Case Reports

Lymphomatoid Granulomatosis of the Skin

A New Clinicopathologic Entity

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Lymphomatoid granulomatosis is a necrotizing arteritis primarily affecting the lungs but also found in the skin, kidneys, central nervous system, and other extrapulmonary sites. Cutaneous involvement occurred in 45% of the cases described by Liebow in his original series.

Light microscopy studies were performed. The IgA and IgG levels were slightly decreased and the IgE level was elevated. Cell-mediated immunity was impaired. No viruses were isolated or identified by immunofluorescence.

A man had cutaneous lesions as the first sign of lymphomatoid granulomatosis.

In 1972, Liebow, et al[1] described 40 cases of a new clinicopathologic entity entitled lymphomatoid granulomatosis. They described the process as an angiocentric and angiodestructive lymphoreticular proliferative and granulomatous disease. It primarily affects the lungs but also can be found in extrapulmonary sites, especially the skin and kidneys. Cutaneous involvement occurred in 45% of their patients and was sometimes the first sign of the illness.

We saw a patient who had skin lesions as the first manifestations of lymphomatoid granulomatosis. Additional information was obtained from virological studies and from the assessment of the immunological status of this patient.

REPORT OF A CASE

A 71-year-old man complained to his dermatologist of ulcerated nodules on his feet in November 1972. He was admitted to Richmond Memorial Hospital in January 1973 for evaluation of vascular insufficiency of the feet. An arteriogram of the lower extremity was normal, and there was no intermittent claudication. However, reddish to purple nodules were present on both ankles and feet. Some had progressed to form deep, wide ulcers. Both feet were slightly swollen after standing or sitting. A routine admission chest x-ray film showed an asymptomatic mass in the lower lobe of the lung. This mass was surgically removed, and at the same time biopsy specimens were taken from the skin lesions of the lower extremities. A diagnosis of lymphomatoid granulomatosis was made following histopathologic examination of specimens of lung and skin.

On June 25, 1973, the patient was admitted to the Medical College of Virginia because of new and enlarging ulcerative lesions (Fig 1 and 2) and a 9.1 kg (20 lb) weight loss. The past and family histories were noncontributory. There was no history of allergy. Physical examination revealed the following pertinent findings: erythematous and violaceous nodules and tumors, with and without ulcerations, were present on the buttocks, legs, and feet; numerous macular and nodular areas of erythema and hyperpigmentation were scattered over the extremities.

Laboratory studies showed normal findings for urinalysis, determination of the cryoglobulin level, serum protein electrophoresis, and differential white blood cell count. The Sia and Coomb tests were negative.

Laboratory studies showed the following values: hemoglobin, 9.8 gm/100 ml; hema-

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Fig 1.—Ulcerated nodules and tumors are seen on left foot and toes.

Fig 2.—Tumors, plaques, and hyperpigmented macules are seen on lower part of left leg and ankle. Several ulcerated, crusted plaques are evident.

Fig 3.—Skin biopsy specimen showing perivascular lymphocytic and histiocytic infiltrate most prominent in subcutis (hematoxylin-eosin, × 125).

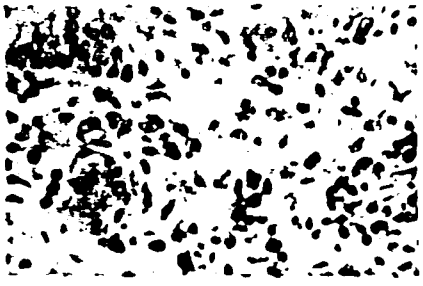

Fig 4.—Details of perivascular infiltrate in upper cutis (hematoxylin-eosin, × 400).

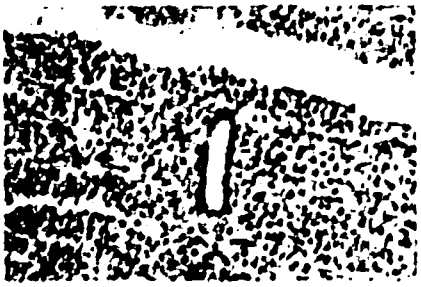

Fig 5.—Infiltrate in subcutis consisting principally of histiocytes surrounding an eccrine sweat gland (hematoxylin-eosin, × 400).

