Hemophagocytic Syndrome: A Misleading Complication of Visceral Leishmaniasis in Children—A Series of 12 Cases

Marie-Helene Gagnaire, MD*; Claire Galambrun, MD†; and Jean Louis Stéphan, MD*

ABSTRACT. Objective. To describe the difficulties in diagnosing visceral leishmaniasis (VL) when revealed by hemophagocytic syndrome (HS) in young children.

Design. Retrospective study of patients identified over a 17-year period in French pediatric units.

Results. This series comprises 12 cases of VL that were either revealed \((n = 11)\) or complicated \((n = 1)\) by HS. Clinical manifestations were those of severe VL with sustained high fever and hepatosplenomegaly in children in very poor condition. Biological manifestations always included pancytopenia, marked hypofibrinogenemia and hypertriglyceridemia, hepatic cytolysis, and prominent hemophagocytosis on the bone marrow smear. These features led to transfer to a hematology unit. Ten children were very young \((<38\) months) at onset \((and consequently at infection)\). Signs of autoimmune (Coombs’ test-positive erythrocytes, antinuclear factors, and various autoantibodies) were found in 4 cases and were probably secondary to polyclonal B cell activation. Serologic tests for Leishmania were negative at onset in 6 children, and no amastigotes were found on the first marrow smear in 8 of 12 cases despite extensive search. Seven patients had not visited foreign countries. All these factors explain the initial diagnostic confusion. Three cases were initially misdiagnosed as familial erythrophagocytic lymphohistiocytosis or infection-associated HS, and these patients were treated with etoposide (once for 5 months) to control the HS after failure of steroids. The diagnostic delay in these cases was 50, 74, and 134 days. When VL was finally diagnosed, amphotericin B monotherapy was effective in 4 cases. Eight patients were treated with antimony salts; 4 were cured, 3 required adjunctive treatment, and 1 worsened (HS) and was cured with steroids and liposomal amphotericin.

Regardless of the type of therapy, all 12 children are presumed cured with a mean follow-up of 7 years \((range: 6 months–16 years)\).

Conclusions. A diagnosis of VL should, therefore, be seriously considered in all young patients with HS exposed to visceralizing Leishmania sp in Southern Europe. Clinicians and cytopathologists must be aware of the association. Early diagnosis of VL will minimize unnecessary hospitalization and potentially harmful investigations and treatments. Pediatrics 2000;106(4). URL: http://www.pediatrics.org/cgi/content/full/106/4/e58; hemophagocytic syndrome, children, visceral leishmaniasis.

ABBREVIATIONS. HS, hemophagocytic syndrome; FEL, familial erythrophagocytic lymphohistiocytosis; VL, visceral leishmaniasis; RHS, reactive hemophagocytic syndrome; HB, hemoglobin; VAHS, virus-associated hemophagocytic syndrome; CRP, C-reactive protein; IgG, immunoglobulin G.

Hemophagocytic syndrome (HS) is a clinicopathologic entity characterized by activation and uncontrolled nonmalignant proliferation of T lymphocytes and macrophages, leading to cytokine overproduction. The latter accounts for the primary biological signs. Patients usually present with an acute febrile illness, hepatosplenomegaly, pancytopenia, marked hypofibrinogenemia, and hypertriglyceridemia. HS in children has been linked to viral, bacterial, fungal, and parasitic infections \(\text{(the so-called infection-associated HS)}\) and to a broad spectrum of malignancies and genetic disorders, such as Chédiak-Higashi disease, Griscelli disease, XLP syndrome, and familial erythrophagocytic lymphohistiocytosis \(\text{(FEL)}\).1,2

Infection by the protozoan pathogen Leishmania is a public health problem in most countries bordering the Mediterranean basin. One important reservoir is dogs. Although there are a number of different species, all of which are transmitted by phlebotomine sandflies, there are only 2 primary types of clinical disease. Cutaneous leishmaniasis is extremely common in tropical countries, the Middle East, and many Mediterranean areas. Visceral leishmaniasis \(\text{(VL)}\) is somewhat less common, affecting tropical areas of the Old World.3 However, VL may be contracted on short visits.4 Particularly in young children, VL revealed by HS \(\text{(an exceedingly rare event)}\) can cause considerable diagnostic difficulty. The first case of leishmaniasis revealed by a reactive HS \(\text{(RHS)}\) was reported by Matzner et al5 and concerned a 22-year-old adult. We are aware of only 2 other reported pediatric cases, both in Scandinavia.6,7

We reviewed the medical records of 12 children with RHS associated with VL diagnosed in France during the past 16 years. Clinical and biological features of this misleading presentation of VL are discussed together with treatment.

