

Hepatosplenic Gamma-Delta T-cell Lymphoma Presenting With Disseminated Intravascular Coagulation and Coexistent Systemic Mastocytosis

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Case Report

A 75-year-old white man presented with 4 days of continued bleeding from the forearm after a cat scratch wound. He also complained of a recent 20-pound weight loss, night sweats, fevers, weakness, and arthralgia. He was diagnosed with indolent systemic mastocytosis in 2006 by bone marrow biopsy, which showed increased mast cell infiltrate with no other associated hematologic or lymphoproliferative disorders. The patient was treated with oral prednisone and followed closely. He had a history of prostate cancer treated with radical prostatectomy in 2001, and was in remission. On physical exam, the patient was alert and oriented. His temperature was 102.3°F, his blood pressure was 90/45 mmHg, his heart rate was 116 beats per minute, and he had a forearm puncture site with no signs of infection that continued to bleed despite multiple pressure dressings. Skin examination revealed extensive lesions of urticaria pigmentosa. There were no palpable lymph nodes or hepatosplenomegaly.

Significant laboratory values included platelets 24,000/cmm (normal range, 150,000–450,000/cmm), partial thromboplastin time 39.8 seconds (normal range, 21.3–31.9 seconds), prothrombin time 18.4 (normal range, 8.8–11.7 seconds), D-dimer of 29.5 mg/L (normal range, 0.54–2.09 mg/L), fibrinogen of 95 mg/dL (normal range, 200–400 mg/dL), and fibrin split products greater than 40 g/mL (normal, <10 g/mL). Lactate dehydrogenase was 319 units/L (normal range, 111–211 units/L) and prostate specific antigen was 0.3 ng/mL (normal, <4 ng/mL). An abdominal computed tomography scan displayed mesenteric lymphadenopathy and minimal bilateral inguinal lymphadenopathy but no hepatosplenomegaly.

The patient was diagnosed with disseminated intravascular coagulation (DIC) based on these abnormali-

ties. Peripheral smear showed rare abnormal-appearing lymphocytes that were medium-sized and that had pale cytoplasm. Bone marrow biopsy showed a hypercellular bone marrow with abnormal lymphocytes comprising approximately 20% of the cells. Immunophenotyping showed the abnormal cells positive for CD3 and CD7 and negative for CD2, CD4, CD5, CD8, CD20, CD25, CD30, CD34, CD56, CD61, CD117, ALK, clusterin, factor VIII, hemoglobin A, lysozyme, myeloperoxidase, PAX5, TdT, and kappa and lambda immunoglobulin light chains. Molecular studies by polymerase chain reaction and DNA extraction displayed T-cell receptor gamma chain rearrangement. This was consistent with hepatosplenic gamma-delta T-cell lymphoma (HS $\gamma\delta$ TCL). Cytogenetics showed complex cytogenetic abnormalities with no evidence of isochromosome 7. Mastocytosis involvement of the bone marrow was also confirmed through positive anti-CD117 and tryptase staining (Figure 1). Dyserythropoiesis was also noted. Unfortunately, the patient's clinical status deteriorated rapidly resulting

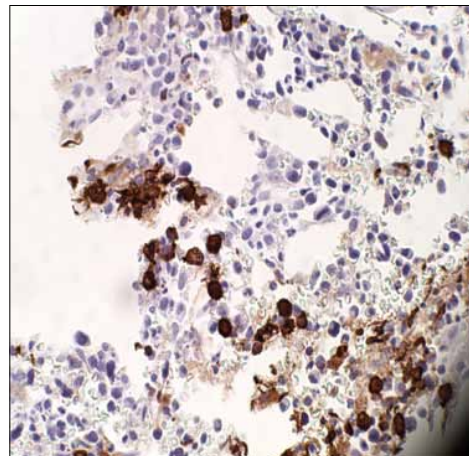


Figure 1. Mastocytosis involvement of the bone marrow as seen by tryptase staining.

