Letter to the Editor

Hepatosplenic alpha/beta T-cell lymphoma presenting with cold agglutinin disease

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1 Table

Dear editor, We read an article in your journal reported by Sallah et al [1] that showed autoimmune hemolytic anemia associated with hepatosplenic γδ T-cell lymphoma with a great interest. Here, we report a case of a patient who had cold agglutinin disease (CAD) as the initial manifestation of hepatosplenic αβ T-cell lymphoma and had a regression of hemolytic anemia following the chemotherapy and allogeneic stem cell transplantation.

In January 2005, a 58-year-old Japanese woman was admitted to Hokkaido University Hospital with increasing general fatigue. She had a 6-month history of chronic hemolytic anemia and had been seen by a local physician without any medication. Upon examination, she was very pale and jaundiced, with a tachycardia and pitting ankle edema. Splenomegaly and hepatomegaly were evident. A laboratory work-up showed a hemoglobin level of 6.3 g/dL, a hematocrit of 16.7%, and a reticulocyte count of 50.9 $x10^9$/L. The white blood cell count was 2.5 $x10^9$/L with 9% of atypical lymphocytes with both round and irregular nuclei, clumped chromatin, and a rim of pale blue cytoplasm. The platelet count was 116 $x10^9$/L. Hemolysis was suspected with an elevated indirect bilirubin concentration (2.2 mg/dL; normal 0-0.3 mg/dL), an elevated lactate dehydrogenase level (318 IU/L; normal 119-229 IU/L) and a decreased level of haptoglobin (2 mg/dL; normal 90-170 mg/dL). The direct antiglobulin test was positive for complement, but negative for IgG. Polyclonal cold agglutinin showing anti-I specificity was strongly positive with a titer of 1:2048 (normal < 1:32). Donath-Landsteiner autoantibody was not detected. Serum protein electrophoresis showed no abnormal monoclonal component. Serologic tests for human T-lymphotropic virus type-I and human immunodeficiency virus were negative. The serum Interleukin-4 (IL-4) level has increased to 14.2 pg/ml (normal <6.0 pg/ml).

Computed tomography confirmed an enlargement of liver and spleen without lymphadenopathy.

A biopsy specimen of iliac bone marrow disclosed severe hypercellular marrow containing an infiltration by atypical small sized lymphoid cells with hypechromatic nuclei identical to those seen in the peripheral blood. Immunohistochemical staining on the section of bone marrow showed positive findings for CD3, CD5, CD8 and negative findings for CD10, CD23, terminal deoxynucleotidyl transferase (TdT), T-cell intracellular antigen-1 (TIA-1), CD56 and Epstein-Barr viral-encoded RNA-1 (EBER) in atypical lymphocytes. We performed a splenectomy and liver biopsy to confirm the diagnosis of hepatosplenic T-cell lymphoma (HSTCL). Liver histology revealed the sinusoidal infiltration of small atypical lymphocytes. A complete sparing of the liver parenchyma was observed. The spleen was massively enlarged and free from nodules on the cut surfaces. The general architecture was well preserved with marked hyperplasia of the white pulp. Likewise, splenic red pulp was infiltrated with similar lymphocytes. Flow cytometry of these spleen atypical cells revealed positive findings for CD3, CD5, and CD8 and negative for CD4, CD10 and CD56. These malignant cells were positive for αβ T-cell receptors (TCRs) and negative for γδ TCRs. Clonal rearrangement of TCRs beta-chain was evident in the Southern blot analysis. The results of our investigations were consistent with a diagnosis of CAD secondary to hepatosplenic αβ T-cell lymphoma.