METHODS

Study Design

All pediatric units in France were surveyed for cases of HS in patients with VL. The charts of 12 patients referred to 8 pediatric hematology units between 1983 and 1999 were studied. The history, physical findings, and laboratory results were recorded. The diagnostic criteria for reactive HS included fever, splenomegaly,
obtained by dermal scraping. Which amastigotes were identified in a thin smear found in 2 cases: one (patient 1) in which a chronic showed slow waves. A likely portal of entry was fluid studies were normal. Electroencephalogram neurologic signs (obtundation, weakness, and hypo- edema and ascitis in 3 patients. Two patients had nodes (1–2 cm in diameter) were nontender. Extreme fuse adenopathy was appreciable in 3 patients, in-

Clinical Findings

The median incubation period for full-blown VL in this series was ~6 months. The clinical manifestations were fairly uniform. Persistent fever was found in all 12 cases and was irregular, high (>39°C), and accompanied by a marked alteration of the general state, pallor, fatigue, severe weight loss, and poor feeding. Failure to thrive (weight: <2 standard deviations) was observed in 6 cases. Splenomegaly, reaching the iliac crest in 7 cases, was always present at initial presentation. The liver was also enlarged (n = 11), often >5 cm below the costal margin. Diffuse adenopathy was appreciable in 3 patients, including axillary and inguinal chains. The enlarged nodes (1–2 cm in diameter) were nontender. Extensive hypoalbuminemia (serum level: <20 g/L) caused edema and ascitis in 3 patients. Two patients had neurologic signs (obtundation, weakness, and hypotonia). Computed tomography and cerebrospinal fluid studies were normal. Electroencephalogram showed slow waves. A likely portal of entry was found in 2 cases: one (patient 1) in which a chronic lesion on the forehead disappeared after a few days of treatment, and also in the other (patient 2) in which amastigotes were identified in a thin smear obtained by dermal scraping. The other signs are shown in Table 1.

TABLE 1. Clinical Findings

<table>
<thead>
<tr>
<th>Clinical Manifestations</th>
<th>N/12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen enlargement (median: 11 cm; 5–26)*</td>
<td>12</td>
</tr>
<tr>
<td>Hepatomegaly (median: 8 cm; 3–17)*</td>
<td>11</td>
</tr>
<tr>
<td>Purpura</td>
<td>4</td>
</tr>
<tr>
<td>Edema or ascites†</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue, pallor, general deterioration</td>
<td>8</td>
</tr>
<tr>
<td>Weight loss</td>
<td>6</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>3</td>
</tr>
<tr>
<td>Protracted fever &gt;15 d</td>
<td>12</td>
</tr>
<tr>
<td>Enlarged abdomen</td>
<td>2</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>6</td>
</tr>
<tr>
<td>Identified portal of entry‡</td>
<td>2</td>
</tr>
<tr>
<td>Neurological deterioration (lethargy, hypotonia)</td>
<td>2</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>3</td>
</tr>
<tr>
<td>Joint pain</td>
<td>3</td>
</tr>
</tbody>
</table>

* Below the costal margin.
† Physical or ultrasound examination.
‡ One case formally documented by dermal scraping.

RESULTS

The study population was composed of 6 boys and 6 girls, whose age at onset ranged from 7 months to 9 years (median: 18.5 months; 10 patients: <38 months old). Six were of French origin and 6 were of other origins (Algeria, 3; Rwanda, 1; and Morocco, 2). Three children lived in the South of France (an endemic area for leishmaniasis) and 9 had stayed in the South of France (4) or in North Africa (5) for a mean of 5.8 months (3 weeks–10 months) before clinical onset.

Laboratory Investigations

All the patients had signs of bone marrow hemophagocytosis (Fig 1) associated with absolute or relative hypofibrinemia in 3 cases (fibrinogen values of 2.5, 1.6, and 2.13 g/L; C-reactive protein (CRP) elevated at 221, 60, and 120 mg/L), hypertriglyceride- demia and hypergammaglobulinemia, on which the diagnosis of HS was based. Transaminase activity was high in 10 cases and was 8 times normal on average. Pancytopenia was found in 9 cases, with severe anemia (hemoglobin [Hb]: <7 g/dL) in 10 cases. Two children had severe hypocalemia (1.43 and 1.79 mmol/L) at onset (Table 2).

Four children had the following autoantibodies at onset: antinuclear (n = 1), positive direct Coombs’ test and antiplatelet antibodies (n = 3), antisMOOTH muscle (n = 2), and rheumatoid factor (n = 1).

