CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 24-2012: A 38-Year-Old Man with Abdominal Pain and Altered Mental Status

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PRESENTATION OF CASE

Dr. Gabriel A. Brooks (Medical Oncology): A 38-year-old man was admitted to this hospital because of abdominal pain, altered mental status, hypercalcemia, and thrombocytopenia.

The patient had been well until 11 days before admission, when weakness developed. The next day, nausea, abdominal pain, and fatigue developed and he had multiple episodes of nonbilious, nonbloody emesis. Nine days before admission, he went to another hospital. He reported being in distress because of nausea; the vital signs were reportedly normal, the epigastrium was mildly tender, and the remainder of the examination was normal. Results of laboratory tests are shown in Table 1. The electrocardiogram reportedly showed sinus rhythm at 46 beats per minute and early repolarization. The patient was admitted to the other hospital, and normal saline and pamidronate were administered intravenously, with improvement in the symptoms and blood calcium level. Results of urinalysis were normal. Ultrasonography of the kidneys revealed normal size, a slight increase in the echotexture, and mild ascites. He was discharged on the fourth day, taking potassium phosphate tablets, with plans for additional outpatient evaluation.

That evening after dinner, dull and constant lower abdominal pain developed and prevented the patient from sleeping. The next morning, he returned to the other hospital because of the pain, which he rated at 8 on a scale of 0 to 10, with 10 indicating the most severe pain. He reported no fever, chills, nausea, vomiting, diarrhea, dizziness, chest pain, or dyspnea. On examination, the vital signs were normal. There was moderate cervical and inguinal lymphadenopathy (≤1.5 cm in diameter) and mild abdominal tenderness in the right lower quadrant, without rebound or guarding; the remainder of the examination was normal. Laboratory-test results are shown in Table 1. Computed tomography (CT) of the abdomen, with the administration of contrast material, reportedly showed diffuse heterogeneous attenuation in the liver, borderline splenomegaly (span, 14 cm), and a small amount of ascites, without masses or evidence of appendicitis. Intravenous fluids, potassium phosphate, pantoprazole, ibuprofen, tramadol, and morphine were administered.

On the second day, testing for hepatitis B surface antigen and antibodies to

hepatitis C virus was negative; Western blot testing for the human immunodeficiency virus was initially indeterminate; follow-up testing was negative. CT of the chest and neck, with the administration of contrast material, reportedly revealed changes consistent with a large right pulmonary embolism, as well as moderate bilateral pleural effusions and lymphadenopathy in the cervical, supraclavicular, hilar, and axillary regions. An electrocardiogram was unchanged. An echocardiogram was normal. Intravenous heparin and oral prednisone (80 mg daily) were administered. On the third day, the blood level of amylase was normal; other test results are shown in Table 1. Ultrasonography of the legs revealed thrombi in the right popliteal and posterior tibial veins. The abdominal pain diminished. Analysis of the peripheral blood by means of flow cytometry reportedly revealed 10% T lymphocytes, which had an abnormal immunophenotype. Test results from the fifth hospital day are shown in Table 1; other test results were pending. The patient was transferred to this hospital. Shortly before transfer, confusion, somnolence, and intermittent agitation developed.

The patient had had hemorrhoid surgery and a right ankle sprain in the past and was otherwise well and took no medications. The calcium level 3 years earlier was reportedly normal (9.3 mg per deciliter [2.3 mmol per liter]). He had no known allergies. He was born in Haiti and had moved to the United States 6 years earlier. He lived with his wife, was physically active, and had recently lost a job in transportation. He drank alcohol rarely, smoked cigarettes occasionally, and did not use illicit drugs. He visited Haiti frequently.

On examination, the patient appeared well; he was alert but oriented to person only. The temperature was 36.4°C, the blood pressure 135/89 mm Hg, the pulse 73 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 96% while he was breathing ambient air. Lymph nodes (1 cm in diameter) were palpable in the supraclavicular and cervical regions. The abdomen was soft and diffusely tender, with bowel sounds and without masses or distention. Neurologic examination revealed psychomotor slowing. The patient's behavior ranged from passive to aggressive; multiple requests in English or Creole were needed before he followed simple commands. Motor strength was 4 to 5 out of 5 throughout and symmetric. The remainder of the examination, within the limitations of decreased cooperation, was normal. The red-cell indexes were normal, as were levels of fibrinogen, glucose, direct bilirubin, and amylase. Tests of renal function were also normal; additional test results are shown in Table 1. An electrocardiogram was unchanged.

Intravenous hydration with normal saline and sodium bicarbonate was initiated, and allopurinol, rasburicase, and lactulose were administered. Ciprofloxacin, cefepime, and vancomycin were given, and platelets (irradiated and leukocyte-reduced) and fresh-frozen plasma were transfused. Testing for antibodies against platelet factor 4–heparin complexes was negative.

