A Case of Malignant Histiocytosis Showing Papulosquamous Skin Lesions and Fever as Initial Manifestations

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We report a case of malignant histiocytosis which began with intermittent fever and scaly skin lesions. A 3-year-old girl presented with erythematous scaly papules on the face and the trunk, and high fever for 3 months. The cutaneous lesions consisted of widespread coin-sized erythematous scaly papules with marginal brownish pigmentation. She was anemic and thrombocytopenic and had impairment of the liver function. Histopathologic study of the skin lesions showed non-specific findings except for hyperkeratosis. However, bone marrow examination revealed an increased number of histiocytes, mostly immature with active phagocytosis of erythroid cells, myeloid cells, and platelets. She was diagnosed as having malignant histiocytosis and treated with cyclophosphamide and vincristine. She died the next day after the treatment had begun. (Ann Dermatol 8:2) 117-120, 1996).

Key Words: Malignant histiocytosis, Skin lesions, Fever, Bone marrow examination

In 1939, Scott and Robb-Smith described 4 patients of their own and 6 from the literature with a disease characterized by “fever, wasting and generalized lymphadenopathy associated with splenic and hepatic enlargement and in the final stages of jaundice, purpura and anemia with profound leukopenia”; a pathologic syndrome characterized by a systemic proliferation of histiocytes, which actually engage in erythrophagocytosis. In 1966, Rappaport introduced the term “malignant histiocytosis” (MH) to describe this disorder characterized by “systemic, progressive, invasive proliferation of morphologically atypical histiocytes.”

We report a case of malignant histiocytosis that presented initially with erythematous scaly skin lesions and high fever.

REPORT OF A CASE

In December 1994, a 3-year old girl presented with intermittent, spiking, and high fever up to 39°C, rhinorrhea, and erythematous skin lesions which started from the face and extended to trunk and limbs. She had relatively well defined disseminated pea to bean-sized erythematous fine scaly confluent papules with marginal brownish pigmentation on the face, trunk, arms, legs, and feet (Fig. 1). Mucosal lesion was absent. Pea-sized non-tender submandibular lymph nodes and 5 cm-sized left axillary lymph nodes were palpable. The liver was 2 finger breadth palpable, but the spleen was not palpable. Results of laboratory tests on admission showed a hemoglobin level of 9.4 gm/dl, a platelet count of 91,000/mm³, and a white blood cell count of 2,020/mm³. A peripheral blood smear showed a feature of microcytic and normochromic anemia with mild leukopenia. Blood chemistry re-
Fig. 1. Relatively well-defined disseminated pea-to-bean-sized erythematous fine scaly confluent papules with marginal brownish pigmentation on face (A), trunk, arms, leg (B), and feet (C).

Fig. 2. Skin biopsy; postinflammatory hyperpigmentation and hyperkeratosis (H & E stain, × 100).

Fig. 3. Bone marrow aspiration revealed erythrophagocytic cells with basophilic cytoplasm (Wright & Giemsa stain, × 1,000).

HCV-Ab, FANA, and EBV VCA IgM were negative. On the chest X-ray an ill-defined patchy haziness was seen on both upper lung and right lower lung. A skin biopsy revealed postinflammatory hyperpigmentation and hyperkeratosis (Fig. 2).

There was an episode of high fever 2 days after admission, which resolved with antibiotic therapy. After her transfer to the pediatric department she was initially diagnosed and treated for viral infections for 20 days. However, high spiking fever recurred. Finally, a bone marrow examination revealed increased myeloid blasts with hemophagocytosis (Fig. 3) stained positively with alphanaphthyl acetate esterase (ANAE) and acid phos-
Fig. 4. Positive staining of bone marrow aspiration for ANAE and acid phosphatase; A (ANAE stain, ×1,000) B (acid phosphatase stain, ×1,000).

phatase (Fig. 4). MH having been diagnosed, she was treated by chemotherapy composed of vincristine and cytoxan, but she died the next day due to acute renal failure.