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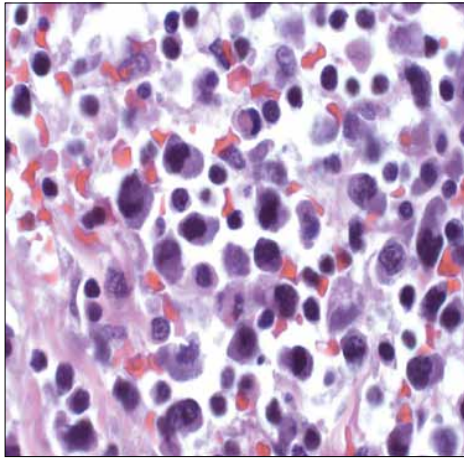


Figure 2. Hepatosplenic T-cell lymphoma involvement of the hepatic sinusoids.

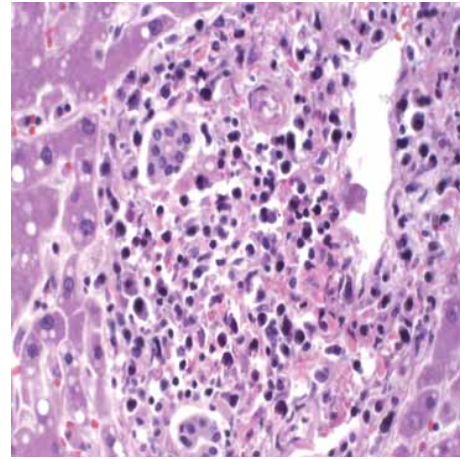


Figure 3. Hepatosplenic T-cell lymphoma involvement of the portal tract.

in multi-system organ failure requiring intubation and mechanical ventilation, and after discussion with the family, he was terminally extubated. Autopsy examination of the liver showed extensive involvement by lymphoma. The hepatic sinusoids and portal tract were seen to be affected (Figures 2 and 3). The abnormal lymphocytes in the liver showed similar immunophenotypic (Figure 4 shows positive CD3 stain) characteristics as the bone marrow, and confirmed the diagnosis of HS $\gamma\delta$ TCL. The spleen had autolyzed by the time of autopsy and therefore was a poor specimen for examination.

Discussion

HS $\gamma\delta$ TCL is a rare form of peripheral T-cell lymphoma that was first described in 1990 and subsequently included as a provisional entity in the Revised European and American Lymphoma (REAL) classification.^{1,2} In the recently reported International T-cell and Natural Killer (NK)/T-cell lymphoma study, it constituted 1.4% of T-cell/NK cell lymphoma.³ The term *hepatosplenic T-cell lymphoma* is used in the current World Health Organization classification after patients were identified who had features of hepatosplenic T-cell lymphoma but demonstrated an alpha-beta phenotype.⁴ Human $\gamma\delta$ T lymphocytes are a normal subset of postthymic cytotoxic T-cells that preferentially locate to the epithelial layer of the intestines and the sinusoidal red pulp of the spleen.⁵ HS $\gamma\delta$ TCL is characterized by malignant T-cell proliferation in the sinusoids of the liver, sinuses, and red pulp of the spleen, and sinuses of the bone marrow.⁶ Median age at diagnosis in 3 separate reviews has been reported to be 29, 34, and 38 years, with a range of 5–68

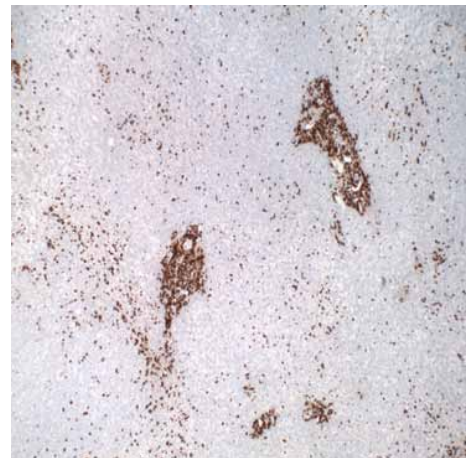


Figure 4. CD3-positive staining of lymphoma cells in the hepatic sinusoids and portal tracts.

years, and there is a clear male predominance.⁶⁻⁸ Clinical features of HS $\gamma\delta$ TCL include hepatosplenomegaly, cytopenias (especially thrombocytopenia), bone marrow involvement in the majority of patients, and a marked absence of lymphadenopathy. There seems to be a predilection in patients on immunosuppressive therapy after solid organ transplants, rheumatologic diseases, or inflammatory bowel disease.^{7,8} Two patients had a history of falciparum malaria.⁷