Diagnosis (Table 3)

Six of the 12 patients were seropositive for Leishmania, with indirect fluorescence values of 1/160 to 1/1280 at onset. The threshold titer for positivity was 1:80. All but 4 of the patients’ bone marrow aspirates were negative for Leishmania (direct examination) at onset. Eight children who had negative smears at diagnosis had repeat marrow smears, and the parasite was finally identified in 4 of these patients after 1 to 4 months. These last 4 children were also seronegative at onset and only 2 seroconverted after 1 and 2.5 months (Table 3).

The 4 children whose marrow smears remained negative (n = 4) despite repeated testing were sero- positive at onset, and their favorable outcome during antiinfective therapy supported the diagnosis of VL. None of the patients had needle biopsy of the spleen.

Culture results were positive in 2 cases. The pathogen (L infantum MON 1) was identified only once by means of an immunoenzymatic method 8 (case 1).

Despite massive infection and positive marrow smears, 3 children remained seronegative. The lymphocyte count, proliferative T-cell responses, and vaccinal antibody assays were normal, and all the children were human immunodeficiency virus-seronegative (data not shown), ruling out an underlying immunodeficiency. One child had Turner’s syn- drome.

In one case in which the diagnosis of VL was made
rapidly, the diagnosis of HS was made retrospectively during marrow slide review 11 years later, based on bone marrow hemophagocytosis and other biological signs.

**Treatment and Outcome**

The mean interval between the first visit to a general practitioner and diagnosis of VL was 49.5 days (range: 13–174 days; median: 34 days). Most (8/12) received ambulatory treatment with antibiotics for a suspected bacterial infection. The mean period between hospitalization and diagnosis was 29.6 days (range: 2–134 days; median: 19 days).

The diagnosis on admission was wrong in 4 cases, all involving very young children (13, 14, 23, and 30 months) and was only corrected after 2, 2.5, and 4 months. The erroneous diagnoses were chronic juvenile myelomonocytic leukemia, FEL (2 cases), and virus-associated HS (VAHS). The diagnostic error led to etoposide therapy in 3 cases and planned bone marrow allografting in 2. These cases are now briefly summarized.

**Case 8 (1992)**

This 13-month-old child of Moroccan origin was admitted to the intensive care unit for gastrointestinal bleeding and fever (40°C). On physical examination, he was chronically ill appearing, febrile, pale, and ecchymotic. His spleen reached the iliac crest.

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**TABLE 3. Evidence of Leishmaniasis at Onset**

<table>
<thead>
<tr>
<th>Test</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow aspirate positive for <em>Leishmania</em></td>
<td>4/12</td>
</tr>
<tr>
<td>Seropositivity (indirect fluorescence)†</td>
<td>6/12‡</td>
</tr>
<tr>
<td>Culture-positive§</td>
<td>2/3 tested</td>
</tr>
</tbody>
</table>

* Eight of 12 marrow smears were positive after repeated examination.
† Indirect fluorescence was used to detect IgG antibodies to *Leishmania*. The antigen was prepared from promastigotes of the World Health Organization reference strain of *L. infantum*.
‡ Titer: ≥1:160 to 1:1280; the serology was positive in 3 cases between 1 and 2.5 months after onset.
§ Isoenzyme analysis of cultured promastigotes identified *L. infantum* MON 1 in 1 case.
and the liver was palpable 7 cm below the costal margin. The Hb level was 3.5 g/dL, the platelet count 25,000/µL, and the fibrinogen .45 g/L. Tumoral hepatosplenomegaly, together with signs of hemophagocytosis on the marrow smear and sero-negative for *Leishmania*, led to a tentative diagnosis of familial lymphohistiocytosis. The child received methylprednisolone intravenously (3 mg/kg/day for 3 weeks), combined with etoposide (230 mg/m²/week for 21 weeks; cumulative etoposide dose: 4.8 g). After a period of clinical improvement (including apyrexia) but persistently low platelet count and hypofibrinogenemia, bone marrow transplantation was envisaged with a genoidentical brother as donor. Etoposide was withdrawn, leading to renewed fever and a deterioration of the overall condition. A fifth marrow smear performed during the pregraft workup revealed *Leishmania* and hemophagocytosis. The child was then treated with sodium stibogluconate (Pentostam) &gt;6 months after initial presentation. The improvement was judged inadequate and the patient was switched to meglumine antimony (Glucantime) then pentamidine isethionate (Pentacarinat), followed by a final course of Glucantime. Recovery was slow, with gradual weight gain, after a disease history of 10 months. Biological abnormalities were corrected after 4.5 months. The pathogen disappeared from the marrow smear 9 months after onset. The serology remained negative 1 year after onset and has not been checked since. The child is considered cured with a follow-up of 9 years.

