Hemophagocytic lymphohistiocytosis associated with hepatosplenic T-cell lymphoma: case report

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ABSTRACT

Hepatosplenic T-cell lymphoma (HSTCL) is a rare non-Hodgkin lymphoma, marked by liver, spleen, and bone marrow sinusoidal infiltration, with an aggressive clinical course, which represents a difficult diagnostic task for clinicians and pathologists. Another equally severe and challenging condition is the hemophagocytic lymphohistiocytosis (also called hemophagocytic syndrome [HS]), which is often associated with hematologic malignancies and infectious diseases. The authors report the case of a 56-year-old woman diagnosed with HSTCL based on bone marrow aspirate flow cytometry and skin biopsy. The patient underwent a cycle of chemotherapy but the outcome was unfavorable with multiple organ failure. The laboratory analysis was consistent with HS. The autopsy confirmed both the remaining lymphoma in the pulmonary vessels and the hemophagocytic cells in the spleen and bone marrow.

Keywords
Lymphoma, T-cell, Peripheral; Lymphohistiocytosis, Hemophagocytic; Autopsy.

CASE REPORT

A 56-year-old woman sought medical care because of intermittent fever. Cervical lymphadenomegaly, hepatosplenomegaly, lower limbs edema, and hyperchromic skin lesions that were diffusely scattered characterized her physical examination.

Laboratory work-up showed pancytopenia (hemoglobin = 7.7 g/dL (reference value [RV]: 12-16 g/dL); 970 leukocytes/mm³ (RV: 4,000-11,000 leukocytes/mm³); 170 neutrophils/mm³ (RV: 1,600-7,000 neutrophils/mm³) and 14,000 platelets/mm³ (RV: 140,000-450,000 platelets/mm³); and mild elevation of hepatic enzymes (aspartate aminotransferase 101 U/L (RV < 31 U/L) and alanine aminotransferase 108 U/L (RV < 31 U/L).

The patient was hospitalized with the diagnosis of febrile neutropenia and treated with piperacillin/tazobactam.

The myelogram showed the presence of moderate-to-large cells, with a moderate nucleus/cytoplasm ratio, dense chromatin, with some evident nucleolar shadows, and abundant, grayish, agranular cytoplasm but with some vacuoles. The flow cytometry showed positivity for CD45, CD3, CD57, and T-cell receptor (TCR) gamma-delta (γδ), and negativity for CD20, CD56, CD2, CD4, CD8, CD56, CD14, CD33, and CD25, which was consistent with the diagnosis of peripheral T-cell lymphoma, gamma-delta type. A skin biopsy revealed lymphomatous/leukemic infiltration with immunohistochemical positivity for CD3, CD57.
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(Figure 1), Ki-67 (60%), and negativity for CD45 and CD20.

The bone marrow biopsy showed hypercellularity due to lymphoid cell sinusoidal infiltration with a similar immunohistochemical pattern observed in the skin (Figure 2).

Such findings, added to the clinical features, permitted the diagnosis of hepatosplenic T-cell lymphoma. Chemotherapy was started with doxorubicin, vincristine, cyclophosphamide, etoposide, and dexamethasone.

The outcome was unfavorable with renal failure (creatinine 1.3 mg/dL (RV: 0.5-0.9 mg/dL), enlarged prothrombin time (INR 3.09; RV: 0.95-1.2), fibrinogen 60 mg/dL (RV: 150-200 mg/dL), while ferritin and triglyceride determinations raised to 7225 ng/mL.

**Figure 1.** Photomicrography of the skin. A and B – Dermal infiltration by monomorphic cells (H&E, 100X in A and 200X in B); C and D – Immunohistochemical positivity for CD3 (C) and CD57 (D), consistent with the diagnosis of hepatosplenic T-cell lymphoma.

**Figure 2.** Photomicrography of the bone marrow. A – Hypercellularity; B – Neoplastic sinusoidal infiltration with immunohistochemical positivity for CD57.
(RV: 13-150 ng/mL) and 387 mg/dL (RV < 150 mg/dL), respectively. The hypothesis of hemophagocytic syndrome (HS) was raised and corticosteroid pulse therapy was started. The patient was referred to the intensive care unit but died on the ninth day of hospitalization. An autopsy was performed.

**AUTOPSY FINDINGS**

The patient weighed 58.8 kg and measured 1.62 m. The ectoscopy revealed the presence of petechiae and bruising in the right flank and periorbitary region, with no trauma signs. Hematomas were present at the vein puncture sites in the cervical and groin regions. Lymphadenomegaly and remaining skin lesions weren’t identified.

At the thoracic and abdominal cavities opening, 500 mL of citrine effusion was drained from each cavity. The right lung weighed 524 g and the left lung 688 g (RV: 400-800 g), both exhibited a rubbery consistency and exhibited friability in some scattered areas. Hemorrhage and alveolar edema associated with fibrinous exudate and vascular neoplastic leukostasis (Figure 3A and 3B) were present (immunohistochemical positivity for CD3 and CD57) (Figure 3C and 3D). The heart weighed 298 g (RV: 350 g) exhibiting normal chamber size and thickness.