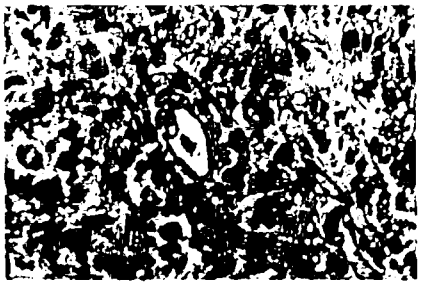

Fig 6.—Detail of histiocytic infiltrate as seen in thin-thick section embedded in epoxy resin. Note scattered erythrocytes and capillary in center of field (toluidine blue, × 600).

tocrit, 29%; white blood cell count 9,000/cu mm; platelet count 490,000/cu mm; reticulocyte count, 3.4%; serum iron, 20μg/100 ml (normal, 80μg-160μg/ml), and iron binding capacity, 113μg/100 ml (normal, 250μg-350μg/ml). Several stool specimens were guaiac-positive for occult blood. Blood chemistry studies using an automated multiple analysis system of nonfasting blood showed the following values: glucose, 140mg/100 ml; alkaline phosphatase, 95 milliunits (mU) per milliliter (normal, 30-85 mU/ml); lactic acid dehydrogenase (LDH), 260 mU/ml 9 (normal, 100-250 mU/ml); other values were normal. Quantitative immunoglobulins studies using the radial diffusion method showed the following values: IgG, 670 mg/100 ml (normal, 975 ± 201 mg/100 ml); IgA, 108 mg/100 ml (normal, 202 ± 83 mg/100 ml); IgM, 107 mg/100 ml (normal, 93 ± 30 mg/100 ml); IgD, nondetectable; IgE, 2,600 international units (IU) per milliliter (normal, 300-700 IU/ml). The serum C'3 complement value was 225 mg/100 ml (normal, 145 ± 22 mg/100 ml). A chest x-ray film showed blunting of the left costophrenic angle due to old adhesions, but it was otherwise normal. An upper gastrointestinal tract series was normal. Additional biopsy specimens of cutaneous nodules were taken for light and electron microscopic studies; the findings have been published elsewhere.[2]

The patient's ulcers were treated with Burow's compresses and debriding enzymes. Chemotherapy consisted of 100 mg of prednisone, given every other day, and 100 mg of cyclophosphamide, administered daily. Prior to therapy, attempted sensitization to dinitrochlorobenzene, and intradermal skin tests to PPD (5 tuberculin units), *Candida* (1:100), and mumps antigen were negative. Culture studies of the patient's lymphocytes with phytohemagglutinin (PHA) showed no blastic transformation or mitoses after three days; however, the cells could not be kept viable for a longer period. The patient was seen by the Hematology service, in consultation, for his chronic anemia. It was thought that the anemia was probably due to chronic inflammatory disease or was secondary to a neoplasm, but iron deficiency could also be a possible cause. The patient's condition seemed to improve, and the size of the nodules and tumors decreased. Some of the larger lesions became necrotic with ulceration. Periodic fever developed and was thought to represent a response to a drug or active disease or both. The patient was discharged on July 20, 1973 on a regimen of 100 mg/day of cyclophosphamide and 100 mg of prednisone administered every other day. Despite all systemic and local measures, the lesions on the left foot continued to get worse, with complications of infection and local gangrene.

