Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2013 October ; 13(5): 610–613. doi:10.1016/j.clml.2013.04.010.

CD4⁻/CD8⁻ Variant of T-Cell Large Granular Lymphocytic Leukemia or Hepatosplenic T-Cell Lymphoma: A Clinicopathologic Dilemma

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Keywords

CD4⁻/CD8⁻ variant; HSTCL; T-LGL leukemia

Introduction

Large granular lymphocytic (LGL) leukemia is an uncommon type of lymphocytic leukemia derived from either T cells or natural killer cells. The classic presentation of T-LGL leukemia is with mild lymphocytosis of LGL cells, cytopenia with recurrent infections, and splenomegaly. Rheumatoid arthritis and other autoimmune diseases, including autoimmune hemolytic anemia (AIHA) and pure red cell aplasia, are often associated with T-LGL leukemia.^{1,2} According to the World Health Organization, T-LGL leukemia is classified as a neoplasm of mature T cells. Hepatosplenic T-cell lymphoma (HSTCL) represents a clinically aggressive lymphoma that usually has clinical and pathologic features that are different from T-LGL leukemia. A CD4⁻/CD8⁻ variant form of T-LGL can be easily

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Disclosure

The authors have stated that they have no conflicts of interest.

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confused with HSTCL. Careful assessment of the clinicopathologic features can distinguish these 2 entities, particularly at early stages.

Case Report

A 49-year-old man presented to our clinic in November 2010 with pancytopenia, splenomegaly, and hemolytic anemia. He had a history of seminoma diagnosed and treated with orchiectomy and localized radiotherapy in 2008. The patient presented with weight loss, a palpable spleen (5 cm), and no lymphadenopathy. His complete blood count demonstrated pancytopenia, with a white blood cell (WBC) count of 1 K/ μ L, absolute neutrophil count (ANC) of 0.36 K/ μ L, red blood cell count of 3.42 M/ μ L, hemoglobin (Hb) level of 11.1 g/dL, and platelet count of 96 K/ μ L. In addition, his reticulocyte count was 2.7%, his lactate dehydrogenase (LDH) level was 723 IU/L (normal range, 313–618 IU/L), and his haptoglobin level was < 8 mg/dL (normal range, 30–200 mg/dL). He had possible hemolytic anemia. A direct Coombs test was negative for anti-IgG and anti-C3 antibodies. A bone marrow (BM) biopsy revealed hypercellular (50%–70%) marrow with minimal dysplasia in megakaryocytes and erythrocyte lineages. Cytogenetic analysis revealed a normal diploid male karyotype. Fluorescence in situ hybridization (FISH) was negative for conventional myelodysplastic syndrome–related changes. Flow cytometry was negative for paroxysmal nocturnal hemoglobinuria. Erythrocyte sedimentation rate, human immunodeficiency virus, antinuclear factor, and rheumatoid factor test results were negative. The patient underwent treatment of possible AIHA with 1 mg/kg oral prednisone and exhibited a transient response. He then received 4 weekly doses of rituximab and methylprednisolone, with a partial response. In October 2011, the patient underwent splenectomy as a diagnostic and therapeutic procedure owing to refractory pancytopenia. Histopathologic examination of his spleen showed diffuse parenchymal lymphocytic infiltration with effacement of the red pulp and few residual white pulp nodules (Figure 1A). The lymphocytes were small, with dense nuclear chromatin, irregularly shaped nuclei, and scant cytoplasm. Also, the lymphocytes were positive for CD3, CD7, granzyme B, and TIA-1 (Figure 1B–D) but negative for CD4, CD8, CD5, CD20, CD57, CD79a, CD68, and PAX-5. A subset of the neoplastic cells had weak CD56 expression. In situ hybridization was negative for Epstein-Barr virus. Polymerase chain reaction analysis of DNA extracted from the patient's spleen detected monoclonal T-cell receptor (TCR) γ -chain rearrangement (Figure 1E). We made the provisional diagnosis of CD4⁺/CD8⁺ T-cell LGL leukemia confined to the spleen (no peripheral blood or BM involvement). After splenectomy, the patient's laboratory values returned to normal. Within 6 months after splenectomy, the patient experienced gradually increasing fatigue and intermittent fever. His physical examination was remarkable for hepatomegaly, with liver palpable 12 cm below the right costal margin. At that time, his WBC count was 6 K/ μ L, ANC was 1.26 K/ μ L, Hb was 7 g/dL, reticulocyte count was 0.5%, and platelet count was 69 K/ μ L. In addition, he had an elevated serum bilirubin level of 1.9 mg/dL, alkaline phosphatase level of 160 IU/L (normal range, 38–126 IU/L), and alanine transaminase/aspartate transaminase levels of 113/59 IU/L. A computed tomographic scan showed an enlarged liver, specifically 24 cm in craniocaudal dimension. He received rituximab 1000 mg for 1 day, 250 mg of oral cyclophosphamide, and 20 mg of dexamethasone daily for 4 days (RCD regimen) for

