrading" or "downgrading," and type 2 reactions, or erythema nodosum leprosum.

BACKGROUND

Erythema nodosum leprosum (ENL), occurs in a patient with lepromatous leprosy or, occasionally, with borderline lepromatous leprosy. Erythema nodosum leprosum is usually associated with multi-drug therapy, but it can be seen in untreated patients.[1] Pfaltzgraff et al.[2] reported that over 50% of lepromatous leprosy patients and 25% of borderline lepromatous leprosy patients experience an ENL reaction. Within the first year of sulfone therapy, more than one half of patients with lepromatous leprosy in Southeast Asia develop ENL.[3] Generally, there have been reports of between 15 and 50% of lepromatous leprosy patients developing ENL within the first year of treatment;[4,5] however, ENL can develop later during therapy or even after discontinuation of therapy.[6] The reaction is not always related to therapy and seems to be a manifestation of the disease.[7] Precipitating factors include surgical operations, pregnancy, parturition, lactation, menstruation, trauma, intercurrent infection, vaccination (especially smallpox), physical or mental stress, and sometimes therapy.[4,8-12] Precipitating drugs include iodides and bromides,[13] diaminodiphenylsulfone (DDS),[14] and chaulmoogra.[15] One study reported an increased incidence of ENL in glucose-6-phosphate dehydrogenase-deficient patients.[16] A statistically significant increase in the frequency of HLA-A11 was found in ENL patients as compared to patients with lepromatous leprosy.[17]

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CLINICAL AND HISTOLOGIC PRESENTATION

Clinically, there are crops of tender, red-purple papules, plaques, or nodules that appear in previously normal skin between existing lepromatous lesions that remain morphologically unchanged except for some edema noted histologically.[8] Less commonly, the lesions may be hemorrhagic, vesicular, erythema multiforme-like, pustular, or ulcerating.[10] The lesions are most commonly located on the face and extensor surfaces of extremities and usually occur bilaterally and symmetrically.[15] Although specific lesions usually only last for 7 to 10 days, recurrences can continue to appear for weeks, months, or years.[5] Repeated attacks can lead to loss of elasticity of the skin.[14] Erythema nodosum leprosum can also involve the eyes, joints, viscera (e.g., the liver[18]), nerves, and lymph nodes.[19] A case of isolated ENL-lymphadenitis without skin lesions has been reported recently.[20]

Extracutaneous manifestations include fever, painful neuropathy, epididymoorchitis, immune complex glomerulonephritis, synovitis, large joint arthritis, lymphadenopathy, iridocyclitis,[21] uveitis, dactylitis, arthralgias, myositis, malaise, weight loss,[6] hepatosplenomegaly,[10] leukocytosis, generalized or dependent edema, epistaxis, iritis,[5] proteinuria, rhinitis, insomnia, and depression.[8] The severity of the reaction seems to be related to the size of the bacterial load.[10] Sterility or gynecomastia can result from testicular damage and blindness can occur from iritis if the patient is not adequately treated.[8]

Histologically, there is classically an intense vasculitis with a neutrophilic and lymphocytic infiltrate and granulomas made up of foamy histiocytes, many filled with *Mycobacterium leprae*.[5] There is swelling of endothelial cells and edema of vessel walls.[9] Acute necrotizing vasculitis is a variable finding.[5] The ulcerating form, called necrotizing ENL or ENL necroticans, shows the same histologic features but to a greater degree. In-

filtrates are heavier, the granuloma is larger, and edema and vasculitis are more severe.[22]

As lesions age, the number of lymphocytes and plasma cells increases and that of neutrophils and eosinophils declines.[9] The subcutaneous fat is variably involved with a lobular panniculitis consisting of an acute neutrophilic infiltrate or a chronic lymphocytic and histiocytic infiltrate with fibrosis.[9] Direct immunofluorescence shows granular deposits of immunoglobulin and complement in the vessels of lesional skin.[23,24]

An Arthus reaction involves deposition of immune complexes with vasculitis and a polymorphonuclear infiltrate. The concept that ENL is a form of Arthus reaction is supported by the presence of circulating immune complexes, the demonstration of mycobacterial antigens, complement, and immunoglobulins around blood vessels in some lesions and the occurrence of an immune-complex glomerulonephritis in some patients;[23,25,26] however, others suggest that the immune complexes are extravascular and in this way, ENL is different from the Arthus "serum sickness" reaction.[27]

Both humoral and cell-mediated mechanisms are involved in the pathogenesis of ENL. There is evidence of an increased percentage of B lymphocytes with low levels of complement in one study,[28] and of an increased number of helper T cells and a higher helper-supressor ratio in the lesions of ENL in other studies.[29,30]

Various substances have been studied to determine their significance in the course of ENL reactions. Adenosine deaminase is an enzyme that is found in cells of the body actively involved in nucleotide metabolism,[31] and seems to play a role in cellular immune function.[32] Lymphocyte adenosine deaminase (L-ADA) activity was found to be higher in leprosy patients compared to healthy controls and was 10-fold higher in leprosy patients undergoing reactions, including ENL, than in those not in reaction;[33] however, there were no significant differences in L-ADA levels between the leprosy controls or reaction groups before and after treatment.[33]