Case 10 (1983)

This 23-month-old child of Moroccan origin was hospitalized in poor general condition (decreased activity, pallor, and tachycardia), with high fever and pancytopenia (Hb, 6 g/dL; platelets, 7000/µL; neutropenia, 580/µL; immunoglobulin G [IgG], 22 g/L; protein, 83 g/L; calcium, 1.79 mmol/L; fibrinogen, 2.1 g/L; CRP, 16 mg/L; triglycerides, 3.16 mmol/L). She was living in Morocco 7 months before onset. Serologic test results for leishmaniasis were negative, and several smears showed a cell-poor marrow without parasites. No diagnosis was made for 2 months, during which the child’s condition deteriorated slowly despite parenteral nutrition. In particular, the splenomegaly became tumorous and was palpable 17 cm below the costal margin, the fever persisted, and empirical antibiotic therapy was ineffective. Hemophagocytosis was found on a new marrow sample and familial lymphohistiocytosis was suspected. The child received etoposide (100 mg/m²; 3 injections in 10 days) and was then transferred to a hematology unit for bone marrow transplantation. During the pregraft workup a new bone marrow smear revealed rare amastigotes. The child received three 10-day courses of antimony meglumine and recovered rapidly. The serology remained negative 3 months after onset but was not subsequently tested. The child is cured, with a follow-up of 16 years.

Case 7 (1992)

This 2½-year-old boy was hospitalized with a 10-day history of high-grade fever (&gt;40°C) with pancytopenia. He had a protuberant abdomen with enlarged liver (10 cm) and spleen (15 cm). Laboratory values were as follows: neutrophils, 640/µL; platelets, 23,000/µL; Hb, 6.7/dL; IgG, 31 g/L; fibrinogen, 1.6 g/L; CRP, 116 mg/L; triglycerides, 3.06 mmol/L; Coombs’ positivity, complement type; antisMOOTH muscle antibodies and rheumatoid factor were repeatedly positive. *Leishmania* serology was negative. After failure of empiric antibiotic therapy (intravenous cefotaxime + amikacin) followed by intravenous immunoglobulin (1 g/kg), the child was administered oral steroids (60 mg/m²/day = 40 mg/day for 1 month) for suspected VAHS (infiltration by activated lymphocytes and hemophagocytosis on the first marrow smear). An underlying inflammatory condition was suspected because of arthralgia. Despite a transient improvement after 2 months on steroids, the patient’s condition again deteriorated. Failure to control the HS led to etoposide therapy at a dose of 150 mg/m² × 3, with a rapid clinical improvement (apyrexia after the second injection) and full correction of biological abnormalities. A new *Leishmania* serology was performed 2.5 months after onset and was positive. A fourth marrow smear showed very rare intracellular amastigotes. The child was treated with standard fungizone for 2 months and is cured with 7 years of follow-up.

The more recent cases were diagnosed rapidly, and the patients were treated successfully with standard amphoterin B in 2 cases (cumulative dose: 20 and 60 mg/kg) or with liposomal amphoterin (Ambisome) in 2 cases (total doses: 18 and 29 mg/kg; Table 4). Treatment was well-tolerated. Defervescence was obtained after 4 days on average. The marrow smear 1 month later was normal, with complete disappearance of hemophagocytosis and *Leishmania*. Eight patients received antimony salts: 4 were cured; 3 required a third course of Glucantime and Pentamidine, and 1 underwent splenectomy because of hypersplenism. One patient developed HS before responding to steroids and liposomal amphoterin.

Apart from the 2 cases in which etoposide was prescribed, steroids were used 4 times in combination with the antiparasitic treatment at various doses (1–2 mg/kg/day).

Final outcome was excellent, whatever the therapeutic modality and despite the diagnostic delay, etoposide treatment in 3 cases, and the failure of some specific therapies. All 12 children are presumed cured with a mean follow-up of 7 years (range: 6 months–16 years).

**DISCUSSION**

All these acutely ill children had an abnormal coagulation profile, elevated liver enzyme activities (except 2), very high triglyceride levels, low plasma fibrinogen levels, and bone marrow hemophagocytosis, in keeping with all the diagnostic criteria of HS as defined by the FHL Study Group of the Histiocyte Society in 1991.9 No other cause of HS was found, despite extensive microbiologic and serologic investigations (not shown). The other signs presented by these children were common to HS and VL (ie, hepatosplenomegaly, fever, and pancytopenia). We
found autoantibodies in 4 cases, but their significance was unclear. These findings complicated the diagnosis and were probably the result of polyclonal B-lymphocyte activation, suggested notably by strikingly high levels of serum IgG. During progressive Leishmania infection in mice, Th2-type CD4 T cells expand and secrete interleukin-4, resulting in polyclonal B-cell activation. The association of VL with hemophagocytosis has previously been reported but is poorly documented.

