Cutaneous Manifestations of Hemophagocytic Lymphohistiocytosis

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Background: Hemophagocytic lymphohistiocytosis is a rare, rapidly progressive, and potentially fatal disorder of activated histiocytes. The initial clinical presentation commonly includes fever, hepatosplenomegaly, and pancytopenia. Skin eruptions are described in up to 65% of patients. Information regarding the morphological features, configuration, and distribution of these eruptions is lacking and is typically reported as nonspecific and “maculopapular.” The aim of this report is to better delineate the cutaneous manifestations of the disorder to assist in differentiating the process from other systemic diseases.

Observation: A case report of a neonate with hemophagocytic lymphohistiocytosis with generalized purpuric macules is described. The clinical features of 5 other patients with hemophagocytic lymphohistiocytosis at Children’s Hospital of Wisconsin, Milwaukee, are summarized. Clinical images of 1 additional neonatal patient with hemophagocytic lymphohistiocytosis are presented as well. These observations demonstrate the varied cutaneous manifestations of hemophagocytic lymphohistiocytosis: erythroderma, generalized purpuric macules and papules, and morbilliform eruptions.

Conclusion: Awareness of cutaneous involvement can assist in the initial diagnosis of hemophagocytic lymphohistiocytosis and potentially signify recurrences.

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The following values were revealed: white blood cell count, 7.3 × 10^3/µL; hemoglobin, 10.8 g/dL; platelets, 112 × 10^3/µL; aspartate aminotransferase, 71 U/L; alanine aminotransferase, 124 U/L; and lactate dehydrogenase, 1727 U/L. A peripheral blood smear reviewed by one of us (J.P.S.) demonstrated no blast forms. A skin biopsy specimen was obtained and demonstrated an interstitial and perivascular mixed infiltrate. Immunohistochemical staining revealed a CD3-positive lymphocyte population. Special stains with CD1a and toluidine blue were negative.

At follow-up 1 week later, the initial cutaneous eruption had faded to a dusky, nonblanching reticulated pattern. Multiple fine petechiae were present. Liver and spleen were now both enlarged to 3 cm below the costal margin. Laboratory evaluation revealed continued deterioration with the following values: platelets, 12 × 10^3/µL; aspartate aminotransferase, 124 U/L; and lactate dehydrogenase, 1727 U/L. A peripheral blood smear reviewed by one of us (J.P.S.) demonstrated no blast forms. A skin biopsy specimen was obtained and demonstrated an interstitial and perivascular mixed infiltrate. Immunohistochemical staining revealed a CD3-positive lymphocyte population. Special stains with CD1a and toluidine blue were negative.

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During hospitalization, an extensive investigation for viral infections, including Epstein-Barr virus, was negative. Head imaging, ophthalmological, and auditory examinations failed to demonstrate findings typical of congenital viral infections. Maternal antiplatelet antibodies were absent. An abdominal ultrasound revealed hepatosplenomegaly, but no expansive vascular lesion within the liver to account for the cytopenias. Thrombocytopenia reached a nadir of 1 × 10^3/µL despite multiple platelet transfusions and intravenous immunoglobulin. Triglyceride levels increased from 172 mg/dL (1.94 mmol/L) at admission to 797 mg/dL (9.01 mmol/L) on day of life 27. Hypofibrinogenemia was present. Bone marrow aspirate and biopsy on day of life 17 revealed a hypercellular marrow with abundant megakaryocytes, but no interstitial histiocytes or phagocytic activity. A specimen obtained by open liver biopsy on day of life 22 revealed extensive erythrophagocytosis by benign-appearing histiocytes. Epstein-Barr viral stains demonstrated nuclear staining in more than 80% of hepatocytes and 20% of bile duct epithelial cells.

The patient was started on treatment with dexamethasone followed by induction chemotherapy with etoposide. A gradual normalization of hepatic transaminases, triglycerides, and platelet counts occurred. All skin manifestations resolved. At 3 months of age, the patient was observed to have a recurrence of purpuric macules at her bilateral temples and temporal scalp. At this time, triglyceride levels were elevated to 1269 mg/dL (14.3 mmol/L). Hepatic enzymes, platelet counts, and blood cell counts remained normal. At 10 months of age, the patient is well with no evidence of recurrence.