During the first 12 hours after admission, increasing somnolence alternating with episodes of agitation developed. CT of the head, without the administration of contrast material, revealed effacement of the cerebral sulci (a finding thought to represent cerebral swelling) and no evidence of hemorrhage or masses. CT of the neck, chest, abdomen, and pelvis, after the administration of oral and intravenous contrast material, revealed bilateral prominent cervical lymph nodes, a change consistent with emboli in the right pulmonary arterial system; atelectasis in the right middle and lower lobes and the lingula; mediastinal and axillary lymphadenopathy and bilateral small pleural effusions; enlargement and heterogeneous attenuation of the liver and spleen, with wedge-shaped hypodense lesions in the spleen; free fluid throughout the abdomen; and multiple enlarged nodes (≤1.3 cm in diameter) in the abdomen and both inguinal regions.

On the second day, a lumbar puncture was performed. Analysis of the cerebrospinal fluid (CSF) revealed colorless clear fluid, with no red cells and 1 white cell per cubic millimeter in tube 4 (50% lymphocytes and 50% monocytes); normal glucose and protein levels; and no organisms on Gram's staining.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Amir T. Fathi: May we review the imaging studies?

Dr. Brett W. Carter: Head CT scans obtained on the day of admission (Fig. 1) show effacement of the cerebral sulci (Fig. 1A) that suggests cerebral edema. A linear focus of hypoattenuation in the right inferior cerebellum (Fig. 1B) is consistent with an

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	Other Hospital‡					This Hospital
		On 1st Admission	On Discharge	On 2nd Admission	2nd and 3rd Hospital Days	5th Hospital Day (Day of Transfer)	On Admission
Hematocrit (%)	41.0–53.0 (men)	54.6	51.6	51.0	48.8	50.0	48.3
Hemoglobin (g/dl)	13.5–17.5 (men)	18.7	17.8	17.7	16.9	17.3	16.7
White-cell count (per mm^3)	4500–11,000	15,300	12,400	14,100	19,700	24,300	26,200
Differential count (%)							
Neutrophils	40–70	65.2		57	60.1		60
Band forms	0–10			2			8
Lymphocytes	22–44	22.6		22	25.8		20
Atypical lymphocytes	0			13			5
Monocytes	4–11	11.7		6	13.2		7
Eosinophils	0–8	0.1			0.1		0
Basophils	0–3	0.4			0.8		0
Platelet count (per mm^3)	150,000–400,000	130,000	58,000	52,000	25,000	21,000	25,000
Activated partial-thromboplastin time (sec)	21.0–33.0			61.9	73.0	64.3	27.5
Prothrombin time (sec)	11.0–13.7			14.4	15.3		19.0
International normalized ratio for prothrombin time				1.4	1.5		1.7
Sodium (mmol/liter)	135–145	141	142	139	140	141	137
Potassium (mmol/liter)	3.4–4.8	4.3	4.0	4.2	4.4	5.2	5.0
Chloride (mmol/liter)	100–108	97	106	105	104	104	100
Carbon dioxide (mmol/liter)	23.0–31.9	31	27	25	19	23	21.3
Urea nitrogen (mg/dl)	8–25	11	16		15	25	25
Creatinine (mg/dl)	0.6–1.5	1.3	2.1		1.1	1.1	0.9
Calcium (mg/dl)	8.5–10.5	17.7	11.5	11.0	10.9	11.7	12.5
Ionized calcium (mmol/liter)	1.14–1.30						1.38
Phosphorus (mg/dl)	2.6–4.5		2.0	1.9	2.0		2.0
Magnesium (mg/dl)	1.7–2.4		2.1 (ref 1.8–2.6)		2.3		2.7
Total bilirubin (mg/dl)	0.0–1.0			1.1	1.2		1.3

Protein (g/dl)						
Total	6.0–8.3		5.0	5.2		5.7
Albumin	3.3–5.0	4.2	2.7	2.6		3.1
Globulin	2.3–4.1					2.6
Lactate dehydrogenase (U/liter)	110–210	1150				4855
Alkaline phosphatase (U/liter)	45–115	124	148	155		182
Aspartate aminotransferase (U/liter)	10–40	73	97	166		182
Alanine aminotransferase (U/liter)	10–55	47	45	46		43
CA 19-9 (U/ml)	0–35		13			
Carcinoembryonic antigen (ng/ml)	0–3.0			0.8		
Lipase (U/liter)	13–60			31		73
Lactic acid (mmol/liter)	0.5–2.2			10.0		8.2
Uric acid (mg/dl)	3.6–8.5					10.7
Alpha-fetoprotein (ng/ml)	0–9				1.8	
Parathyroid hormone (pg/ml)	12–88	5				
Parathyroid hormone–related protein (pmol/ml)	0–1.5		1.7			
Angiotensin-converting enzyme (U/liter)	12–68	62				
25-Hydroxyvitamin D (ng/ml)	30–100		34			
B-type natriuretic peptide (pg/ml)	5–100			41		
D-Dimer (ng/ml)	<500					3220
Ferritin (ng/ml)	30–300					459
Ammonia (μmol/liter)	12–48					124
pH	7.30–7.40 (venous)					7.49
Partial pressure of carbon dioxide (mm Hg)	38–50 (venous)					38
Partial pressure of oxygen (mm Hg)	35–50 (venous)					69

