Histioctytic Sarcoma in a 3-Year-Old Male: A Case Report

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ABSTRACT. We describe a pediatric patient with histiocytic sarcoma involving the T6 and L4 vertebral bodies and the lungs. His tumor progressed during chemotherapy designed for Langerhans’ cell histiocytosis and sarcoma. High-dose radiation, on the other hand, was effective. Pediatrics 2005;116:e322–e325. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0026; sarcoma, histiocytes, Langerhans’ cell histiocytosis, histiocytic sarcoma.

Histiocytic and dendritic neoplasms are rare, especially in children. These tumors arise from antigen-processing phagocytes (histiocytes) and antigen-presenting dendritic cells. The cell types are derived from hematopoietic or mesenchymal stem cells.1 Currently, the World Health Organization includes the following 6 entities under this designation: Langerhans’ cell histiocytosis (LCH), Langerhans’ cell sarcoma, follicular dendritic cell sarcoma, interdigitating dendritic cell sarcoma, dendritic cell sarcoma not otherwise specified, and histiocytic sarcoma.2 The latter malignancy is a proliferation of histiocytes (tissue macrophages), which are characterized by positive expression of the macrophage-associated antigen CD68, negative expression of the T-cell–associated antigen CD1a, negative expression of the dendritic cell–associated antigens CD21/CD35, and lack of Birbeck granules on electron microscopy.3

The rarity of histiocytic sarcoma continues to make its management challenging, and we are unaware of any recommended therapy for young children. We describe a child with histiocytic sarcoma to highlight his poor response to LCH- and sarcoma-based chemotherapy. By contrast, high-dose radiation proved to be effective.

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CASE REPORT

This previously healthy 3-year-old boy experienced intermittent low back pain radiating to the right inguinal region for ~2 months. His symptoms initially responded to ibuprofen. The pain intensity increased over a 2-week period, and he refused to walk. Review of systems was significant for pain with urination. With the exception of being unable to stand, his physical examination was unremarkable. The laboratory tests showed normal blood counts and normal liver and renal function. An MRI showed collapse of the T6 and L4 vertebral bodies and a soft tissue mass in the anterior epidural space at the level of L4 (Fig 1 A and B). The chest and abdominal computed tomography (CT) scans were normal. Bone marrow aspiration revealed no malignant infiltration. A technetium bone scan showed increased uptake limited to the T6 and L4 regions. CT-scan–guided needle biopsy of the L4 mass revealed infiltrative proliferation of the bone and soft tissue by sheets and clusters of large ovoid cells with abundant eosinophilic cytoplasm (Fig 2A). The nuclei were round/oval, eccentric, and pleomorphic with occasional grooving. Distinct, small nucleoli were present. Multinucleated giant cells were also present (Fig 2B). Immunohistochemistry showed expression of CD68 (macrophage/histiocytic marker; Fig 2C) and focal expression of S100 protein and CD15 (granulocyte marker). The following markers were negative: CD1a (Langerhans’ and immature T-cell marker; Fig 2D), CD3 (T-cell marker), CD20/CD79a (B-cell markers), CD32 (B-cell chronic lymphocytic leukemia/lymphoproliferative disease marker), CD21 (mature B-cell and follicular dendritic cell marker), CD35 (follicular dendritic cell marker), CD30 (anaplastic large-cell lymphoma and Reed-Sternberg cell marker), ALK (anaplastic large-cell lymphoma marker), desmin, smooth muscle actin, and myeloperoxidase (myeloid cell marker). Electron microscopy revealed numerous cytoplasmic lysosomes; however, Birbeck granules (typical of Langerhans’ cells), interdigitating cell junctions, cytoplasmic projections, and desmosomes were not identified. These morphologic and immunohistochemical features are typical of histiocytic sarcoma (Table 1).

The patient was started on LCH-based therapy (prednisone, 6-merpactopurine, methotrexate, vinblastine, and etoposide). However, within ~2 weeks, his condition deteriorated and he developed neurogenic bladder. He then received radiation (4500 cGy in 180-cGy fractions) to the L4 vertebral body and associated paraspinal mass. He gradually improved. At the end of the radiation treatment, he was walking without limitation and had full bladder control. A follow-up MRI showed significant diminution of the paraspinal mass (Fig 1 C and D); the T6 vertebra remained unchanged.