**COMMENT**

Hemophagocytic lymphohistiocytosis was first described by Farquhar and Claireaux in 1952 as hereditary medullary reticulosis. Thorough descriptions of the clinical features of hemophagocytic lymphohistiocytosis are presented in reviews by Janka, Henter et al, Favara, and Imashuku et al. Previously, a distinction between primary or familial hemophagocytic lymphohistiocytosis and secondary or infection-associated hemophagocytic syndrome was made because immunosuppressed adults with renal transplant were observed to develop a hemophagocytic syndrome in response to viral infections. attempts to distinguish primary and secondary hemophagocytic lymphohistiocytosis in children have been inconclusive, a unifying diagnosis of hemophagocytic lymphohistiocytosis is appropriate. In fact, viral infections may initiate the disease process in familial hemophagocytic lymphohistiocytosis.
In hemophagocytic lymphohistiocytosis, there is uncontrolled activation or lack of down-regulation of the cellular immune system causing a generalized proliferation of benign-appearing histiocytes. Previous reports have described hemophagocytic lymphohistiocytosis as a hypercytokinemia or macrophage activation syndrome. This reactive disorder lacks the typical cells of Langerhans cell histiocytosis, but involves the widespread infiltration of lymphocytes and macrophages into the liver, spleen, lymph nodes, and central nervous system. Although not consistently present, viral infections and impaired natural killer activity have been reported in cases of hemophagocytic lymphohistiocytosis. Linkage analysis indicates genetic heterogeneity with linkage of some individuals to multiple gene loci. Defects in the perforin gene have been recognized in approximately 20% of unrelated patients with familial hemophagocytical lymphohistiocytosis.8,9 Perforin-based mechanisms appear to be important in the control of activated immune activity.

In 1991, the International Histiocyte Society established diagnostic guidelines in an effort to facilitate early diagnosis and management.1 According to the guidelines, the diagnosis of hemophagocytic lymphohistiocytosis requires the features noted in Table 1. Strong supportive evidence for the diagnosis of hemophagocytic lymphohistiocytosis includes cerebral spinal fluid pleocytosis, histopathological evidence of chronic persistent hepatitis, and low natural killer cell activity. “Skin rash” is considered to be a potential abnormal finding in hemophagocytic lymphohistiocytosis.4 Atypical presentations have been reported; failure to demonstrate all diagnostic criteria does not preclude the diagnosis of hemophagocytic lymphohistiocytosis. As in our patient, fever is a less prominent feature in neonatal cases.

A computerized review of all patient diagnoses at Children’s Hospital of Wisconsin between 1990 and 2000 revealed 5 additional patients with hemophagocytic lymphohistiocytosis. The details of their clinical features are summarized in Table 2 and Table 3. Our patient (patient 1) had cutaneous involvement at presentation while 2 other patients developed a hemophagocytic lymphohistiocytosis–associated eruption within 2 months of presentation (patients 2 and 3). Skin biopsy specimens revealed epidermal spongiosis, necrotic keratinocytes, and sparse exocytosis. Perivascular lymphohistiocytic infiltrates and extravasated red blood cells were located in the dermis. No evidence of erythrophagocytosis was present in the skin biopsy specimens. Two of the 3 surviving patients received bone marrow transplantation 1 (patient 5) and 5 (patient 4) years ago, while 3 patients died secondary to disseminated candidiasis (patients 2 and 3) and bacterial sepsis (patient 6).

A review of the literature reveals approximately 30 cases with reference to cutaneous manifestations.2,3 Janka5 reports skin changes early in the disease in 6% of 108 cases of familial hemophagocytic lymphohistiocytosis. In another retrospective chart review of 32 cases with familial hemophagocytic lymphohistiocytosis, 43% were cited to have skin involvement early in the disease (<10 days) and 65% to have skin lesions at some time during the disease.3 The discrepancy between these reports may reflect the review of hospital charts in the latter study in which it was assumed that all skin involvement was related to the underlying disease. The Familial Hemophagocytic Lymphohistiocytosis Registry cites “skin rash” in 24% of patients.10 Cutaneous involvement was present in 3 of the 6 patients with hemophagocytic lymphohistiocytosis at our institution.

In the majority of cases with cutaneous involvement, a transient generalized maculopapular eruption is reported. Our patient (patient 1) had extensive petechial and purpuric macules at presentation similar to cases of neonatal purpura secondary to congenital viral infections. Similar primary lesions limited to an acral distribution in a neonate were seen in patient 3. Although not a neonate, patient 2 demonstrated a generalized, purpuric, and papular eruption.