* Ref denotes reference range at the other hospital. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for ionized calcium to milligrams per deciliter, divide by 0.250. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to millimoles per liter, multiply by 0.4114. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for uric acid to micromoles per liter, multiply by 59.48. To convert the values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496. To convert the values for ammonia to micrograms per deciliter, divide by 0.5872.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

‡ At the other hospital, the first admission was 9 days before admission to this hospital, discharge was 5 days before admission to this hospital, and the second admission was 4 days before admission to this hospital.

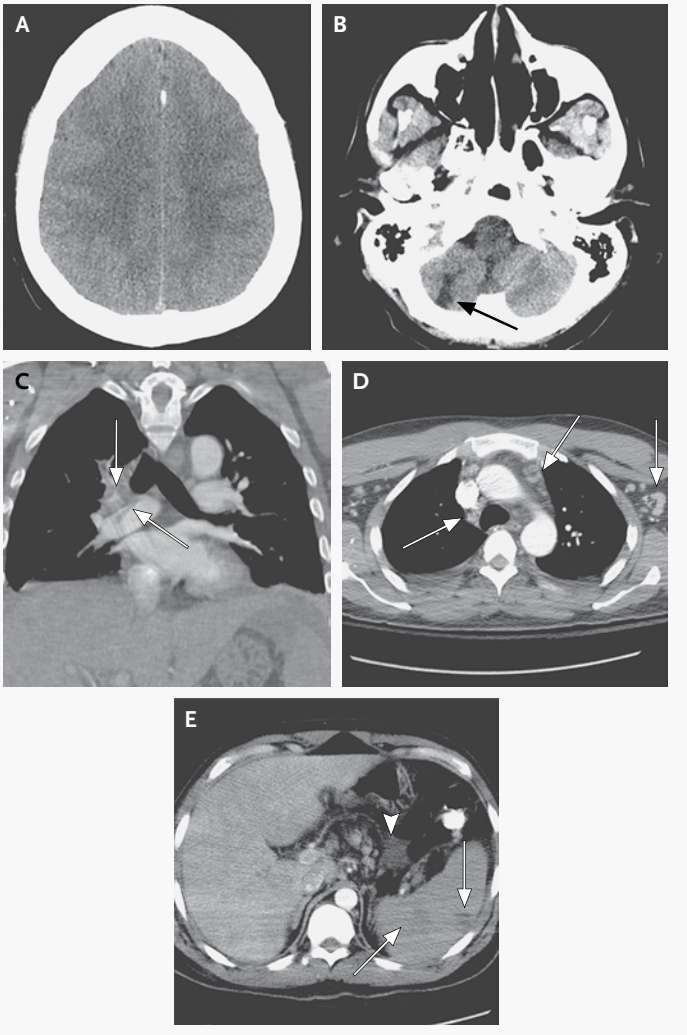

Figure 1. CT Imaging Studies.

Axial images from CT of the head performed without the administration of contrast material show effacement of the cerebral sulci (Panel A) and an infarct in the right inferior cerebellum (Panel B, arrow). A coronal image of the chest obtained with the administration of contrast material (Panel C) shows pulmonary emboli within the truncus anterior and interlobar segments of the right pulmonary artery (arrows). An axial image of the chest with contrast material (Panel D) shows multiple prominent axillary, prevascular, and right paratracheal lymph nodes (arrows). An axial image of the abdomen and pelvis with contrast material, obtained at a liver window (Panel E), shows a heterogeneous appearance of the liver and spleen. Multiple foci of hypoattenuation are present in the spleen (arrows), and abdominal ascites is present (arrowhead).

infarct. CT of the neck reveals multiple enlarged lymph nodes in the neck and the supraclavicular fossae bilaterally. CT of the chest reveals filling defects within the truncus anterior and interlobar segments of the right pulmonary artery that are consistent with pulmonary emboli, as well as multiple enlarged prevascular, right paratracheal, and bilateral axillary lymph nodes (Fig. 1D). There are small bilateral pleural effusions and relaxation atelectasis in the lower lobes. CT of the abdomen and pelvis reveals a heterogeneous appearance of the liver and spleen (Fig. 1E). Multiple foci of hypoattenuation are present in the spleen, several of which are peripheral in location and may represent infarcts. There are multiple, enlarged upper abdominal and bilateral inguinal lymph nodes. Abdominal and pelvic ascites is present.

