Clonal Cytophagic Histiocytic Panniculitis in Children May Be Cured by Cyclosporine A

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KEY WORDS
cytophagic histiocytic panniculitis, clonality, children, macrophage activation syndrome

ABBREVIATIONS
CHP—cytophagic histiocytic panniculitis
CSA—cyclosporine A
EBV—Epstein-Barr virus
FLH—familial hemophagocytic lymphohistiocytosis
HLA—human leucocyte antigen
HLH—hemophagocytic lymphohistiocytosis
IFN—interferon
IL—interleukin
MAS—macrophage activation syndrome
NK—natural killer
SPTCL—subcutaneous panniculitis-like T-cell lymphoma
TNF—tumor necrosis factor
Dr Bader-Meunier, Dr Fraitag, Dr Wouters, and Dr Bodemer contributed equally to this work.

Drs Bader-Meunier and Fraitag conceptualized and designed the study and drafted the initial manuscript; Mr Janssen performed immunohistochemical staining and reviewed and revised the manuscript; Drs Brochard and Lamant reviewed and revised the manuscript; Drs Wouters and Bodemer coordinated and supervised data collection and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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abstract

Cytophagic histiocytic panniculitis (CHP) is a rare panniculitis in childhood, associated either with nonmalignant conditions or with subcutaneous panniculitis-like T-cell lymphoma (SPTCL), and often also associated with macrophage activation syndrome (MAS). Discriminating between these 2 conditions is therapeutically important because nonmalignant CHP often improves under cyclosporine and prednisone, whereas most cases of SPTCL may be best treated with more aggressive therapy. We report the cases of a 6-month-old boy and a 16-month-old girl who, after viral infection, developed multiple infiltrating skin nodules on the limbs and face, associated with MAS. Histopathologic findings for skin biopsy specimens revealed CHP associated with heavily cellular lobular panniculitis. Hemophagocytosis and immunohistochemical staining features were consistent with typical characteristics of in situ MAS in adipose tissue: the lymphocytes were mostly TCD8+ cells with an activated phenotype (human leucocyte antigen (HLA) -DR+) and expressed interferon-γ; CD68+ macrophages expressed tumor necrosis factor-α and interleukin-6. A monoclonal rearrangement of the T-cell receptor γ gene was present in skin tissue but not in peripheral blood or bone marrow lymphocytes. Cyclosporine A treatment resulted in the complete remission of cutaneous and systemic manifestations in both patients for 66 and 29 months, respectively. This report suggests that the diagnosis of a reactive T-cell lymphoproliferation should be the treatment of choice in young children with severe CHP, even if there is a SPTCL-like aspect with an in situ T-cell clonality. It also suggests that CSA is the optimal treatment of this condition and postulates the possible pathologic process underlying this efficacy.
Panniculitides are rare in children and include a group of diseases that manifest as inflamed nodules in the subcutaneous tissue. Among this group of heterogeneous disorders, cytophagic histiocytic panniculitis (CHP) is lobular panniculitis, characterized by subcutaneous proliferation of cytophagic histiocytes and lymphocytes, often associated with macrophage activation syndrome (MAS). It may be an isolated skin disease or associated with non-malignant conditions, such as infections or connective tissue disorders as well as with malignancies, including subcutaneous panniculitis-like T-cell lymphoma (SPTCL). It is clinically important to be able to distinguish between these 2 conditions to identify appropriate treatment: benign CHP often improves with cyclosporine A (CSA) and prednisone, whereas most cases of SPTCL may require a more aggressive therapy. We report the clinical course and the histopathologic and immunohistochemical findings in skin biopsies for 2 children who presented with clonal CHP and SPTCL aspect preceding MAS. Our observations suggest that a reactive T-cell lymphoproliferation in young children may mimic SPTCL with T-cell monoclonality and may be best cured by CSA in young children. Thus, these results highlight the need for a careful clinicopathologic analysis in cases of CHP to avoid an erroneous diagnosis of SPTCL and consequently unnecessary cytotoxic chemotherapy.

**CASE REPORTS**

A 6-month-old African boy (patient 1) and a 16-month-old white girl (patient 2), without any history of familial hemophagocytic lymphohistiocytosis (FLH), developed multiple infiltrating skin nodules on the limbs and face, 1 and 2 weeks after chickenpox and upper-respiratory tract infection, respectively. Other initial clinical findings and blood cell count were normal. Skin involvement evolved to ulcerative lesions in patient 1 (Fig 1) and partially improved without treatment in patient 2. Both patients presented with high-grade fever associated with lymphadenopathy 3.5 months (patient 1) and 22 months (patient 2) after the onset of skin disease, respectively. Both cases developed anemia, thrombocytopenia, neutropenia, elevated ferritin and triglycerides, hypofibrinogenemia, and hemophagocytosis on bone marrow aspirate, consistent with the diagnosis of MAS (Table 1).