She was treated with CHOP chemotherapy [2]. After 3 cycles, her hemoglobin level became sustained without transfusion, and the haptoglobin level reverted to a normal range. After 6 cycles of CHOP, a bone marrow biopsy revealed no residual lymphoma cells and a Southernblot analysis showed a germline of the

TCRs. Her serum IL-4 levels had decreased to 9.9 pg/ml. A complete remission (CR) was thus achieved. The cold agglutinin titer decreased to 1:256 thus suggesting an association between lymphoma and CAD. As HSTCL has a poor outcome, she underwent allogeneic peripheral blood stem cell transplantation with the use of a non-myeloablative conditioning regimen (25 mg/m^2 fludarabine monophosphate on days -6 to -2, 70 mg/m^2 melphalan on days -3 and -2) in July 2005 [3]. As the time this report is written, she has been in CR for 14 months.

In HSTCL, anemia has been described in many patients and it seems to be one of the prominent features of this rare type lymphoma. Splenomegaly, infiltration of the bone marrow by the malignant lymphocytes, and the release of various cytokines by the neoplastic cells have all been implicated as possible mechanisms for the cytpoenia in these patients [4]. In addition, hemolysis appears to be another possible mechanism seen in HSTCL. Among the different types of hemolytic anemia, the occurrence of autoimmune hemolytic anemia (AIH) secondary to non-Hodgkin lymphoma is well known [5].

To our knowledge, however, there have been only three cases of AIH secondary to HSTCL reported (Table 1) [1,6,7]. HSTCL is supposed to have a very aggressive clinical course [8]. However, three out of four cases with AIH, including ours, seemed to have some stable period in which only hemolytic anemia, thrombocytopenia or hepatosplenomegaly were evident without fever or general deterioration, which are all signs for the progression of lymphoma. In this stable period, those patients were treated with intravenous immunoglobulin administration or steroids, or they were just observed without being diagnosed as HSTCL (Table 1). Considering the poor outcome of HSTCL, we recommend that a proper diagnosis of

secondary AIH should be made in such patients so that the underlying HSTCL can be properly treated.

The pathogenesis of this AIH is mainly unknown. Although Motta et al proposed that γδ T cells are attractive candidates as mediators of autoimmune disease in several conditions for both humans and laboratory animals [6], Lai et al already has reported AIH in HSTCL of the αβ lineage [7]. This finding suggests that mechanisms other than pathological γδ T cells of HSTCL in AIH should also be considered. Our case reinforced this concept. It is possible that the antibody production is the result of an aberrant immune interaction between the neoplastic T lymphocytes and the B-cell population. The Th-2 type cytokines IL-4 are produced from helper T cells, which usually express αβTCRs and stimulate B cells thus causing an expansion of B cells and the production of immunoglobulin. In our case, the levels of IL-4 decreased with the improvement of the hemolysis. IL-4 might therefore play some role in the productions of cold agglutinin in our case. However, more studies are needed to conclude a definite pattern of the serum IL-4 levels in patients who develop CAD with HSTCL αβ subtype.

In summary, we herein presented a case of HSTCL of αβ lineage complicated with CAD. We recommend to consider hemolysis as a cause of anemia in this type of lymphoma, or to consider lymphoma whenever one sees a patient with CAD.

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Table 1 Reported cases of HSTCL with autoimmune hemolytic anemia

	Age	Sex	Subtype	D.Coombs	I.Coombs	CA	Initial diagnosis	B symptoms	Initial treatment	References
1	42	M	γδ	+	-	+	HSTCL	-	CHOP	Sallah et al[1]
2	61	M	γδ	+	+	NA	HSTCL	+	Steroids/CPA	Motta et al[6]
3	16	M	αβ	+	NA	NA	Evan's syndrome	-	IVIG, steroids	Lai et al[7]
4	56	F	αβ	+	-	+	CAD	-	Observation	Present case

M: Male, F: Female, D.Coombs: direct Coombs, I.Coombs: indirect Coombs, NA: Not available
CA:Cold agglutinin, HSTCL: hepatosplenic T-cell lymphoma, CAD: Cold agglutinin disease
CHOP: cyclophosphamide, adriamycin, vincristine, predonine, CPA: cyclophosphamide
IVIG: intravenous immunoglobulin