Hairy cell leukemia with an associated lupus-type anticoagulant

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Hairy cell leukemia is a rare, lymphoproliferative disorder usually of B-cell origin. It affects men more often than women by a ratio of 4:1, with approximately 600 cases per year in the United States. Leukemias in general are known to be associated with coagulopathies; however, the case reported here represents only the fourth reported case of hairy cell leukemia with an associated lupus anticoagulant. The lupus anticoagulant is unusual in that it is not truly a coagulation-preventing entity, but rather may result in a hypercoagulable state. The nomenclature for this manifestation derives from its ability to interfere with *in vitro* phospholipid-dependent tests of coagulation. This report includes a review and discussion of the case presented, as well as a review of both hairy cell leukemia and the lupus anticoagulant.

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Hairy cell leukemia (HCL), formerly known as leukemic reticuloendotheliosis, is an uncommon malignant lymphoproliferative cancer first confirmed as a distinctive clinicopathologic manifestation by Bouroncle and associates¹ in 1958. They reported 26 cases in which the origin of the malignant cells was thought to be of the monocyte-macrophage system. And, in 1966, Schrek and Donnelly² first introduced the name "hairy cell leukemia."

Hairy cell leukemia is rare, with only approximately 600 cases diagnosed in the United States each year. The disease affects men predominantly, with a male-to-female ratio of 4:1. The average age at diagnosis is 50 years.³

The neoplastic cells of HCL are almost always of B-cell lineage, although rare cases of HCL of T-cell origin have been reported.^{4,5} The characteristic phenotype is identified through the use of flow cytometry, which reveals a uniform and consistent B-cell phenotype.

Peripheral blood smears may show the classic cell type of this cancer, but a bone marrow biopsy is the most reliable method of disease confirmation. This method may, however, prove difficult because of an increase in marrow reticulin fibers.

The laboratory method most commonly used for verification of this disease is immunophenotypic analysis. Hairy cells may express the pan B-cell antigens CD19, CD20, and CD22 and the interleukin 2 (IL-2) receptor CD25. Additionally, CD-11c, a marker present on some activated B cells, phagocytes, and cytolytic T cells, may also be associated.⁶ Cytogenetic analysis of the malignant cells shows numerous clonal chromosomal abnormalities. These abnormalities most commonly involve,

in descending order of frequency, chromosomes 14, 12, 7, and 22.

In addition, hairy cells often show a varying degree of positive cytoplasmic uptake of tartrate-resistant acid phosphatase (TRAP) stain. Indeed, TRAP staining was once the method of choice for verification of the disease. However, TRAP staining may also be positive in other lymphoproliferative disorders, thus making it an unreliable test for differential diagnosis, especially in conjunction with cytogenetic markers.⁸

Although IL-2 receptors are present on hairy cells, these cells do not respond to IL-2 stimulation. Further, the presence of the IL-2 receptor is not unique to T cells. Normal human B cells and marginal zone B cells in the spleen may also express IL-2 receptors.⁷

Some common presenting signs and symptoms of HCL are:

- ☐ palpable splenomegaly, which is by far the most consistent physical finding;
- ☐ pancytopenia;
- ☐ ecchymosis;
- ☐ petechiae;
- ☐ night sweats, and
- ☐ autoimmune disorders.

Patients may also complain of abdominal fullness or discomfort, weakness, or fatigue.⁸

This disease generally follows a chronic course and, with current chemotherapy alternatives, it carries with it a relatively high rate of remission (76% to 85%, depending on the agent used) at 5 years.^{9,10} Complete remission rates vary, with investigators reporting rates as high as 90% in one study.¹¹

Splenectomy was once the preferred treatment modality for HCL.¹² This procedure has since been supplanted by numerous chemotherapeutic agents, the most promising of which is 2-chlorodeoxyadenosine (2CdA, cladribine).^{13,14} Other active agents include interferon-alfa and 2' deoxycoformycin (pentostatin).

We present the case of a patient who was admitted to our service for an unrelated medical problem, at which time this leukemia was diagnosed. During routine laboratory tests, the patient was

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found to have a coagulopathy that was eventually attributed to the lupus-type anticoagulant. This association has been reported only twice previously in the setting of HCL^{15,16} and once in a patient infected with the human immunodeficiency virus (HIV) who had HCL and multiple autoimmune manifestations.¹⁷

Further evidence of the presence of the lupus anticoagulant in patients with the acquired immunodeficiency syndrome (AIDS) has been reported by Cohen and colleagues.¹⁸ In their review of 50 patients with AIDS and coagulation defects, Cohen and colleagues¹⁸ detected this phenomenon in 10 of the patients tested. None of these patients, however, was diagnosed with HCL.