The radiation was followed by 3 monthly cycles of cyclophosphamide (2.2 g/m²) and actinomycin D (0.045 mg/kg). At the end of the third cycle, his chest CT scan revealed 2 nodules in the right and left upper lobes. A positron emission tomography scan showed abnormal uptake limited to the lung nodules. The metastatic lesions were confirmed by a CT-guided biopsy. He received 2 monthly cycles of idarubicin (10 mg/m²) and 2-chlorodeoxyadenosine (2CdA [or cladribine] at 8 mg/m²). A follow-up chest CT showed diminution of the lung lesions. Localized radiation (4500 cGy at 180 cGy per fraction) was delivered to the metastatic lung nodules. This treatment was followed by 6 monthly cycles of 2CdA (8 mg/m²).

DISCUSSION

Histiocytes (tissue macrophages) are derived from hematopoietic monoblasts. These phagocytes contain...
organelles (vacuoles and lysosomes) and enzymes (lysozyme, α-1-antitrypsin, acid phosphatase, and nonspecific esterases) capable of processing antigens for T lymphocytes. The cells also lack Birbeck granules (typical of Langerhans’ cells), complex cell junctions (typical of interdigitating dendritic cells), and desmosomes (typical of follicular dendritic cells). CD68 (a lysosome-associated protein) is the most important antigen that detects macrophages.2

Histiocytic sarcoma is an exceedingly rare malignancy that demonstrates morphologic and immunophenotypic features of macrophage/histiocytic differentiation. Before the development of immunohistochemistry, this diagnosis was more common. It is now recognized that most cases of “histiocytic sarcoma” described in the past actually represented diffuse/anaplastic large B-cell lymphoma, peripheral T-cell lymphoma associated with hemophagocytic syndrome, or lymphoma with associated reactive macrophages (eg, histiocyte recruitments by macrophage-activating factors).4,5

Morphologically, tumor cells are characterized by abundant eosinophilic cytoplasm (Fig 2A). The nuclei are eccentric and round/oval, with atypia varying from mild to pleomorphic. The nucleoli are small and distinct. Binucleated giant cells are common (Fig 2B). The ultrastructural features show numerous vacuoles and lysosomes. Interdigitating cell junctions and Birbeck granules are essentially absent. The latter features distinguish this entity from Langerhans’ and dendritic cell tumors, especially when S100 protein is positive (Table 1). The immunohisto-
chemical profile shows expression of the lysosome-associated (macrophage/histiocytic) markers CD68 (in 100% of cases) and lysozyme (in 94% of cases). The Langerhans’ cell, follicular dendritic cell, myeloid, B cell, T cell (CD4 is usually positive), epithelial cell, and melanocyte markers are negative. Focal reactivity for the S100 protein (typically expressed in Langerhans’ cell tumors) can be present in normal macrophages and histiocytic sarcoma (Table 1). Because of the monocytic origin of histiocytes, monocytic leukemia should be especially excluded. The entity should also be distinguished from hemophagocytic syndrome (a nonmalignant, cytokine-induced macrophage proliferation), which is commonly associated with viral infection (eg, Epstein-Barr virus).

Histiocytic sarcoma–like tumors have been reported in association with other malignancies. Recently, histiocytic sarcoma involving bone marrow, bones, kidney, and spleen was reported in a 14-year-old patient on maintenance chemotherapy for acute lymphoblastic leukemia. It was interesting to note that both histiocytic tumor and leukemic blasts shared the rearrangements involving immunoglobulin heavy chain and T-cell receptor γ-chain genes, suggesting lineage infidelity for the recurrent disease. Two other similar cases have also been described. A potential role for the transcription factor EBF/Pax5 is proposed. As previously noted, true histiocytic sarcoma demonstrates germ-line configuration for immunoglobulin and T-cell receptors.

Only a few reports of bona fide histiocytic sarcoma exist in the literature, mostly involving adults. Pileri et al described 18 patients; 3 had complete remission induced by chemotherapy, 6 had no response to initial treatment, and 7 died as a result of disease. Three patients were children (0.5, 4, and 7 years old) who presented with widespread disease that progressed during chemotherapy. In 1 child, the disease infiltrated the bone marrow, liver, spleen, lymph nodes, thymus, gut, pancreas, brain, lungs, myocardium, and kidneys. In another child, intestinal anaplastic large-cell lymphoma subsequently developed. Ralfkiaer et al reported 4 adults with widespread disease who failed chemotherapy and died within 0.5 to 14 months after diagnosis. Laurit-