Leishmania binds to complement receptor CR3 and is then phagocytized by macrophages. Amastigote sequestration and chronic intracellular infection of macrophages could prompt uncontrolled macrophage activation, with secretion of proinflammatory cytokines. Activated Th1 cells can express FasL and thus kill infected macrophages. The young age of the children (10 of 12 were younger than 38 months) and the diagnostic delay could have been favoring factors. In one case (case 9), the diagnosis of RHS was made retrospectively by slide review, suggesting that the frequency of the RHS linked to VL may be underestimated. Activated erythrophagocytosis is also a conspicuous feature of other common intracellular parasitic diseases in children, such as vivax and falciparum malaria.

The diagnosis of VL was particularly difficult in these cases. VL was considered by the hematologist as a differential diagnosis, but Leishmania amastigotes were very few in number on the first marrow smear (Table 3), as in the 2 previously published pediatric cases. In a recently reported French series of VL, the parasite was not detected in 22% of cases. The reason for the parasite scarcity in bone marrow smears of patients with leishmaniasis-associated HS is unclear. Serostatus at diagnosis was noncontributory in one half of the patients who seroconverted either long after their recovery or not at all. This is somewhat surprising because with the exception of patients with acquired immunodeficiency syndrome, anti-Leishmania antibodies are usually present at high titers in patients with VL. US soldiers who served in Operation Desert Storm and developed systemic infection with L tropica (the cause of urban VL in the Middle East) also had low or undetectable antibody titers. Spleen needle-aspiration biopsy seems to have a sensitivity as high as 98%, but the risk of hemorrhage in such fragile children with low fibrinogen levels is unacceptable.

FEL is another differential diagnosis in a young child with an intense HS and a negative microbiologic workup. This genetically heterogeneous autosomal recessive disease generally affects very young children, sometimes during the first days of life. In the absence of a relevant family history or parental consanguinity, it is difficult to diagnose this disease, which can be cured only by bone marrow transplantation but is initially managed by cytotoxic and immunosuppressive treatment. Neurologic involvement is nearly always present, with meningeal infiltration by blast-like lymphoid cells and hemophagocytic macrophages, and this should distinguish it from a sporadic HS linked to an infection. The recent description of mutations in the perforin gene in patients with FEL linked to 10q22 should facilitate its diagnosis. Thus, etoposide was wrongly prescribed to 3 patients. This drug, which is cytotoxic for the monocyte-macrophage lineage, can
seem effective in some forms of HS, but it can have catastrophic consequences by increasing the risk of aplasia and aggravating the VL. Moreover, secondary malignancies after epipodophyllotoxin therapy, including myelodysplastic syndromes and acute myelocytic leukemia, have been reported. Bone marrow transplantation was planned in 2 cases, but fortunately the correct diagnosis was made during the pretransplant workup.

Various treatments were prescribed in this retrospective series, which includes a number of old observations. Case 5 is remarkable in that the HS, which was very severe (the patient had required transfusions for a clinical hemorrhagic syndrome), was not present at diagnosis but seems to have been triggered by pentavalent antimonials, because it occurred after 48 hours on treatment. The antimony salts were rapidly withdrawn and the patient recovered after 48 hours on treatment. The antimony regimen.

The efficacy and indications of steroids could not be determined in this small retrospective series. However, intravenous steroid therapy (1 mg/kg/day) should be given when gravity signs of HS are present (especially clotting disorders), pending eradication of the parasite by the antibiotic regimen.

In the western Mediterranean basin, the number of human VL cases, which used to be relatively low, has increased during the last decade. This is related to the recent increase in the canine population because of sociocultural changes. L infantum zymodeme MON 1 has been isoenzymatically identified as the primary agent. In the South of France from 1985 to 1994, the number of recorded VL cases was 30 to 35 per year, and one third involved children (personal communication, J. P. Dedet). VL may also be contracted during short visits to sub-Saharan countries (6 children in this series).

These cases stress the fact that leishmaniasis can be acquired in Europe, not only in tropical countries, and that it should be considered when discussing the cause of hemophagocytosis in infants. Amastigotes should be sought stubbornly on bone marrow smears, with repeated sampling and use of modern diagnostic methods. Leishmania can now be identified in tissues by means of PCR with species-specific probes, and this should simplify the diagnosis of these unusual forms.

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