Report of case

A 78-year-old woman was seen at our facility with fractures of the third and fourth phalanges on the right hand after a work-related accident.

The patient's medical history included abdominal surgery 30 years previously for a problem that she could not recall and a mastectomy 8 years previously. She had surgery for a diverticulum 5 years earlier, a cholecystectomy 4.5 years before this admission, and the removal of a benign cyst on her back 2 years previously.

The patient denied the excessive use of aspirin, as well as other nonprescription anti-inflammatory agents. She had no history of vitamin use, and she did not participate in any fad diets. She had no history of extended bleeding times, bleeding gums, or blood in the stools. She denied a history of night sweats.

The patient noticed that her abdominal girth had increased some in the preceding weeks, with her clothes fitting tighter. However, she denied any noticeable weight gain or loss.

The patient's travel history was noncontributory to the presenting complaint.

The patient did not know if she had received blood or blood products during the surgical procedures in the past, and these records were unavailable. She did not have any pets living in the home,

she did not smoke or use alcohol, and she had no history of exposure to ionizing radiation or known environmental toxins.

Routine preoperative laboratory studies were done. The values for prothrombin time (PT) and activated partial thromboplastin time (aPTT) were markedly elevated (35.7 seconds and 53.1 seconds, respectively). These tests were repeated by using a 50:50 mix with normal plasma. The results of dilutional mixing studies were also prolonged. Pancytopenia was noted with a white blood cell count of 4300/mm³ and platelet count of 127/mm³.

Tests for occult blood in stools and an HIV-antibody screen were both negative.

The patient was well nourished, well hydrated, and alert and oriented to person, place, and time. She was in no apparent distress and was afebrile. With the exception of marked splenomegaly, with the spleen being palpable approximately 12 cm below the costal margin, the findings of the physical examination were unremarkable.

A computed tomography scan of the abdomen confirmed the splenomegaly (Figure 1).

Peripheral blood smears showed apparent hairy cells (Figure 2). These cells were later confirmed with a bone marrow biopsy (Figure 3). Bone marrow aspiration was successful despite the hypercellular nature of the specimen. Smears of the bone marrow of the cells with cytoplasmic projections stained positive for B-cell markers. Flow cytometry was also consistent with HCL with IgM and kappa surface markers and an increase in total B cells. Smears of the bone marrow and peripheral blood TRAP stain revealed a score of 7, which is consistent with HCL. Results obtained from the serum specimens, sent to an outside laboratory, indicated that the likely cause of the coagulation defect was the presence of a lupus-type anticoagulant (Table).

Cytogenetic studies showed a normal female chromosome complement, and the immunophenotypic profile revealed positive markers for CD20, CD19, and

HLA-DR. These immunophenotypic features are common in HCL.

Results of additional serum tests for anti-DNA antibodies, antinuclear antibodies, and total hemolytic complement (CH₅₀) were all negative, thus ruling out the possibility of an underlying condition such as systemic lupus erythematosus (SLE) or complement deficiencies.

Because of the patient's splenomegaly, anemia, and thrombocytopenia, surgery was postponed, and the patient was scheduled for inpatient chemotherapy with 2CdA.

The patient received a continuous, 7-day infusion of 2CdA, during which time leukopenia was noted. She did not, however, have any infectious sequelae and was discharged on the 7th day. Although she still had notable splenomegaly, she was otherwise in relatively good health. No additional major side effects of the chemotherapy were noted.

A second bone marrow specimen, which was obtained 9 weeks after the cessation of chemotherapy, revealed variable cellularity from 50% to 90%. This cellularity was increased from the previous bone marrow specimen, which was notably hypercellular with variability of only 30% to 70%. However, a few lymphocytes with cytoplasmic projections and an absolute erythroid hyperplasia were still present. However, this bone marrow specimen contained approximately 12% lymphocytes, down from the previous value of 19% when the leukemia was first diagnosed. Finally, the previous myeloid-to-erythroid ratio of 1.5:1 had reversed to a value of 1.03:1.