The patient was rehospitalized on Aug 8, 1973, with complaints of fever, chills, and malaise. Osteomyelitis of the left foot was discovered on x-ray examination and on Aug 12, 1973; an amputation below the knee was performed, without complications. The patient's fever continued despite parenteral administration of nafcillin and gentamicin or after all other medication had been discontinued. No source of infection was discovered. An upper gastrointestinal tract series, barium enema, and endoscopy failed to reveal an active source of bleeding. A bone-marrow biopsy was performed and did not show any granulomata, organisms, or atypical cells. Normal iron stores were present. Despite positive tests for blood in the stools, no source of bleeding could be found. The alkaline phosphatase level rose to 370 milliunits/ml (study using automated multiple analysis system). The LDH isoenzymes showed it to be derived from liver and intestines. The patient was transferred to a local Veteran's Administration Hospital on Aug 24, 1973. He continued to do poorly despite reinstitution of prednisone and cyclosphosphamide therapy and died on Aug 27, 1973, presumably because of myocardial infarction. Unfortunately, permission for postmortem examination was refused.

FINDINGS

Microbiological Studies

Results of studies done during the patient's first admission to the Medical College of Virginia are as follows:

Bacteriological cultures from ulcers of the left foot grew *Pseudomonas aeruginosa*. Cultures and guinea pig inoculation for acid-fast bacilli were negative.

Viral isolation from ulcers of the left foot was unsuccessful. Primary Rhesus monkey kidney and human embryonic kidney, diploid WI-38, and heteroploid H Ep-2 cell cultures were used. Minced fragments from biopsy material of the left foot were prepared for tissue culture in Eagle's minimal essential medium with 20% fetal calf serum, but the presence of microorganisms could not be established and the tissue cultures failed to show any cytopathogenic effect.

Immunofluorescent studies using anti-IgG antiserum and antisera to cytomegalo viruses, Epstein-Barr (EB), and herpes hominis viruses were carried out for detection of viral antigens in biopsy histological sections from the same source as that for virus isolation, but the tests were consistently negative.

The patient's serum was tested for EB virus antibodies but was negative with diffused early antigens and viral capsid antigens when the lowest dilution of serum tested was 1:10. The VDRL test for syphilis and the fluorescent treponemal antibody-absorption (FTA-ABS) tests were nonreactive.

Pathologic Findings

Only the skin lesions will be described.

Specimen 1.—*Gross Description.*—The specimen consisted of three pieces of skin, each 4 mm in diameter, removed from the ankle region on June 25, 1973.

Microscopic Description.—The epidermis showed hyperkeratosis, with absence of rete ridges. In the upper part of the cutis, there were mild perivascular collections of lymphocytes and histiocytes (Fig 3 and 4). In the deeper areas, a severe vasculitis affecting small arterioles was noted. The infiltrate consisted of lymphocytes, plasmacytoid cells, and lymphoreticular cells, some of which were atypical and had scattered mitoses.

Specimen 2.—*Gross Description.*—The specimen consisted of skin, 4 × 4 × 3 mm in size, removed by punch biopsy on July 2, 1973.

Microscopic Description.—The dermis was diffusely infiltrated by a polymorphous infiltrate consisting principally of lymphocytes, reticulum cells, and scattered eosinophils. Evidence of mitosis was fairly abundant. Isolated sweat ducts in the depth were surrounded by the infiltrating elements (Fig 5), but a narrow clear zone was seen just beneath the epidermis (Grenz zone). Superficially, many capillary and arteriolar walls were infiltrated by the cells described above. In a thin-thick section embedded in epoxy resin (Epon) and stained with toluidine blue, details of the perivascular histiocytic infiltration were seen (Fig 6).

Specimen 3.—*Gross Description.*—

The specimen consisted of a left leg amputated below the knee on Aug 13, 1973.

Microscopic Description.—Several veins were occluded by recent, unorganized thrombi. The major arteries were not unusual except for Mönckeberg sclerosis. The skin in various areas showed nodular accumulations of polymorphous cells similar to the cells previously described. Mitotic activity was more abundant, suggesting possible conversion to neoplasia.