Acute phase reactant responses have been studied to assess their roles in leprosy reactions. Alpha$_1$-antitrypsin levels have been studied as a possible indicator of ENL reaction[34,35] and C-reactive protein levels have been shown to correlate better with the changes in ENL reactions.[36]

Levels of soluble interleukin-2 receptors have also been studied, and although they were shown to be significantly higher in leprosy patients compared to controls, especially multibacillary patients, there was no significant change in those for ENL-reactional patients before or after treatment.[37]

MANAGEMENT

The treatment of choice for ENL is thalidomide. It increases motor conduction velocities of nerves involved in ENL.[38] Among theories on the action of thalidomide in ENL, there have been reports of patients with ENL who have an increased ratio of helper/inducer T cells (CD4+) to suppressor/cytotoxic T cells (CD8+) in their blood,[39–41] which does not seem to occur during non-reactional lepromatous disease. Skin lesions of ENL also show an increased CD4+ to CD8+ ratio,[29,30,42–44] whereas the skin lesions of nonreaction lepromatous patients showed an excess of CD8+ lymphocytes.[29,42,43] It has been suggested that ENL is a disease of insufficient T-cell-mediated suppression,[45] resulting in the exaggeration of B and T cell responses[41] and in enhanced mitogenic action.[39–41,46] Therefore, in the transition from quiescent lepromatous disease to ENL, there seems to be a shift from CD8+ to CD4+ prevalence.[44] Thalidomide caused a decrease in the CD4+ to CD8+ ratio in the blood of healthy men,[47] by reducing CD4+ cell numbers and increasing those of CD8+ cells. It is thought that thalidomide acts as a treatment for ENL by modulating T cells in this fashion.[48,49] A similar mechanism of inhibition of T-helper cell function is observed with cyclosporine A that also has been used to treat ENL.[48,50] A decrease in the number of CD4+ cells is seen during treatment.[50]

Another possible mechanism of thalidomide action relates to tumor necrosis factor-alpha (TNF-alpha) levels in serum that are increased in ENL patients.[51,52] When intradermal injections of recombinant interferon-gamma (INF-gamma) were given, ENL was induced in 6 of 10 borderline and lepromatous leprosy patients within 7 months.[53] This is significant because IFN-gamma increases the release of TNF-alpha from monocytes.[53] Improvement of symptoms of ENL with thalidomide was associated with a reduction of TNF-alpha levels.[6,53]

Initial dosages of thalidomide are 100 mg, three to four times daily. This usually will control the reaction within a couple of days and the dose may then be tapered.[10] Some authors suggest tapering to a maintenance level of 100 mg a day; however, other protocols have opted for a slow dose decrease over a 3-week period. Side effects of thalidomide include teratogenicity, neuropathy, drowsiness, eosinophilia and peripheral edema.[54] In the past, patients, who had developed neuropathy from thalidomide, were for the most part non-leprosy patients. These patients were taking the drug as a sedative,[55] or for the management of chronic discoid lupus erythematosus,[56] prurigo nodularis, or aphthous stomatitis;[57] however, there are those who have questioned the previous statement by leprologists that neuropathy does not occur in patients with ENL given the drug and suggested that these leprologists were perhaps unable to detect signs of nerve damage.[58] It is also difficult to differentiate nerve damage caused by thalidomide from that caused by leprosy itself.

If the patient is a premenopausal woman or if signs and symptoms persist with thalidomide therapy, corticosteroids can be administered. Prednisone will control ENL rapidly but treatment for months to years with high doses are often required.[8] At least 60 mg, and

even as high as 120 mg, of prednisone per day should be given as an initial dose to treat ENL, especially when the patient has active neuropathy.[54] After 1 week, when the reaction is usually under control, prednisone should be tapered very slowly to avoid exacerbation.[54]

Clofazimine is useful only on a chronic basis, because it may not be effective for several weeks or months. It is especially useful in premenopausal women with chronic ENL, in whom thalidomide is contraindicated, because it will reduce the dosage of corticosteroids needed to control the disease.[54] Initial dosages up to 300 mg per day are given, tapered to 100 mg every day or three times per week.[54] The two most common side effects of clofazimine are discoloration of the skin secondary to tissue deposits of aniline dye and gastrointestinal (GI) symptoms due to GI-tract deposition of the drug.[54]

Other treatments for ENL used for mild to moderate disease include nonsteroidal antiinflammatory drugs (NSAIDS),[59] colchicine,[60] aspirin, chloroquine,[61] levamisole,[62,63] and antimonials,[60,64] as well as zinc with or without concomitant corticosteroids.[59,65]

DRUG NAMES

chloroquine: Aralen, Resochin
clofazimine: Lamprene
colchicine with benemid: Colbenemid
diaminodiphenylsulfone (Dapsone): Avlosulfon, Diasone Sodium, Glucosulfone Sodium
levamisole: Vermisol, Vizole

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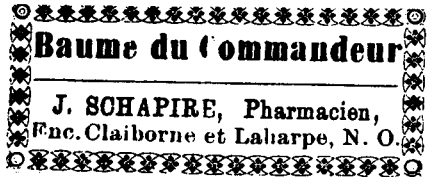

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