suspicion of autoimmune hemolysis but had no response. His disease progressed with a high WBC count, monocytosis, and further elevation of liver enzyme and LDH levels. A complete blood count showed a WBC count of 13.1 K/ μ L, ANC of 9.62 K/ μ L, monocyte count of 2.2 K/ μ L, Hb level of 8.7 g/dL, and platelet count of 94 K/ μ L. In addition, he had a serum bilirubin level of 3.1 mg/dL (direct and indirect: 1.9 mg/dL and 1.1 mg/dL, respectively), alkaline phosphatase level of 311 IU/L, alanine transaminase level of 466 IU/L, and elevated serum LDH level of 1149 IU/L. Surprisingly, a BM biopsy sample revealed dense lymphoid infiltration in an interstitial pattern (Figure 1G). Immunohistochemical analysis was positive for CD3, TIA-1, and granzyme B in some cells but was negative for CD4 and CD8 (Figure 1H–J). Flow cytometry immunophenotypic studies performed using BM aspirate detected that the neoplastic cells were positive for CD2, CD3, CD5, CD25, CD56, CD94, CD158a, and CD158e and negative for CD4, CD8, CD7, CD16, CD52, CD26, CD57, and CD158b. DNA extracted from the patient's BM exhibited a monoclonal TCR γ -chain rearrangement with a polymerase chain reaction product that had the same size (250 base pairs) as that seen in splenic tissue (Figure 1F). FISH analysis of the patient's BM was negative for the iso7q abnormality, whereas FISH analysis of a spleen biopsy specimen for iso7q was noncontributory because of technical issues. The patient then underwent intensive chemotherapy with high-dose methotrexate and high-dose cytarabine and then hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) alternating with high-dose methotrexate and cytarabine. He had a complete remission after completing 3 cycles of hyper-CVAD. The patient underwent allogeneic stem cell transplantation from a matched unrelated donor. Three months after stem cell transplantation, the patient had complete donor chimerism and no monoclonal TCR gene rearrangement in the BM.