Dr. Fathi: All discussants were involved in the care of this patient, and the diagnosis is known to us. This 38-year-old Haitian man presented with abdominal pain and nausea and was found to have severe hypercalcemia; imaging studies revealed splenomegaly, lymphadenopathy, and pulmonary emboli. His condition deteriorated quickly, and he had a progressive decline in mental status. Laboratory tests revealed thrombocytopenia and circulating abnormal T lymphocytes, as well as elevated levels of uric acid and lactate dehydrogenase, features consistent with tumor lysis. At the time of admission to this hospital, the presumptive diagnosis was an aggressive T-cell neoplasm.

T-CELL LYMPHOMAS WITH LEUKEMIC MANIFESTATIONS

An important consideration in this patient is T-cell acute lymphoblastic leukemia–lymphoma. This is a highly aggressive disease that is typically seen in adolescent boys and young adult men who present with a mediastinal mass or lymphadenopathy in the thorax and neck, bone marrow infiltration with resultant cytopenias, abnormal T cells in the peripheral blood, and frequent involvement of the central nervous system (CNS). This patient has circulating abnormal T cells and lymphadenopathy, but he does not have a dominant mediastinal mass and is older than the usual patient with T-cell acute lymphoblastic leukemia–lymphoma. In addition, patients with this disease rarely present with hypercalcemia.

T-cell prolymphocytic leukemia is also in the differential diagnosis. Unlike this patient, however, patients present with marked leukocytosis (usually >100×10^9 cells per liter, consisting mostly of prolymphocytes). The presentation can include marked splenomegaly, lymphadenopathy, cytopenias, spontaneous tumor lysis syndrome, and skin involvement.

Angioimmunoblastic T-cell lymphoma is an aggressive nodal T-cell lymphoma. Patients often present with fever, night sweats, a pruritic rash, hypergammaglobulinemia, and autoimmune abnormalities. This disease typically affects patients older than this man; the median age of affected patients is 60 years.

Anaplastic large-cell lymphoma, anaplastic lymphoma kinase–positive, is a disease of adolescent boys and young men, who may present with lymphadenopathy, constitutional symptoms, and the tumor lysis syndrome. However, circulating tumor cells and severe hypercalcemia are not common features.

Circulating abnormal T cells can be a feature of primary cutaneous T-cell lymphomas, particularly the Sézary syndrome. This is a leukemic variant characterized by abnormal circulating lymphocytes and generalized erythroderma. This patient did not have cutaneous manifestations.

HTLV-I–ASSOCIATED ADULT T-CELL LEUKEMIA–LYMPHOMA

In this case, the most likely diagnosis is adult T-cell leukemia–lymphoma (ATLL). ATLL is geographically clustered, with prevalence in the Caribbean, southern Japan, western Africa, and parts of South America, Iran, and Central Asia, mirroring areas where infection with human T-cell lymphotropic virus type I (HTLV-I) is endemic.[1-4] HTLV-I is a member of the deltaretrovirus family and was isolated in the early 1980s from a patient with ATLL[5,6]; all malignant T cells contain integrated HTLV-I provirus. Although as many as 20 million people worldwide are infected with HTLV-I, ATLL ultimately develops in only a small minority (approximately 4% or 5%).[6,7] Transmission of HTLV-I is thought to occur predominantly through breast-feeding, although the virus can also be transmitted by blood transfusion, sexual intercourse, and the sharing of hypodermic needles. There is typically a long latency period from initial infection to the onset of disease, and the majority of patients in whom ATLL develops are older than 40 years of age.[8,9]

The clinical presentation and disease course vary markedly; some patients have an indolent, asymptomatic course for years, but the majority of patients present with aggressive manifestations, as seen in this case. As the name of the disease implies, patients can present with peripheral-blood involvement (leukemia), lymphadenopathy without circulating tumor cells (lymphoma), or both. There are four variants of ATLL (Table 2).[10-12] This patient's disease is marked by a highly aggressive clinical course, which is consistent with the acute, or leukemic, variant of ATLL, with circulating malignant T cells, lymphadenopathy, splenomegaly, severe hypercalcemia, and bone marrow involvement with progressive thrombocytopenia.

In view of this patient's Haitian background (and consequently his high risk of infection with HTLV-I) and the clinical and laboratory findings, our clinical diagnosis was HTLV-I–associated acute ATLL. The diagnostic procedures were review of the peripheral-blood smear by a hematopathologist and bone marrow biopsy and aspiration.