Punch skin biopsies were taken from the 2 patients at onset of the cutaneous manifestations (biopsy 1) and at onset of the febrile illness (biopsy 2). The specimens were embedded in paraffin, stained with hematoxylin-eosin (biopsies 1 and 2) and processed for immunohistochemistry (biopsies 2). Degranulation assays to quantify cytotoxic granule exocytosis and natural killer (NK) cell cytotoxicity were performed as previously described. Histopathologic and immunohistochemical findings for the skin biopsy specimens were similar for the 2 patients. Hematoxylin-eosin staining revealed a substantial cellular lobular panniculitis with large areas of fat necrosis and karyorrhexis associated with superficial dermal-epidermal involvement. There were numerous infiltrating small lymphocytes with macrophages associated with mild to prominent hemophagocytosis of red blood cells and more rarely of lymphocytes in the subdermal fat constituting a CHP at onset of skin disease as well as onset of fever. Immunohistochemical staining showed that the lymphocytes were mostly cytotoxic T lymphocytes (T CD8+ cells) with an activated phenotype (human leukocyte antigen-DR+), and expressed interferon-γ (IFN-γ) and the cytotoxic proteins granzyme B and TIA-1, but were negative for CD56, a marker of NK T cells. There were also numerous macrophages expressing tumor necrosis factor-α (TNF-α) and, interleukin 6 (IL-6). In both patients, a monoclonal rearrangement of the T-cell receptor γ gene was present in skin tissue but not in the peripheral blood or bone marrow lymphocytes. In situ hybridization to detect Epstein-Barr virus (EBV) EBER-1 was negative. Polymerase chain reaction tests were used to detect EBV, herpes virus 8, and varicella zoster virus in skin biopsies from patient 1; all were negative. The numbers of peripheral T, B, and NK cells and the degranulation assay to quantify cytotoxic granule exocytosis and NK cell cytotoxicity were normal. Both patients received 3 pulses of methylprednisolone (30 mg/kg/day) followed by daily treatment with prednisone. This corticosteroid treatment led to remission, but systemic and cutaneous manifestations relapsed when the doses were tapered from 1.2 to 0.5 mg/kg/day (patient 1) and from 1.5 to 1.3 mg/kg/day (patient 2). Eventually, complete remission of both cutaneous and systemic manifestations was achieved by adding CSA (5 mg/kg/day) to the
TABLE 1 Demographic, Clinical, Biological, and Cytologic Features and Disease Course in 2 Patients With CHP

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of skin manifestations</td>
<td>6 mo</td>
</tr>
<tr>
<td>Family history</td>
<td>Consanguineous parents</td>
</tr>
<tr>
<td>Clinical manifestations (delay from onset of skin manifestations to onset of systemic manifestations)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin value (g/dL)*</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Neutrophil count (×10³/L)*</td>
<td>1.2 (2)</td>
</tr>
<tr>
<td>Platelet count (×10³/L)*</td>
<td>112 (45)</td>
</tr>
<tr>
<td>Fibrinogen concentration (g/L)*</td>
<td>1.5 (40)</td>
</tr>
<tr>
<td>Triglyceride concentration (mmol/L)*</td>
<td>3.6 (2)</td>
</tr>
<tr>
<td>Serum ferritin level (µg/L)*</td>
<td>1 700 (45)</td>
</tr>
<tr>
<td>Bone marrow smear examination (delay from onset of fever, d)</td>
<td>Normocellular, no atypical cells, hemophagocytosis</td>
</tr>
<tr>
<td>Therapy</td>
<td>Methylprednisolone (3 × 500 mg/m²), prednisone (1.2 mg/kg/d), cyclosporineb (5 mg/kg/d)</td>
</tr>
<tr>
<td>Duration of treatment with steroids/CSA (mo)</td>
<td>16/31</td>
</tr>
<tr>
<td>Duration of follow-up since the initiation of CSA/duration of follow-up off treatment (mo)</td>
<td>66/35</td>
</tr>
</tbody>
</table>

* Most pathologic value before treatment with steroids.

b Cyclosporine A was added 4 and 12 mo after the initiation of steroid administration in patients 1 and 2, respectively.

regimen for both patients. CSA was well tolerated, and remission was sustained at 66 and 29 months, respectively (Table 1).