On light microscopy, the abnormal cells are medium-sized lymphoid cells with round nuclei, moderately condensed chromatin, and moderately abundant but pale cytoplasm. Immunophenotyping reveals CD2+,

CD3+, CD4-, CD5-, CD7+/-, CD8-, CD16+, CD25-, CD56+/- cells.⁶ Cytotoxic granule protein TIA-1 is expressed, but perforin and granzyme B are absent, suggesting a nonactivated T-cell phenotype. There is rearrangement of T-cell receptor gamma and delta genes, and isochromosome 7q is the most frequent abnormality on cytogenetic evaluation.^{7,9}

Prognosis is quite dismal with median survival reported as 16 months, 11 months, and 9.5 months in the 3 studies previously mentioned.⁶⁻⁸ In the International T-cell Lymphoma project study, 5-year failure-free survival and overall survival were 0% and 7%, respectively.³ The majority of patients in the above studies have been treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based treatments, and although responses are seen in the majority of patients, they are usually short lived. In a study of 21 patients with HS γ δ TCL, 2 of the 21 patients who were treated with platinum/cytarabine-based induction regimens remain in complete remission at 42 and 52 months.⁷ In another study describing the M.D. Anderson experience of 15 patients with HS γ δ TCL, a wide array of induction treatments were used, including 4 patients treated with fractionated cyclophosphamide, liposomal doxorubicin, vincristine, and dexamethasone (HyperCVIDDoxil) alternating with methotrexate and cytarabine.⁸ Complete response was 50%, and median duration of complete response was 8 months. Once again, responses tended to be longer in patients receiving the dose-intense HyperCVIDDoxil regimen. Interestingly, more women had complete response, and median survival was 25 months in women compared to 8 months in men.⁸ It is clearly evident that CHOP-like treatments are inadequate, and, from the above case series, it appears that dose-intense regimens have better outcomes. Significant knowledge needs to be gained in this entity, and when possible, patients should be enrolled in clinical trials. The presence of systemic mastocytosis (SM) may have predisposed the patient to HS γ δ TCL, but there is no way of knowing that definitively. In fact, the classification of SM includes a subclass called systemic mastocytosis with associated hematologic non-mast cell

lineage disorder, in which the associated disorder could be myeloproliferative, myelodysplastic, or lymphoproliferative, and treatment in this situation is directed towards the associated disorder.

Our case represents a unique presentation of HS γ δ TCL. To our knowledge, this is not only the first case of HS γ δ TCL presenting as DIC but it is also the first case presenting with coexistent SM. As this disease process is both novel and rare, it is important to characterize it in order to better augment our understanding of the disease and its manifestations and aid in finding a more effective treatment. We hope this unique case can add to the current understanding of HS γ δ TCL.

Acknowledgment: *We thank Dr. Silvia Verde de Peralta for her assistance with this manuscript.*

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Review

Hepatosplenic Gamma-Delta T-cell Lymphoma, Disseminated Intravascular Coagulation, and Systemic Mastocytosis: An Unusual Presentation for a Rare Disease

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Jahangiri and Mahesh¹ reported an uncommon case of hepatosplenic gamma-delta T-cell lymphoma (HS $\gamma\delta$ TCL) presenting with disseminated intravascular coagulation (DIC) in a patient with a history of systemic mastocytosis. In this report, a 75-year-old man sought medical attention due to continuous bleeding in the forearm after a cat scratch wound, and further evaluation demonstrated evidence of DIC. Peripheral smear revealed suspicious lymphocytes, and bone marrow examination showed infiltration by abnormal $\gamma\delta$ T-cells, as well as CD117-positive mast cells.

Many aspects of this case are rather peculiar. HS $\gamma\delta$ TCL is a rare peripheral T-cell lymphoma, with fewer than 200 cases described in the literature since the entity was first described in 1981. This disease typically affects young men in their second or third decade of life.² A strong association with long-term administration of immunosuppressive therapy for various medical conditions, including organ transplantation and other conditions that require immune-modifying agents, has been observed.^{3,4} Although the patient described in this report had previously received corticosteroids, there was no history of immunosuppressive treatment.