DR. AMIR T. FATHI'S DIAGNOSIS

HTLV-I–associated adult T-cell leukemia–lymphoma.

PATHOLOGICAL DISCUSSION

Dr. Russell J.H. Ryan: Review of the peripheral-blood smear (Fig. 2A and 2B) revealed a population of morphologically abnormal lymphoid cells, including small, medium-size, and large forms with basophilic cytoplasm, some with irregular nuclear contours, and occasional cells with prominent nucleoli. Cells with highly convoluted nuclei ("flower cells"), characteristic of ATLL, were not identified. Flow-cytometric analysis of the specimen of peripheral blood (Fig. 2C and 2D) revealed that the majority of circulating lymphoid cells had aberrant expression of T-lineage markers, including bright expression of CD2, dim expression of surface CD3, partial absence of expression of CD5, absence of expression of CD7, and uniform expression of CD4 with variable coexpression of CD8. The combination of morphologic and immunophenotypic findings were diagnostic of a T-cell neoplasm with a leukemic component.

The core-biopsy specimen of the bone marrow (Fig. 2E, 2F, and 2G) revealed markedly increased cellularity at 95%. An extensive population of morphologically abnormal lymphoid cells of varying sizes, similar to those seen in the blood, infiltrated the normal marrow elements. Immunohistochemical staining revealed that the atypical cells were positive for CD2 and CD3, with

Table 2. Variants of Adult T-Cell Leukemia–Lymphoma.

Acute	Chronic	Smoldering	Lymphomatous
Approximately 60% of cases	Approximately 15% of cases	Approximately 5% of cases	Approximately 20% of cases
Circulating malignant cells, lymphocytosis	Stable, moderate lymphocytosis	No lymphocytosis	Absence of circulating malignant T cells
Tumor lysis	Minimal lymphadenopathy	Skin lesions	Hepatosplenomegaly
Hepatosplenomegaly	Skin lesions	Possible leukemic transformation	Hypercalcemia
Lymphadenopathy	Normal calcium level		Organ and skin involvement
Hypercalcemia			Constitutional symptoms
Possible central nervous system involvement			
Immunosuppression (opportunistic infections)			
Skin lesions			

decreased expression of CD5 and CD7; the cells were negative for CD34, terminal deoxynucleotidyl transferase, and CD1a, markers of lymphoblasts. The alpha chain of the interleukin-2 receptor, CD25 (Fig. 2F), was strongly expressed in the tumor cells, a finding that is characteristic of but not specific for ATLL.[13]

The bone marrow also showed an abundance of osteoclasts, which were associated with resorption pits (Howship's lacunae) in the trabecular bone. The pathophysiology of hypercalcemia in patients with ATLL has been linked, in part, to increased osteoclast activity. The neoplastic cells express soluble factors linked to osteoclastic differentiation and bone loss,[14] including parathyroid hormone–related protein,[15] the level of which was mildly elevated in this patient. ATLL cells may have surface expression of the receptor activator of nuclear factor-κB ligand (known as RANKL) and may secrete the chemokine macrophage inflammatory protein 1α, both of which induce osteoclast differentiation, suggesting that direct interactions between hematopoietic progenitors and malignant T cells in the bone marrow may play a role in this process.[16-19]

An enzyme-linked immunosorbent assay was positive for antibodies that were consistent with exposure to either HTLV-I or HTLV-II. A confirmatory line immunoassay showed reactivity with HTLV antigens in a pattern diagnostic of HTLV-I infection. Evidence of HTLV-I infection is a prerequisite for the diagnosis of ATLL, although a T-cell neoplasm develops in only a small proportion of HTLV-I carriers.[20] In this case, the combination of characteristic morphologic and immunophenotypic features in the peripheral blood and bone marrow, in conjunction with the positive HTLV-I studies, allowed for a conclusive diagnosis of HTLV-I–associated ATLL.

DISCUSSION OF MANAGEMENT

HYPERCALCEMIA, TUMOR LYSIS SYNDROME, AND PAIN

Dr. Fathi: The initial treatment of patients with acute ATLL may require management of hypercalcemia, tumor lysis syndrome, cytopenias, pain, or any combination of these. This patient's hypercalcemia was initially treated with vigorous intravenous hydration, calcitonin, and bisphosphonates. Levels of electrolytes and uric acid were closely monitored, and he was treated with allopurinol and rasburicase for increasing levels of uric acid. Pain in the context of acute ATLL can be related to bony lesions, hypercalcemia, or rapidly worsening splenomegaly. This patient's course was punctuated by periods of severe abdominal pain, most likely related to hypercalcemia and splenomegaly with infarcts, which was responsive to intravenous narcotics and eventually to antineoplastic therapy.