DISCUSSION

These cases emphasize that CHP may be associated with a reactive T-cell lymphoproliferation in young children, even if it mimics SPTCL with T-cell clonality, and this has profound therapeutic implications. In addition, our study is the first to demonstrate features of in situ MAS in cases of CHP. Panniculitides are rare in children and refer to disorders with inflammation of the subcutaneous fat that manifest as nodules. Histologically, pattern of inflammation is mostly lobular or mostly septal. They can be a primary process; result from trauma, infection, or medications; or be part of a systemic disorder, including malignancy. SPTCL is a T-cell lymphoma with clinicopathologic features simulating a panniculitis, which was often associated with a MAS and an aggressive clinical course. Neoplastic cells are a subset of T cells (CD3⁺, CD8⁺, CD4⁻ T cells), which strongly expressed cytotoxic proteins (granzyme B, TIA-1, perforin), and do not expressed CD56. Our 2 cases were particularly misleading because both...
presented with histopathology and monoclonal rearrangement for T-cell receptor γ gene that were consistent with SPTCL. However, the diagnosis of SPTCL was unlikely in children <2 years old. Indeed, SPTCL mostly affects adults, with 70% of patients presenting between 18 and 60 years of age, and is extremely rare in children. It has been reported in only 1 patient under 2 years old, and the diagnosis in this case is questionable because of the absence of atypical lymphocytes, T- or B-cell monoclonality, and cytogenetic abnormalities in skin and bone marrow. Thus, we did not retain the diagnosis of lymphoma in our 2 young patients because we thought that the early onset of panniculitis was a key point to favor the diagnosis of reactive T-cell lymphoproliferation associated with MAS. Monoclonal T-cell proliferation usually indicates T-cell lymphoproliferative disorder; however, this may rarely be present in nonneoplastic T cells, especially in patients with secondary hemophagocytic lymphohistiocytosis (HLH) triggered by EBV. It has been suggested that this florid clonal T-cell proliferation is reactive, probably driven by a strong immune reaction against EBV infection. Note that a monoclonal rearrangement of the T-cell receptor γ gene in skin has also been reported in other nonmalignant diseases, including lupus erythematosus panniculitis.

Eventually, the sustained remission observed in our patients after treatment with steroids and CSA alone supports the view that they had a reactive T-cell proliferation, despite the in situ T-cell monoclonality. These different considerations suggest that a combination of CSA and corticosteroids is a reasonable therapeutic option in patients <2 years old presenting with clonal CHP and MAS. A switch to other immunosuppressive drugs is mandatory in the absence of prompt clinical remission. Thus, careful clinicopathologic analysis is required for the interpretation of immunophenotypic and clonality data in cases of CHP to avoid an erroneous diagnosis of SPTCL and consequently unnecessary cytotoxic chemotherapy.

In HLH, the ever-expanding population of cytotoxic lymphocytes produces large quantities of cytokines, such as IFN-γ, which sustain macrophage activation. In addition TNF-α and IL-6 are inflammatory cytokines, which induce changes that look like clinical and laboratory findings that characterize HLH. A study of liver biopsies from patients with different types of hemophagocytic syndromes has documented the in situ involvement of activated, IFN-γ-producing cytotoxic T lymphocytes and of TNF-α- and IL-6 producing macrophages whatever the cause of MAS. This typical immunohistochemical characteristics of MAS was observed inside the adipose tissue in our patients, suggesting that CHP could be MAS focused inside the subcutis, preceding a full-blown systemic illness. CHP differs from cutaneous manifestations of MAS. A heterozygous mutation in the PFR1 gene has been reported in 1 patient with CHP, but the absence of functional assessment did not allow diagnosis of FLH. In young children, MAS is mainly due to FLH, but immunologic tests ruled out a classic form such genetic diseases in our patients. However, a genetic predisposition to CHP cannot be excluded.

The remission of the symptoms of CHP and MAS under the association of corticosteroids and cyclosporine A in our 2 patients is consistent with the reported efficacy of this treatment in typical MAS. It suggests that CSA is the treatment of choice for nonmalignant severe CHP associated with MAS. These features and the immunohistochemical pattern of in situ MAS in the panniculitis lesions emphasize the key role of T cells in the pathogenesis of CHP. The substantial activated CD8+ cell infiltration observed in both of our patients may have contributed to the proliferation of cytophagic histiocytes because CD8+ T cell are central to initiating inflammatory cascades by playing a major role in the differentiation, activation, and migration of macrophages in obese adipose tissue.

CONCLUSIONS

This report suggests that the diagnosis of a reactive T-cell lymphoproliferation, possibly triggered by a viral infection, must be favored in young children with severe CHP, even if there is a SPTCL-like aspect with an in situ T-cell clonality. It also suggests that CSA is the optimal treatment of this condition and postulates the possible pathologic process underlying this efficacy.

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