Denouement and Discussion

Anaplastic Large Cell Lymphoma With Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) may occur in a primary form, often associated with mutations in the perforin gene responsible for natural killer cell cytotoxic activity,[1] or secondary to underlying rheumatic disease (most commonly systemic-onset juvenile rheumatoid arthritis), infection (usually herpesvirus infections such as Epstein-Barr virus or virtually any bacteria, fungus, or parasite), immunodeficiency (Griscelli syndrome), lysinuric protein intolerance, and malignancies. Lymphomas are the most common malignancies associated with HLH, and although HLH is frequently associated with subcutaneous T-cell lymphomas,[2] it is exceedingly rare as part of anaplastic large cell lymphoma (ALCL), as was observed in this case.[3]

Lymphomas, including Hodgkin and non-Hodgkin (NHL), account for 10% to 15% of childhood cancer in developed countries, and ALCL accounts for 10% of NHL in childhood. Anaplastic large cell lymphoma is a mature T-cell or null-cell lymphoma that has been recognized as a distinct entity in the classification of NHL.[4] The 2 subtypes of ALCL include systemic or cutaneous; however, the primary cutaneous form is rare in children.[5] In 80% of cases, the systemic form of ALCL is associated with a chromosomal translocation, t(2;5)(p23; q35), specific to this disease. This translocation results in a chimeric protein whose expression has oncogenic properties and may contribute to malignant transformation in these lymphomas.[6]

CLINICAL MANIFESTATIONS

The clinical presentation of HLH is a direct result of the underlying hyperinflammatory syndrome and uncontrolled activation of T lymphocytes and macrophages. Diagnostic criteria include familial disease or known genetic defect and 5 of the following clinical or laboratory criteria: fever, splenomegaly, cytopenias, hypertriglyceridemia with or without hypofibrinogenemia, elevated ferritin level, elevated sCD25 level, decreased or absent natural killer cell activity, and the presence of HLH in the bone marrow, cerebrospinal fluid, or lymph nodes.[7]

Anaplastic large cell lymphoma is more common in males and the clinical presentation is unusual since it can present with a slowly progressive course and patients often have peripheral, intrathoracic, and intra-abdominal nodal involvement instead of the typical extranodal involvement seen in other types of NHL. Other common sites of disease characteristic of patients with ALCL and not often seen in other forms of NHL include skin and bone. Furthermore, this lymphoma can involve less common sites such as soft tissue and lung, and hepatosplenomegaly is common. Finally, ALCL is often associated with systemic symptoms including fever and weight loss.

In this patient, fevers may have been attributable to either HLH or lymphoma, while the significant oral ulceration was likely a manifestation of his neutropenia. The progressive pancytopenia with elevated lactate dehydrogenase and uric acid concentrations were suspicious for either HLH or hematologic malignancy, but the eschar with underlying induration (Figure 1) was suspicious for an infiltrative lesion, such as lymphoma, and necessitated the bone marrow examination and skin biopsies.

DIAGNOSIS

Diagnosis of both ALCL and HLH are made by biopsy of the skin and bone marrow or other involved organs (eg, lymph node). In this case, a biopsy specimen of the skin revealed superficial epidermal ulceration with necrosis and an underlying atypical lymphoid infiltrate within the dermis. The atypical cells were large and contained eosinophilic cytoplasm and convoluted nuclei, suggesting a diagnosis of ALCL. The diagnosis was confirmed by immunohistochemical evaluation, which revealed staining for T-cell antigens and both the epithelial membrane antigen and the anaplastic lymphoma kinase (ALK-1) protein. Thus, the combined histologic and immunohistochemical findings were most consistent with ALCL.

Histologically, HLH is identified by the presence of histiocytes containing engulfed cells and cellular fragments from red and white blood cells, as well as platelets.[8] This can be seen within the skin, the bone marrow, or other involved organs. In the clinical setting, evaluation of a patient for HLH involves obtaining a complete blood cell count to test for cytopenias, hepatic function test results to check for hepatitis, prothrombin and activated partial thromboplastin times, D-dimers levels, and fibrinogen levels to test for coagulopathy. Hyperferritinemia and hypertriglyceridemia are also characteristic of HLH. Once the diagnosis of HLH is made, an evaluation of natural killer cell numbers and function should be performed to distinguish primary from secondary forms of the disease.

TREATMENT

The goals of treatment for HLH are to suppress the significant inflammation responsible for the symptoms and to kill pathogen-infected antigen-presenting cells in order to decrease natural killer cell and T-suppressor cell activation.[7] The pathogenesis of HLH is thought to be due to an uncontrolled cytokine storm from T-lymphocyte activation. Cytokines such as interferon-γ, IL-12, IL-18, and tumor necrosis factor α are believed to contribute to the macrophage activation and cytophagocytosis.[9] To counteract this cytokine storm, high-dose corticosteroids and cyclosporine A are often used to combat the T-cell activation.[8] For severe familial forms, or those refractory to highly immunosuppressive therapy, a protocol using etoposide and dexamethasone is available.[8] If the HLH is eventually controlled, then the underlying associated illness needs to be treated.

Recent advances in the treatment for children with NHL have resulted in a significant improvement in cure rates. Combination chemotherapy protocols are based on the tumor cell immunophenotype, whereas early regimens were based on the histologic features of the tumor.[10-12] With any of the protocols, the long-term survival is estimated to be approximately 60% to 70%; however, newer combinations of chemotherapeutic agents, increasing dose intensity of some medications, and targeted immunotherapy are currently under investigation. For patients with relapse of ALCL after combination chemotherapy, intensive combinations of other drugs have induced remission in a small proportion of patients. Those children would be candidates for high-dose chemotherapy with stem cell rescue.[13] Few patients, late recurrences, disparate staging systems, and treatment by different groups prevent generalizations from being made about optimal treatment, and the approach to this condition continues to evolve.[10-14]

Accepted for Publication: December 8, 2005.
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Author Contributions: *Study concept and design:* Burnham, Kersun, and Cron. *Acquisition of data:* Burnham and Kreiger. *Analysis and interpretation of data:* Burnham and Paessler. *Drafting of the manuscript:* Burnham, Kersun, and Cron. *Critical revision of the manuscript for important intellectual content*: Burnham, Kreiger, Paessler, Kersun, and Cron. *Administrative, technical, and material support:* Burnham. *Study supervision:* Cron.
Financial Disclosure: None reported.

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"Mankind owes to the child the best it has to give."
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