ANTINEOPLASTIC THERAPY FOR ATLL

The traditional treatment for acute ATLL is multiagent cytotoxic chemotherapy, typically with a regimen such as cyclophosphamide, doxorubi-

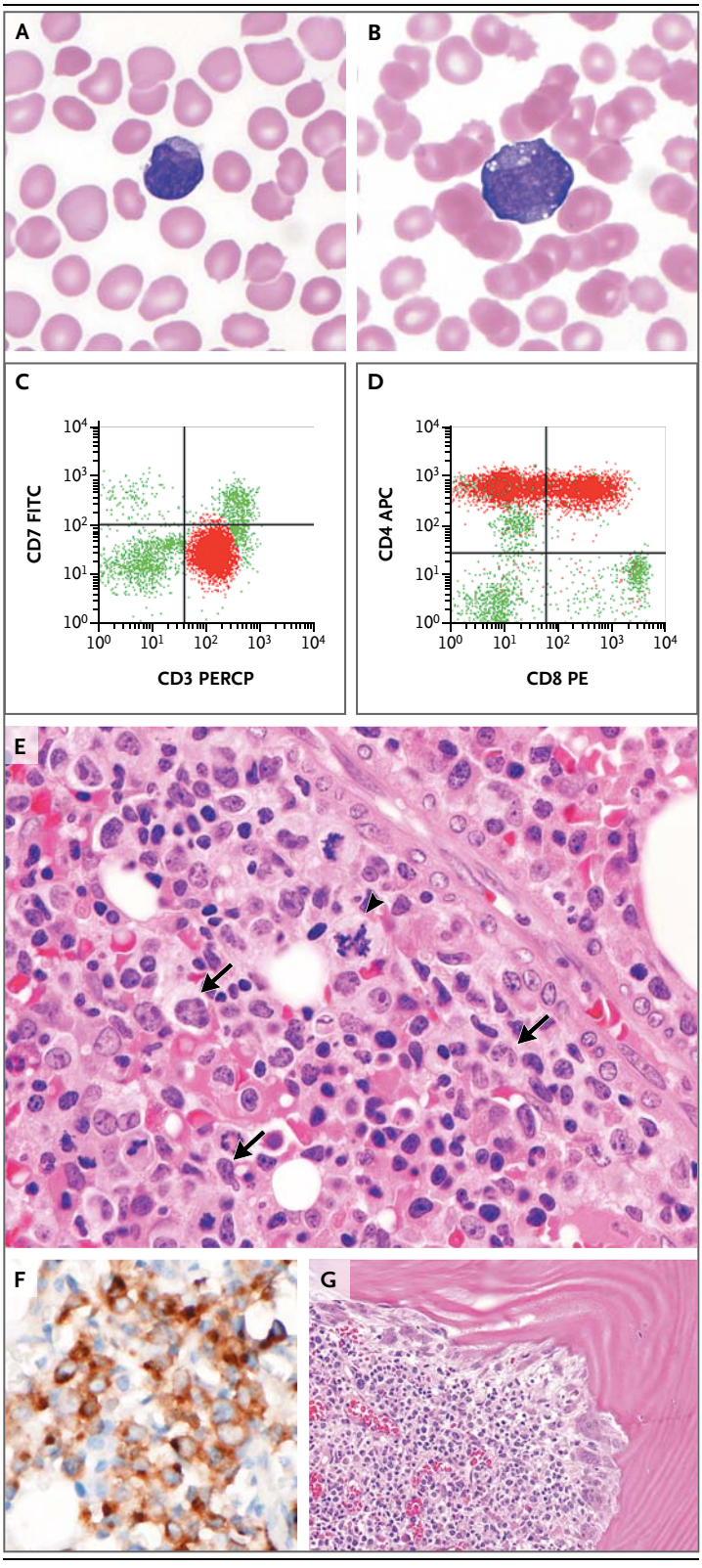

Figure 2. Pathological Features of the Blood and Bone Marrow.

Circulating lymphoma cells were seen on the peripheral-blood smear (Panels A and B, Wright–Giemsa). Panel A shows a medium-size form with mature chromatin and an irregular nuclear contour. Cells with highly convoluted nuclei ("flower cells"), typical of ATLL, were not identified. Panel B shows a large cell with blastlike features, including basophilic, vacuolated cytoplasm and dispersed chromatin. Panels C and D show the findings from four-color flow-cytometric analysis of the peripheral blood. The abnormal population (red) shows dim expression of CD3, an absence of CD7, uniform expression of CD4, and variable coexpression of CD8 (lymphocyte-gate properties, variable forward-scatter [size] and low side-scatter [granularity]). Panel E (hematoxylin and eosin) shows a spectrum of abnormal lymphoid cells (arrows) infiltrating the bone marrow, including large blast forms; a prominent atypical mitotic figure is present (arrowhead). The neoplastic cells are strongly positive for CD25 (Panel F, immunoperoxidase on a paraffin section). Panel G shows a marked proliferation of osteoclasts lining the trabecular bone of the medullary cavity (hematoxylin and eosin).