Discussion

The patient initially presented with pancytopenia and hemolytic anemia. These features are not unusual for T-LGL leukemia, but an immunophenotype of double-negative T cells (CD4[−] and CD8[−]) and isolated splenic involvement was unusual for classic T-LGL leukemia and favored the diagnosis of a variant form of T-LGL leukemia, which was described earlier. The CD4[−]/CD8[−] T-cell LGL leukemia is a rare type of T-cell LGL leukemia, with about 30 cases reported in the literature.³ Chen et al reported on a series of 7 such cases in 2011.⁴ They described a rare CD4[−]/CD8[−] T-cell LGL leukemia that preferentially affects older people, and patients usually present with anemia, pancytopenia, and splenomegaly but not lymphadenopathy. This variant is frequently associated with autoimmune disorders, including rheumatoid arthritis, AIHA, and pure red cell aplasia. A lack of lymphocytosis and increased LGL cells in the peripheral blood and BM leads to delayed diagnosis. Patients with CD4[−]/CD8[−] T-cell LGL leukemia need therapy earlier than do patients with classic LGL leukemia. Diagnosis of this variant is based on clinical presentation and the specific immunophenotype of lymphocytes. However, 6 months after splenectomy, our patient experienced progressive fatigue, hepatomegaly, anemia, and hyperbilirubinemia. BM biopsy results at this time showed an interstitial pattern of lymphocytic infiltration suggestive of a T-cell lymphoproliferative disorder, raising suspicion of HSTCL. HSTCL is a rare and aggressive T-cell non-Hodgkin lymphoma. It

accounts for less than 1% of all non-Hodgkin lymphoma cases. Also, it usually affects young male patients, who usually present with systemic symptoms, marked hepatosplenomegaly, and absence of lymphadenopathy. Thrombocytopenia is common and is mainly related to hypersplenism. Also, LDH levels are markedly elevated.⁵ Our patient's initial clinical presentation was compatible with the CD4⁺/CD8⁻ variant of T-cell LGL leukemia, and most of his symptoms were attributed to splenomegaly and possible AIHA. Furthermore, chromosome 7 abnormalities are described in about 70% of cases of HSTCL⁶ but not in the CD4⁺/CD8⁻ T-cell LGL leukemia variant. FISH analysis of our patient's BM was negative for iso7q, but that of a spleen biopsy specimen was non-contributory. Of note, the monoclonal TCR λ peak in both the spleen and BM biopsy specimens were of the same size, strongly suggesting that they were of the same clone.

This case was very challenging regarding diagnosis and therapy for the T-cell lymphoproliferative disorder for both pathologists and clinicians. In this case, we made a working diagnosis of aggressive T-cell lymphoma with a close differential favoring CD4⁺/CD8⁻ T-cell LGL leukemia variant over HSTCL (Table 1). Our patient had certain characteristics favoring the diagnosis of the T-cell LGL leukemia variant over HSTCL. These features were clinical presentation with splenomegaly, hemolytic anemia, absence of the iso7q abnormality in BM, interstitial pattern (not intrasinusoidal) of lymphocytic infiltration in BM, and an immunophenotype with granzyme B positivity in the spleen and BM. The CD4⁺/CD8⁻ T-cell LGL leukemia variant can be indistinguishable from HSTCL in terms of immunophenotype.⁷ In comparison, features that mimicked HSTCL were hepatosplenomegaly, elevated LDH level, an aggressive clinical course, and the presence of CD56⁺ cells. The clinicopathologic profile of this patient favored the diagnosis of CD4⁺/CD8⁻ T-cell LGL leukemia variant.

Conclusion

CD4⁺/CD8⁻ variant T-cell LGL leukemia mimics HSTCL based on the morphologic and immunophenotypic features. Their disease course is different. The therapeutic approaches for both conditions are not standardized.⁸ Therefore, careful assessment of the clinical course, morphologic, immunophenotypic, and molecular features of T-lymphoproliferative disorders is essential in clinical practice.

Acknowledgments

We sincerely thank Don Norwood for editing the manuscript.