Patients with HS $\gamma\delta$ TCL typically present with constitutional symptoms, hepatosplenomegaly, and pancytopenia. Splenomegaly is observed in virtually all patients, whereas peripheral lymphadenopathy is unusual.⁵ In 2 large series, Belhadji⁶ and Falchook⁷ reported lymphadenopathy in 0% and 13% of patients, respectively. Splenomegaly was observed in all patients and hepatomegaly

in 71% and 40% of cases, respectively. The patient in this case, however, presented with no clinical evidence of hepatosplenomegaly and with mesenteric lymphadenopathy.

The presence of abnormal $\gamma\delta$ T-cells in peripheral blood is observed in up to 50% of patients with HS $\gamma\delta$ TCL and highlights the importance of peripheral blood examination in patients with systemic symptoms and hepatosplenomegaly.^{7,8} Cells are usually CD2+, CD3+, and CD7+, and CD4 and CD8 are usually negative. Aberrant phenotype such as the loss of expression of CD3, CD5, and/or CD7 is not uncommon. T-cell receptor rearrangement by molecular studies usually shows $\gamma\delta$ T-cell receptor phenotype, although few cases of $\alpha\beta$ HSTCL have been described.⁹ Bone marrow infiltration is usually moderate, and the neoplastic infiltrate is usually represented by monomorphic intrasinusoidal lymphocytes, with features that vary from mature to blast-like cells. In cases with low tumor burden, diagnosis may be challenging, and immunohistochemistry may facilitate the diagnosis.¹⁰ With disease progression, bone marrow involvement tends to become interstitial with prominent large blastic cells. Hemophagocytosis is not uncommon, and some patients can present with hemophagocytic syndrome.¹¹ In the spleen, the red pulp may show neoplastic cells infiltrating both cords and sinuses, and atrophy of the white pulp is common. In the liver, neoplastic cells preferentially infiltrate the hepatic sinusoids, and portal triads are usually spared.¹² Pseudopeliotic lesions and perisinusoidal fibrosis without hepatocyte involvement have been described.¹³

The cytogenetic findings in HS $\gamma\delta$ TCL usually involve alterations of chromosome 7; i(7q) is the primary cytogenetic abnormality, and can be found in the majority of patients.¹⁴ Formation of a ring chromosome leading to 7q amplification is reported, as well as secondary cytogenetic alterations, commonly observed with disease progression.¹⁵ Albeit suggestive, i(7q) should not be used as a diagnostic marker, since some authors suggest a lower incidence of this finding.

Although cytopenias are common in HS $\gamma\delta$ TCL, possibly due to hypersplenism, and may explain the patient's thrombocytopenia, DIC has never been described in HS $\gamma\delta$ TCL. These findings may suggest extensive liver impairment, compatible with the dramatic evolution of the case. However, a proinflammatory cytokine-mediated systemic reaction cannot be excluded.

Prognosis of HS $\gamma\delta$ TCL is dismal,¹⁶ with most patients dying within a year of diagnosis. Available data are based mostly on case reports and, to date, only 3 large series have been published, which have attempted to clarify clinicopathologic features and treatment strategies.⁶⁻⁸ Although many questions remain unanswered, it is now clear that conventional treatment with cyclophosphamide

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mide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens is ineffective, and few patients will remain disease free with this strategy. Multi-agent-intensive regimens appear to lead to better outcomes, although the results have not been confirmed in large trials due to the rarity of the disease. The role of stem cell transplantation in the management of HS $\gamma\delta$ TCL is still unclear, as are the type of stem cell transplant (autologous versus allogenic) and conditioning regimens.

Lastly, the patient had a history of systemic mastocytosis (SM). SM can be associated with lymphoproliferative diseases, and is then classified as SM with associated hematologic nonmast cell lineage disorder. However, the majority of cases occur concomitantly with B-cell lymphoproliferative diseases,¹⁷ particularly chronic lymphocytic leukemia or acute lymphoblastic leukemia. The coexistence of SM in this patient makes this case report even more unique.

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