cin, vincristine, and prednisone (CHOP).[21] This and similar regimens produce initial responses in some patients. A Japanese trial showed that another regimen, referred to as VCAP-AMP-VECP (vincristine, cyclophosphamide, doxorubicin, and prednisone; doxorubicin, ranimustine, and prednisone; and vindesine, etoposide, carboplatin, and prednisone), produced higher rates of complete remission than did CHOP but no significant improvement in overall survival.[22] An alternative frontline approach, the combination of the antiviral agent zidovudine and interferon, has been explored.[23,24] A recent meta-analysis suggested that the combination of zidovudine and interferon leads to longer overall survival than do traditional regimens, but the majority of patients did not achieve a complete remission.[25] The median survival for acute ATLL continues to be poor, at approximately 5 to 9 months.[3,21,25,26]

This patient was treated with CHOP for six cycles; he also received concurrent prophylactic treatment of the CNS with high-dose methotrexate. After one cycle, he had a dramatic improvement, with resolution of the altered mental status, hypercalcemia, and pain. After the conclusion of therapy, a bone marrow–biopsy specimen revealed less than 2% residual disease and an imaging study did not reveal lymphadenopathy

or splenomegaly. He received two additional cycles of therapy with ifosfamide, carboplatin, and etoposide. In view of his excellent but partial response and the presence of minimal residual disease, the patient was referred for consideration of allogeneic stem-cell transplantation.

ALLOGENEIC HEMATOPOIETIC STEM-CELL TRANSPLANTATION

Dr. Yi-Bin Chen: Since ATLL is a virally driven hematologic malignant condition, it is an ideal target for the therapeutic mechanisms of allogeneic hematopoietic stem-cell transplantation (HSCT), which include both cytotoxic chemotherapy and radiation in the conditioning regimen and the immunologic attack of the allografted immune system against the tumor. There are two approaches to preparing a patient for HSCT: myeloablative and reduced-intensity regimens. Myeloablative regimens attempt to completely eliminate host hematopoietic cells before transplantation, whereas reduced-intensity regimens leave some host hematopoietic cells, which are later displaced by the successful allograft through a graft-versus-host effect. Early series involving myeloablative approaches to allogeneic HSCT for ATLL were complicated by significant transplantation-related mortality but resulted in a 30 to 40% rate of disease-free survival, which was much higher than historical outcomes involving chemotherapy alone.[27] More recently, reduced-intensity approaches have shown success, and in several cases, patients with relapsed disease after HSCT entered remission after the tapering of immunosuppressive agents alone, illustrating a potent graft-versus-tumor effect.[28] Correlative studies have shown evidence of specific cytotoxic T cells directed against certain HTLV proteins after HSCT.[29] In a large registry study involving 384 patients from Japan, four factors were associated with an adverse prognosis: older age, male sex, active disease at the time of stem-cell transplantation, and use of umbilical-cord blood.[30] For patients such as this one with chemosensitive disease, who are in at least partial remission and otherwise healthy, I would recommend allogeneic HSCT as a potentially curative approach.

Early in this patient's course, we performed HLA typing on him and his eight siblings. Two siblings were HLA-identical, and we initially planned myeloablative HSCT with one of the matched siblings, directly after the near-complete remission achieved with initial chemotherapy. However, one matched sibling lived in Haiti and was unable to travel to the United States because of the recent earthquake. The other matched sibling lived in Canada illegally and was concerned about travel to the United States and the subsequent inability to return home. Efforts to secure the proper paperwork for the siblings were made while the patient was receiving initial chemotherapy but were unsuccessful. Concurrently, a search for an HLA-matched unrelated donor through the National Marrow Donor Program and associated international registries was undertaken; as is unfortunately frequently the case with patients of African ancestry, no match was found.

We then decided to proceed with reduced-intensity haploidentical (partially matched related donor) bone marrow transplantation, since the patient's one local sibling was a partial HLA match. Options for the use of umbilical-cord blood were not explored, since there was a known haploidentical sibling. In several retrospective analyses and phase 2 trials involving haploidentical donors or the use of umbilical-cord blood as a source of stem cells, the outcomes appear to be similar to the outcomes of transplantation involving conventional donors.[31-33] Nevertheless, we currently prefer a fully matched related or unrelated donor over alternative options.