DISCUSSION

Malignant histiocytosis (MH), also known as histiocytic medullary reticulosis, is a rare, and usually fatal, tumor which may involve the skin. Childhood MH is characterized by disseminated, frequently tender lymphadenopathy, skin, bone, and soft tissue localizations. Skin involvement occurs in about 7 to 15% of all cases of malignant histiocytosis. The specific skin lesions include papules, plaques, nodules, noduloulcers with central necrosis and purpura. These features are accompanied by fever, hepatosplenomegaly, deterioration of general condition, and hematological abnormalities including anemia, leukopenia, and thrombocytopenia. The fever, which is a result of the release of pyrogenic factors by monocyte and macrophage cells, is irregular and intermittent. Our patient had no typical skin lesions mentioned above, but had other features of papulosquamous disease. The fever pattern in our patient was similar to that generally described.

MH is characterized by proliferation of large “histiocyte-like,” usually mononucleated cells with cytoplasmic vacuoles and occasional erythroagocytosis: phagocytosis of RBCs and nuclear debris by atypical histiocytes. The nuclei may be single or multiple and demonstrate one or two prominent nucleoli. Large blasts with low nuclear/cytoplasmic ratios, occasional azurophilic granules, and immature nuclei with nucleoli can be seen in bone marrow smears.

The classification of histiocytic proliferations in the skin is confusing. Immunohistochemical staining procedures and ultrastructural studies have made it possible to differentiate the histiocytic syndromes. MH cells can react positively with immunoperoxidase stains of lysozyme and alpha-antichymotrypsin, cytochemical stains of acid-phosphatase, alpha-naphthyl acetate esterase (ANAE), alpha-naphthyl butyrate esterase, and antibodies directed against myeloid surface antigens, HLA DR, CD11, CD13, CD25, CD30, CD53, CD68, and CD71. However, no B- and T-cell antigens are detected. Cytochemical and ultrastructural data support the concept that the neoplastic cells belong to the mononuclear phagocyte system.

Due to the frequent abundance of accompanying granulocytes, lymphoid, and plasma cells, and the presence of areas of necrosis, an initial correct diagnosis of MH is often difficult to establish on skin, bone, and soft tissue biopsies. Our patient showed non-specific findings in the skin biopsy. A definitive diagnosis may require tissue from the bone marrow, lymph nodes, lung or liver. Often a combination of findings from different organs is required for definite diagnosis.

Therapy consists of aggressive combination chemotherapy including cyclophosphamide, doxorubicin (adriamycin), vincristine, and prednisolone (“CHOP”).

Relatively longer survival is correlated with ini-
tional confinement to the skin and the absence of cytopenia or liver function abnormalities\(^1\). In general, the disease is rapidly fatal; patients have a mean survival of 6 to 12 months. Recent advances in chemotherapy suggest that early diagnosis and therapy may significantly prolong survival. Our patient had poor prognostic factors present such as cytopenia and impairment of liver function. Furthermore, an early diagnosis was not made.

The skin lesions of our case were atypical for malignant histiocytosis. Erythematous scaly skin lesions without malignant cell infiltration have rarely been reported in malignant histiocytosis. The clinical findings of cutaneous scaly skin lesions, hepatomegaly, and fever in our case was quite suggestive of histiocytic malignancy.

In histiocytic malignancies, the skin lesions of Langerhans Cell Histiocytosis (LCH) is somewhat similar to those of our case. LCH includes Letterer-Siwe disease, Hand-Schuller-Christian disease, and eosinophilic granuloma. Cutaneous involvement is seen in approximately 80% of Letterer-Siwe disease. Skin lesions may be either seborrheic, papular, or purpuric involving the scalp, face, neck, trunk, buttocks, and intertriginous areas such as the axilla, inguinal folds, and behind the ears. In the case of Hand-Schuller-Christian disease, cutaneous lesions are present in about one third of the patients. They are bronze pigmentation, papulopustular or papulonodular lesions, xanthelasma, and lesions resembling xanthoma disseminatum or juvenile xanthogranuloma. There may be papular crusted eruption of scalp and trunk similar to seborrheic dermatitis. The most frequently observed skin lesions of eosinophilic granuloma is the ulcerative mucocutaneous granuloma of the genitalia or oral cavity\(^2\).

To differentiate MH from LCH, various marker studies and electron microscopic examination are needed. For example, the Langerhans cells are not stained with ANAE, and show Birbeck granules on ultrastructural examination\(^3\). In our case, myeloid cells stained positively with ANAE and acid phosphatase suggested they were malignant histiocytes. A final diagnosis of MH was made only after the bone marrow examination. Further marker study and electron microscopic examination were prevented by the sudden death of the patient.

REFERENCES