### Table 1. Antigen-Detectable Profiles of Macrophage/Histiocytic and Dendritic Neoplasms

<table>
<thead>
<tr>
<th></th>
<th>CD1a</th>
<th>CD21/CD35</th>
<th>CD68</th>
<th>Lysozyme</th>
<th>S100</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCH/sarcoma</td>
<td>+</td>
<td></td>
<td>+</td>
<td>±*</td>
<td>+</td>
</tr>
<tr>
<td>Interdigitating dendritic cell tumor/sarcoma</td>
<td>-</td>
<td></td>
<td>±</td>
<td>±*</td>
<td>+</td>
</tr>
<tr>
<td>Follicular dendritic cell tumor/sarcoma</td>
<td>-</td>
<td>+</td>
<td>±*</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>Dendritic cell sarcoma, not otherwise specified</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Histiocytic sarcoma</td>
<td>-</td>
<td></td>
<td>+</td>
<td>+</td>
<td>±*</td>
</tr>
<tr>
<td>Case patient</td>
<td>-</td>
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<td>+</td>
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</tr>
</tbody>
</table>

* Expressed in ~25% to 50% of cases.
† Focally positive.
zen et al\textsuperscript{6} described 8 adults with various lesions; 6 died as a result of disease 5 to 48 months after diagnosis despite aggressive chemotherapy. Primary involvement of the central nervous system (a 13-year-old boy) and spleen (adults) have been reported.\textsuperscript{12} Hornick et al\textsuperscript{13} followed 14 adults (except 1 15-year-old) with extranodal disease. Follow-up was available in 10 patients: 5 developed distant metastasis, and 2 died as a result of disease 4 and 5 months after diagnosis.

Although the clinical presentation and sites of involvement vary, poor prognosis is a common finding (because of disease spread and poor response to therapy). The therapeutic options include surgery (for focal and accessible lesions), chemotherapy, and radiation. Unfortunately, the L4 mass in this child was not surgically accessible, and the metastatic lung lesions were bilateral. Regardless of margins or nodal involvement, considerable rates of local and distant recurrence after excision have been reported.\textsuperscript{13} Chemotherapy has also shown poor results.\textsuperscript{1,6,11–13} In this child, we report a similar poor response to LCH- and sarcoma-based chemotherapy but a slightly more promising result with idarubicin and 2CdA. He developed neurogenic bladder during LCH therapy and lung metastases during cyclophosphamide plus actinomycin D. By contrast, idarubicin and 2CdA decreased the size of his lung nodules. Several studies have shown the efficacy of 2CdA when used against LCH.\textsuperscript{14–16} Because histiocytes are derived from monocytes, we are hopeful that histiocytic sarcoma may show a favorable response to 2CdA. Although there are no published studies suggesting the efficacy of 2CdA in histiocytic sarcoma, we are aware of an adult patient with this entity who remained free of the disease for 6 months after 5 cycles of 2CdA. Unfortunately, recurrent disease occurred thereafter.

The reason for the initial administration of treatment designed for LCH was for a possible similarity between LCH and histiocytic sarcoma. However, our patient’s failure to respond to LCH therapy confirms that the 2 entities are distinct. Prompt institution of radiotherapy at the time of symptomatic progression lead to radiographic regression of his soft tissue mass (Fig 1 C and D) and eventual complete resolution of the symptoms. Although limited radiotherapy doses are typically effective for LCH with bone involvement,\textsuperscript{47} histiocytic sarcoma is a more resistant entity and requires treatment in line with other soft tissue sarcomas. The decision to proceed to a dose of 4500 cGy to the L4 region was based on minimal radiographic and clinical responses to the initial (eg, 2 weeks) radiation treatment. As noted above, his clinical improvement occurred during the second half of the radiotherapy course, which continued during the next several weeks.

The difference between his 2 spinal lesions (T6 and L4) is interesting. It is unlikely that these sites are unrelated; however, the T6 tumor did not progress despite receiving no radiation. Multifocal spinal lesions\textsuperscript{17} have not been described in histiocytic sarcoma. Interactions between CD1a\textsuperscript{+} and CD3\textsuperscript{+} cells via cytokine production have been suggested as a mechanism for developing LCH lesions.\textsuperscript{18} However, there is no evidence that such a cytokine storm occurs in histiocytic sarcoma.

High-dose radiation was effective in this child with histiocytic sarcoma. The entity is highly malignant, and repetitive evaluations to detect metastases are necessary. Future studies should provide better recommendations for chemotherapy.

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