COMMENT

Liebow and associates have described a new clinicopathologic entity predominantly affecting the lungs of middle-aged men (25 out of 40 cases). The range in age was from 8½ years to the 70's. The presence of nodular lesions in the kidney that were similar to those found in the lungs occurred in 45% of the cases. Other organs were also occasionally involved. A remarkable sparing of the lymph nodes, spleen, and bone marrow was noted. Central nervous system disease occurred in at least 20% of the patients, and peripheral neuritis was found almost as frequently. Skin lesions were found in 45% of patients at some time during the course of the disease. While these were usually associated with pulmonary disease, they sometimes were the first sign of the illness. According to Liebow et al,[1] clinical and radiological improvement followed treatment with steroids and immunosuppressive drugs, such as azathioprine or cyclophosphamide. Although many of Liebow's patients responded to therapy, 26 of the original 40 died. Progression of the disease to atypical lymphoma occurred in 13%. Our patient responded well to steroid and cyclophosphamide therapy, as judged by the decreased size of tumors and nodules.

The pathogenesis of this disease remains obscure. The role of virus infection in the transformation of lymphoreticular cells with the induction of malignant tumor is uncertain. The significance of the association of the EB virus with Burkitt lymphoma is not fully known either.[3,4]

The failure to isolate a viral agent and the negative immunofluorescent tests on biopsy material do not necessarily rule out the possibility of a viral cause. Electron-microscopical studies of skin showed no virus-like particles. Serological tests for EB virus were also negative. Few individuals escape an EB virus infection during a life span of more than 70 years, as shown by immunological studies of the general population. However, the number of antibodies may decline to low levels in certain debilitating diseases. In our patient, quantitative immunoglobulin determinations reflected only slight decreases in IgG and IgA levels, which is not enough to be related to the absence of EB virus antibodies in the case that this patient had been infected and had had negative serologic tests due to a deficiency of his humoral immunity. His IgE level was elevated, but the relationship of this finding to lymphomatoid granulomatosis is not clear at this time. However, his cell-mediated immune response was distinctly impaired, as shown by routine skin testing and T lymphocyte function determinations. This problem might have been a result of his disease process, or it might have contributed to its cause and progression.

According to Liebow et al[1] lymphomatoid granulomatosis differs in many ways from the classic and limited forms of Wegener granulomatosis. There is a 3:2 predominance of males, and a high incidence of central and peripheral nervous system involvement. No focal glomerulitis or hilar adenopathy are found, and only rarely does generalized atypical lymphoid hyperplasia precede the onset of pulmonary lesions. The infiltrate is polymorphous with some cells in mitosis and may contain atypical histiocytic and lymphoid cells. It usually tends to spare the lymph nodes, spleen, and bone marrow; although progress to atypical lymphoma, with involvement of lymph nodes and other reticuloendothelial tissues, occurred in 13% of Liebow's patients. The relationship of these states to each other and to the other vasculitides is still not clear. These numerous syndromes are believed to be related to each other by the histological common denominator of necrotizing angiitis.

The cutaneous lesions of lymphomatoid granulomatosis are protean and include papules, plaques, nodules, tumors, ulcerations, and hyperpigmented macules. These lesions represent an arteritis of the small vessels of the dermal and subcutaneous tissue and are most common on the legs, particularly the lower part of the legs and feet, although they may be seen on any part of the body. In our patient the onset was abrupt with development of ulcerating lesions on the feet, ankles, and buttocks. The patient experienced extreme pain in the lower extremities associated with ulcerations. Edema was not prominent and arterial circulation was adequate, as judged by femoral arteriograms, and examination of peripheral pulses and pathologic specimens.

Clinically, lymphomatoid granulomatosis may be different from other angiitides affecting the skin; but microscopically, this distinction cannot be made, with the possible exception of polyarteritis nodosa, which is characteristic enough to allow for accurate diagnosis.

The high percentage of skin lesions associated with this disease, coupled with the fact that this may be the first manifestation of a systemic disease, provides another opportunity for early diagnosis on dermatologic grounds.

The cost of reproducing the color illustrations was paid by Westwood Pharmaceuticals, Inc. Randolph Trice, MD referred this patient to us. A. A. Liebow, MD, reviewed biopsy specimens and provided confirmation of the diagnosis. Werner Henle, MD, performed the Epstein-Barr virus antibody determinations.

Nonproprietary Name and Trademark of Drug

Azothioprine—*Imuran*.

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