In addition to hemorrhagic and purpuric macules, there are other types of cutaneous lesions in hemophagocytic lymphohistiocytosis. We (J.P.S. and N.B.E.) have observed 3 additional cases of hemophagocytic lymphohistiocytosis in the neonatal period with prominent cutaneous manifestations. Unfortunately, the medical records of these patients were unavailable; therefore, the details of their cases are not included in Tables 2 and 3. One neonate demonstrated generalized purpuric macules similar to patients 1 and 3 (Figure 3). Another neonate with generalized erythroderma and edema presented much like the erythrodermic “sunburnt” integument described by Farquhar and Claireaux.7 A less distinctive morbilliform erythema can also be prominent on skin examination of these patients.

The cutaneous manifestations are not specific to hemophagocytic lymphohistiocytosis. The generalized distribution reveals an underlying systemic process. Skin biopsy findings are not diagnostic and rarely demonstrate...
hemophagocytosis. Favara\(^5\) describes typical histological features to include a lymphohistiocytic perivascular infiltrate in the reticular dermis, without evidence of epidermal changes or vasculitis.\(^5\) Extravagated erythrocytes account for purpuric lesions. Although some cases present much like neonatal purpura of infectious origin, skin biopsies fail to demonstrate extramedullary hematopoeis.

Differential diagnosis includes myofibromatosis, extramedullary hematopoeis, Langerhans cell histiocytosis, and leukemia cutis. Although clinical and pathological features of hemophagocytic lymphohistiocytosis are nonspecific, it is important to histologically rule out other systemic diseases.

The pathological and cutaneous findings are consistent with the current understanding of the pathophysiology of hemophagocytosis lymphohistiocytosis. Activated lymphocytes produce hypercytokinemia involving interleukin 2\(^{11}\) and interferon \(\gamma\),\(^{12}\) causing massive activation of histiocytes and secretion of additional cytokines. Loss or deficiency of potential immune regulatory mechanisms (ie, perforin gene defects) in the setting of hypercytokinemia allows activated lymphocytes and histiocytes to uncontrollably infiltrate organ systems, including skin.

The actual initiator of the process may be variable. Multiple cases (including our patient) demonstrate evidence of preceding Epstein-Barr virus infection,\(^3\) while reports suggest additional infectious etiologies including cytomegalovirus, adenovirus, and parvovirus.\(^7,11\) As in the proliferative phases of Chediak-Higashi, Griscelli, and X-linked lymphoproliferative (Duncan disease) syndromes, stimulated T-lymphocytes create a chemokine environment that activates mononuclear phagocytes that lack features of Langerhans cell and malignant histiocytes. Some cases of hemophagocytic lymphohistiocytosis actually share the same germline mutations in SH2D1A seen in X-linked lymphoproliferative disease.\(^13\) The clinical picture of hemophagocytic lymphohistiocytosis probably represents a phenotypic expression of several different defects in homeostasis of immune activation. Erythrophagocytosis in hemophagocytic lymphohistiocytosis is commonly present in lymphoid tissues (liver, spleen, and bone marrow), but rarely evident in skin biopsy specimens. Phagocytic activity in liver, spleen, and marrow biopsy specimens is not universally present, however. Only one third of initial bone marrow biopsy speci-
bone marrow transplantation are 10% to 44% and 66%, respectively.6,10

Prominent cutaneous manifestations can accompany underlying hemophagocytic lymphohistiocytosis in the form of purpuric, macular, papular, erythodermic, or morbilliform eruptions. The reappearance of cutaneous manifestations in a patient treated with chemotherapy may herald a recurrence of hemophagocytic lymphohistiocytosis. Although clinical features are nonspecific, awareness of the various types of cutaneous presentations can assist in the initial diagnosis. Skin biopsies can assist in differentiating hemophagocytic lymphohistiocytosis from other systemic and potentially malignant diseases.

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REFERENCES


Correction

Omission of Author’s Name. In the Vignette by Hegemann et al titled “Live-doid Vasculitis With Ulcerations: The Role of Antithrombin III Deficiency and Its Therapeutic Consequences” published in the June issue of the ARCHIVES (2002;138:841-842), an author’s name was omitted from the signature block on page 842. Wolfgang Christian Marsch, MD, from Halle (Saale), Germany, should have been listed as the third author. The journal regrets the error.