Discussion

Hairy cell leukemia is a rare lymphoproliferative disease of B-cell lineage. Hairy cell leukemia with an associated lupus-type anticoagulant coagulopathy has been reported only three times in the literature.¹⁵⁻¹⁷

Other autoimmune disorders have also been recognized in patients with HCL, including:

- ☐ polyarteritis nodosa,
- ☐ arthritis,

Figure 1. Computed tomography scan of abdomen. Note massive splenomegaly.

Figure 2. Peripheral blood smear shows lymphocyte with "hairy" cytoplasmic projections (original magnification $\times 400$; Wright's stain).

Figure 3. Bone marrow aspirate, which is notably hypercellular. Cells are distinctly lymphoid with scant to clear cytoplasm (original magnification $\times 100$; Wright's stain).

Table*
Coagulation Profile

Variable	Results	High/low	Units	Normal adult values
F II inactivator†	0	High	Bethesda	0.0 to 0.5
Prothrombin time	15.1	High	s	10.5 to 13.5
PT 1:1NP‡	15.1	High	s	10.5 to 13.5
PT 1:1 saline solution	18.9	High	s	
PT 1:1NP 60' inc§	15.6	High	s	
PT Control 1:1NP 60' inc	15.6	High	s	
aPTT	67.8	High	s	19.0 to 34.0
aPTT 1:1NP	83.6	High	s	19.0 to 34.0
aPTT 1:1 saline solution	66.4	High	s	
aPTT 1:1NP 60' inc	77.4	High	s	
aPTT control 1:1NP 60'	80.8	High	s	
F II activity	78		%	65.0 to 135.0
F V activit	110		%	65.0 to 150.0
F VIII activity	272	High	%	50.0 to 150.0
F VIII inactivator assay	0		Bethesda	0.0 to 0.5
F V inactivator assay	0		Bethesda	0.0 to 0.5
DRVVT (DIL RVV)¶	0.9		Ratio	0.5 to 1.1
Hexagonal phospholipid neutralization	62.5	High	s	0.0 to 10.0
Platelet neutralization test	0		s	0.0 to 7.0
IgG# anticardiolipin antibody	12		GPL# units	0.0 to 25.0
IgM** anticardiolipin antibody	8,900		MPL** units	0.0 to 12.0

* Colorado Coagulation Consultants, 820 Clermont St, Suite 200, Denver, Colo.

† F-factor (coagulation pathway factors).

‡ PT = prothrombin time, NP = normal plasma.

§ inc = incubation.

|| Activated partial thromboplastin time.

¶ Diluted Russell's viper venom test (Stypven).

Immunoglobulin G, GPL = G phospholipid units.

** Immunoglobulin M, MPL = M phospholipid units.

- ☐ arthralgias,
- ☐ palpable purpura, and
- ☐ skin lesions.⁶

When prolonged PT and aPTT values, such as those seen in our patient, are noted, the obvious initial concern is

that of uncontrollable bleeding should the patient have an event leading to blood loss, such as the trauma of surgery. However, with the lupus anticoagulant, it is hypercoagulable states that prevail. Herein lies the discrepan-

cy of the term "anticoagulant" as it applies to this unique entity.

Bowie and associates,¹⁹ in 1963, were the first to describe the occurrence

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Case reports continued

of circulating anticoagulant and thrombosis in a cohort of four patients with SLE. Others have since reported on this correlation.²⁰⁻²² This anticoagulant is an antiphospholipid antibody (either IgG or IgM, or both) that causes a prolongation of phospholipid-dependent coagulation tests. This anticoagulant occurs via binding of the antibody to epitopes on the phospholipid segment of prothrombinase.²³ Hence, it is now clear that the term "anticoagulant," as it applies to this biochemical anomaly, is an incongruous designation.

The lupus anticoagulant is present in only approximately 5% to 10% of patients with SLE,²³ but it may also be found in other clinical settings, such as drug reactions and other autoimmune, neurologic, gynecologic, and neoplastic diseases, as well as in healthy persons.²⁴

Comment

The lupus anticoagulant is an enigmatic anomaly that may occur in numerous clinical settings, the first of which reportedly was SLE. It has since been found in a wide variety of other immune-based sequelae. Our case represents the fourth such reported occurrence in the setting of HCL.

Although some residual hairy cells were observed in our patient's bone marrow specimen obtained 9 weeks after the completion of chemotherapy, further chemotherapy is not warranted at this time. At the time of publication, our patient remains asymptomatic and continues to be followed up closely.

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