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Clinical Practice Points

- Patients with recurrent infections, hepatosplenomegaly, and pancytopenia can have a broad differential diagnosis, including viral infections, auto-immune disease, or lymphoid neoplasms. Immunophenotyping and molecular approaches for T-cell receptor (TCR) gene rearrangements are of great help in deciphering these differential diagnoses.
- T-cell large granular lymphocytic (T-LGL) leukemia is an indolent disease of monoclonal cytotoxic T lymphocytes. It is commonly associated with autoimmune diseases, recurrent infections, and low white blood cell counts. Rarely does T-LGL leukemia pursue an aggressive course. T-LGL leukemia can mimic other T-cell lymphoid malignancies.
- The CD4⁺/CD8⁺ variant of T-LGL is a rare subtype of T-LGL leukemia arising from cytotoxic T cells that has overlapping clinical and immunophenotypic features simulating hepatosplenic T-cell lymphoma (HSTCL). In both these entities, there is generally no peripheral blood lymphocytosis or presence of LGL cells in blood.
- Our case report describes the clinicopathologic evaluation of these 2 T-cell lymphoproliferative disorders. Distinguishing the CD4⁺/CD8⁺ $\gamma\delta$ variant of T-LGL leukemia from HSTCL is challenging and requires careful clinical and pathologic assessment.

Figure 1.

(A) Diffuse Infiltration of the Spleen Parenchyma by Lymphocytes With Effacement of the Red Pulp and Few Residual White Pulp Nodules. The Lymphocytes Were Small, With Dense Nuclear Chromatin, Irregularly Shaped Nuclei, and Scant Cytoplasm (Hematoxylin and Eosin Stain; Magnification, $\times 400$). (B–D) The Lymphocytes in Spleen Tissue Were Positive for CD3, Granzyme B, and TIA-1 (T-cell Intracytoplasmic Antigen) (Magnification, $\times 400$). (E) Polymerase Chain Reaction Analysis of DNA Extracted From the Spleen was Positive for Monoclonal T-Cell Receptor (TCR) γ . (F) DNA Extracted from the Patient's Bone Marrow (BM) Exhibited a Monoclonal TCR γ -Chain Rearrangement With a Size of 250 Base Pairs Similar to That Seen in Splenic Tissue. (G) BM Biopsy

Specimen Revealed Dense Lymphoid Infiltration in an Interstitial Pattern (Hematoxylin and Eosin Stain; Magnification, ×400). (H–J) Immunohistochemical Analysis was Positive for CD3, Granzyme B, and TIA-1 (Magnification, ×400).

Table 1

Features of CD4⁺/CD8⁻ $\gamma\delta$ T-Cell Large Granular Lymphocytic Variant and $\gamma\delta$ Hepatosplenic T-Cell Lymphoma

Characteristic	CD4 ⁺ /CD8 ⁻ $\gamma\delta$ T-LGL Variant	$\gamma\delta$ HSTCL
Clinical features		
Incidence	More than rare	Uncommon
Age	Elderly	Young adult male
B symptoms	Uncommon	Common
Hepatosplenomegaly	Moderate	Marked
Lymphadenopathy	Rare	Rare
Neutropenia/anemia	Common, often severe	Variable
Thrombocytopenia	Uncommon, often mild	Common, often marked
Autoimmune association	Common	Uncommon
Elevated LDH	Uncommon	Common
Clinical course	Indolent	Chemoresistant and aggressive
Morphologic features		
Neoplastic cells	Mature-looking large granular lymphocytes	Immature-looking medium-sized cells, variable morphologic features
Bone marrow	Mostly interstitial infiltration	Predominantly intrasinusoidal infiltration
Spleen	Predominantly cordal infiltration in spleen	Predominantly intrasinusoidal infiltration
Immunophenotype		
Markers	CD3 ⁺ /CD4 ⁺ /CD8 ⁻ /CD7 ⁺ /CD5 ⁻ , CD56 ⁻	CD3 ⁺ /CD4 ⁺ /CD8 ⁻ /CD7 ⁺ /CD5 ⁻ , CD56 ⁺
T-cell receptor	$\gamma\delta$	$\gamma\delta$
TIA-1/granzyme- B/perforin	+/-/-	+/-/- (inactive cytotoxic profile)
Isochromosome 7q	Negative	Majority + (70%)

Abbreviations: HSTCL = hepatosplenic T-cell lymphoma; LDH = lactate dehydrogenase; T-LGL = T-cell large granular lymphocytic.