The patient returned to the clinic 3 weeks after his second cycle of chemotherapy with ifosfamide, carboplatin, and etoposide to finish his pretransplantation workup and to proceed with reduced-intensity-conditioning haploidentical HSCT. Unfortunately, his blood calcium level was elevated, at 16 g per deciliter (4 mmol per liter), indicating progressive disease. The results of allogeneic HSCT in the context of progression of aggressive lymphoid malignant conditions is poor; therefore, the planned bone marrow transplantation was deferred.

TREATMENT OF RELAPSED AND REFRACTORY ATLL

Dr. Fathi: Options for the treatment of refractory or relapsed acute ATLL are limited. Most patients, including this one, do not have long-lasting clinical responses with initial therapy and have increasing resistance to subsequent therapeutic attempts. New and targeted agents have shown some efficacy in clinical trials of patients with

refractory T-cell neoplasms, although only a small percentage of these patients had ATLL. Among these agents are the antimetabolite pralatrexate and the histone deacetylase inhibitor romidepsin.[34,35] Case reports and small studies have also reported efficacy for denileukin diftitox, an engineered combination protein composed of interleukin-2 bound to diphtheria toxin, and alemtuzumab, a monoclonal antibody targeting CD52, an antigen expressed on most T cells.[36-38] Finally, combinations of zidovudine and interferon and arsenic trioxide and interferon are under study for relapsed or refractory ATLL.[39-41] Nevertheless, second-line therapies have at best provided only transient responses.

This patient was given the salvage chemotherapy regimen of etoposide, methylprednisolone sodium succinate, cytarabine, and cisplatin (known as ESHAP). After an initial response, he had a relapse within 10 days after completion of therapy, including hypercalcemia, abdominal pain, and circulating malignant cells. Alemtuzumab was administered, and hypercalcemia and the symptoms resolved, only to reemerge within 1 week. The tumor did not respond to romidepsin or subsequently to denileukin diftitox, and the hypercalcemia became refractory to all measures. The patient was transitioned to hospice care and died at home 9 months after the initial diagnosis.

The patient was aware that his case would be published in a medical journal. Knowing that his experience would help educate and inform a new generation of physicians about this devastating disease provided him and his family with important satisfaction and solace.

Dr. Nancy Lee Harris (Pathology): Are there any questions?

A Physician: Is there a role for vaccination against HTLV-I in either preventing transmission or enhancing the immune response to the tumor once lymphoma develops?

Dr. Fathi: There is currently no preventive or therapeutic vaccine for ATLL. Animal-based models and preclinical strategies are under study to achieve this goal.

A Physician: Is there a role for radiation in the treatment of this disease?

Dr. Fathi: There is no established role for radiotherapy in ATLL, although palliative radiation therapy has been used for isolated lesions.

Dr. Eric S. Rosenberg (Pathology): You mentioned the use of the antiviral agents zidovudine and interferon. Since the virus is already integrated into the genome and has caused a transformation of the cells, it would seem it is too late for antiviral therapy to be effective. How would this work?

Dr. Fathi: The mechanism of efficacy of the zidovudine and interferon combination is unclear. Zidovudine appears to exert a cytostatic effect by blocking DNA replication, suppressing viral assembly and transformation of lymphocytes by HTLV-I, and even displaying a direct antitumor effect. Interferon, efficacious in malignant conditions such as melanoma and renal-cell carcinoma, appears to cause cell death by inhibiting protein synthesis and promoting expression of major histocompatibility complexes, which enhance immunologic recognition of transformed cells.

A Physician: This patient had abnormalities of coagulation. Is this a known complication of ATLL?

Dr. Fathi: This patient's presentation did include a coagulopathy. However, there is no literature that I know of that describes hypercoagulability specific to ATLL.

Dr. Harris: Did this patient have CNS involvement by lymphoma, or was his altered mental status due to hypercalcemia? CSF analysis does not have high sensitivity in detecting CNS lymphoma.

Dr. Fathi: At the time of presentation, samples from the patient's CSF did not reveal involvement with disease, but this does not rule out CNS involvement, so we proceeded with prophylaxis in the form of high-dose methotrexate. Other potential causes for his altered mental status included hyperammonemia, possibly related to hepatic infiltration, cerebral edema, and hypercalcemia.

ANATOMICAL DIAGNOSIS

Adult T-cell leukemia–lymphoma, associated with human T-cell lymphotropic virus type I.

This case was presented at the Medicine Grand Rounds.

Dr. Fathi reports serving as a consultant on advisory boards for Genzyme, Seattle Genetics, Teva Pharmaceuticals, and Concert Pharmaceuticals. Dr. Chen reports receiving consulting fees from Otsuka and Seattle Genetics and grant support to his institution from Otsuka, Millennium, Bayer, and Seattle Genetics. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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