The liver weighed 2064 g (RV: 1400-1600 g) and had a smooth external surface. The cutting surface exhibited a lobular pattern and congestion. On microscopy, chronic hepatitis with nodular transformation was present, but no remaining neoplastic infiltration was found (Figure 4).

The spleen weighed 578 g (RV: 150 g) and showed a firm consistency and a winy color. On microscopy, hemophagocytosis was evident, as well as a marked white pulp depletion and congestion of the red pulp, but neoplastic infiltration was absent (Figure 5).

The kidneys weighed 200 g (left) and 206 g (right) (RV: 250g each). Their cutting surface was pale and the corticomedullary limit was well defined. On

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**Figure 3.** Photomicrography of the lung. A – Edema, diffuse congestion, and hemorrhage (H&E, 50X); B – Leukostasis in pulmonary vessel (H&E, 200X); C – Immunohistochemistry positivity for CD57; D – Immunohistochemistry positivity for CD3.
microscopy, nephrosclerosis and acute tubular necrosis were present.

The bone marrow showed a marked cellular depletion, edema, and gelatinous degeneration as well as hemophagocytosis. Sinusoidal neoplastic infiltration was absent (Figure 6).

With the autopsy findings, we conclude that the cause of death was HS associated with pulmonary

Figure 4. Photomicrography of the liver. A – Chronic hepatitis in a nodular transformation (H&E, 50X); B – Portal triad detail showing an inflammatory infiltration; lymphoma cells were absent (H&E, 100X).

Figure 5. Photomicrography of the spleen. A – Parenchymal congestion and white pulp depletion (H&E, 50X); B – Hemophagocytosis (arrow) observed in the red pulp (H&E, 400X).

Figure 6. Photomicrography of the bone marrow. A – Marked cellular depletion, edema, gelatinous degeneration, and multiple histiocytes with hemophagocytosis (H&E, 100X); B – Detail of histiocytes phagocytizing red cells (arrows) (H&E, 400X).
The presence of T-lymphocytes with γδ receptors among the innate immune cells of the skin makes it a likely site for the HSTCL development. However, cutaneous involvement in hepatosplenic γδ T-cell lymphoma is not as common as it might be expected, in large case series. Yeung et al. reported, in 2012, a case of a 59-year-old male patient, who presented cutaneous lymphomatous infiltration after the diagnosis of HSTCL.

In the case reported herein, after the diagnosis of lymphoma, the HS ensued. Similarly rare, this entity is of challenging diagnosis. Characteristically, this syndrome reflects an overreacted systemic inflammation causing fever, coagulopathy, hepatomegaly, jaundice, and pancytopenia. Among children this syndrome may be triggered by a viral infection or may be related to genetic abnormalities. However, in adults, the main triggering event is represented by lymphoproliferative disorders and sometimes is the first presentation. The diagnosis is based on clinical and laboratory data (Table 1). Immunosupression is the treatment of choice.

The pathophysiology of HS is still not fully understood. However, it is believed that there is an overstimulation of the immune system, accompanied by oversecretion of cytokines, notably tumor necrosis factor-alpha. In this setting, macrophages release ferritin, increase plasmin activity (leading to fibrinolysis, hepatomegaly, raised serum liver enzymes and bilirubin) and inhibit lipoprotein lipase (leading to hypertriglyceridemia). This immune hyperactivity is postulated to be secondary to an increase in NK cell

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<tr>
<th>Table 1. Hemophagocytic lymphohistiocytosis diagnostic criteria (adapted from Côté-Daigneault et al.)</th>
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<tr>
<td><strong>Major criteria (all five should be present)</strong></td>
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<tr>
<td>Fever</td>
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<td>Splenomegaly</td>
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<td>Bicytopenia or pancytopenia</td>
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<tr>
<td>Hypertriglyceridemia and/or hypofibrinogenemia</td>
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<td>Hemophagocytosis in bone marrow biopsy</td>
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<td><strong>Minor criteria (the A criteria or the concomitance of B and C replace the major criteria)</strong></td>
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<td>A: Low or absent NK-cell activity</td>
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<td>B: Ferritin &gt; 500 mg/L</td>
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<td>C: Soluble CD25 (i.e. soluble IL-2 receptor) ≥ 2,400 U/mL</td>
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NK = natural killer.
activity in response to EBV infection. A very similar phenomenon takes place in EBV-related lymphomas.6,10 Therefore, the concurrence of pathogenic factors for both HSTCL and HS is observed, explaining some reports where the lymphoma and the HS ensue concomitantly.3,7,8 Both lymphoma and the HS present a poor prognosis. HSTCL usually has aggressive behavior and premature therapeutic resistance.

Differently from the cases already reported, the diagnosis of HS of this case was based on the autopsy findings. Similarly, remaining neoplasia was solely represent by leukostasis in the pulmonary vessels, infrequently described.

CONCLUSION

HSTL is a rare entity accompanied by a very poor prognosis, especially when associated with hemophagocytic syndrome, which is hardly diagnosed and may present similar physiopatogeny, especially the overstimulation of the immune system.

REFERENCES


