Letter to the Editor

Don Blake, APR

Public Relations
The Hemlock Society USA

The November issue of Hawai Medical Journal just reached my desk. Congratulations on your continued fine work as editor.

By the way, I think your idea of adopting D.A.D.D. as a meaningful acronym is a good one. It is easy for the general public to understand and accept, and it takes the harsh edge from the general public image of physician-assisted death.

Thanks for your support as a national board member. Perhaps we'll have the occasion to meet when you are next in Denver or elsewhere for a board function.

Military Medicine

Military Unique Curriculum

Benjamin W. Berg MD, LTC, U.S. Army

Graduate Medical education in the Military largely mirrors the civilian sector. Educational standards, and program requirements as prescribed by the Accreditation Council for Graduate Medical Education (ACGME) are identical to civilian training programs. The spectrum of programs available in the US Army is broad. There are primary training programs in virtually all specialties, including Family Practice, Internal Medicine, General Surgery, Pediatrics, Psychiatry, Obstetrics and Gynecology, Radiology, and Pathology. Advanced training in subspecialty areas is also available in some fields, where research and clinical fellowships are established. In recent years there has been a decrease in the Military GME programs, as the overall size of the Military is decreased. Army GME takes place largely at "Major Medical Centers" which are located in Honolulu (Tripler), Washington D.C. (Walter Reed), San Antonio (Brooke) and El Paso (William Beaumont) Texas, Tacoma Washington (Madigan), and Augusta Georgia (Eisenhower). The Fitzsimmons Army Medical Center in Denver, Colorado closed its doors about 18 months ago.

Medical students apply for competitive residency training in Military Hospitals from either a Military sponsored civilian Medical School, or from the Uniformed Services University of Health Sciences (USUHS) which is located in Bethesda Maryland. The Majority of applications for Military internships are from Civilian Medical School applicants who have participated in the Health Professions Scholarship Program (HPSP). These candidates have a four year obligation to serve in the Uniformed Service of their choice, after residency training is completed. The program provides

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Harry L. Arnold Jr. MD Case of the Month

HTLV-1 Associated Adult T-Cell Leukemia in a Micronesian Patient: The First Reported Case

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Introduction

Adult T-Cell Leukemia/Lymphoma is an aggressive form of lymphoproliferative disease which is specifically caused by infection with human T-cell lymphotropic virus type I (HTLV-I). Infection with this virus is endemic in southwest Japan, the southeastern United States, the Caribbean Islands, and central Africa.[1] More recently, genetically distinct forms of the virus have been identified in Australian aboriginal tribes as well as various isolated populations in Papua New Guinea and the Solomon Islands in Melanesia.[2]

However, evidence of infection with HTLV-I has not been identified in Micronesian populations.[3] This is a report of a case of Adult T-Cell Leukemia in a Marshallese male medically evacuated to Honolulu from the island of Majuro, Republic of the Marshall Islands (RMI), which is in Pacific Micronesia. This case appears to be the first report of a confirmed HTLV-I associated T-Cell Leukemia in a Micronesian patient.

Case Report

A 52-year-old Marshallese male was admitted to the hospital in Majuro, RMI, because of generalized abdominal pain with distention, jaundice, nausea, vomiting, subjective fever and chills, loss of appetite, and shortness of breath.

Two weeks prior to admission, symptoms of nausea and vomiting, diffuse abdominal pain, and loss of appetite began. He progressively developed jaundice, increasing abdominal girth, and subjective fever and chills. On examination, he was found to be jaundiced. His abdomen was markedly distended with diffuse tenderness and guarding but no peritoneal signs. Initial laboratory tests are shown in Table 1. He was treated with Metronidazole 500mg PO q8hrs, Gentamycin 60mg IV q8hrs, Rocephin 1 gm IV q12hrs, and Ampicillin 1 gm IV q6hrs for obstructive jaundice and ascending cholangitis. While hospitalized in Majuro, the patient's white blood cell count rose to 62,000, and after 5 days he was transferred to Honolulu (Tripler Army Medical Center) for further evaluation.

The patient had a history of Hepatitis B infection twenty years prior to admission and left nephrectomy for renal cell carcinoma several years earlier. He was born and raised on the island of Namodrik and lived there until the age of 16, at which time he traveled to Majuro for three years to receive training as a "Health Aide." He frequently traveled to many of the neighboring islands and atolls but had never traveled outside of Micronesia. He took no medications and did not use tobacco or alcohol.

Examination revealed marked jaundice, hepatosplenomegaly,

and diffuse adenopathy with cervical, supraclavicular, axillary, and inguinal lymph nodes. There was bilateral leg edema extending to the knees. Abdominal and chest computed tomographic (CT) scan showed bilateral axillary, precarinal, anterior mediastinal, and mesenteric adenopathy as well as hepatosplenomegaly and moderate ascites. Peripheral blood smear was suggestive of acute leukemia or high grade lymphoma/leukemia (Fig 1). Peripheral blood flow cytometry studies confirmed T-Cell Leukemia (Table 2). Western Blot analysis confirmed HTLV-I infection. The patient was treated with Zidovudine 200 mg PO five times daily and Alpha-Interferon 10 million units SC daily.

The patient's hospital course was characterized by progressive multiple organ system failure including oliguria, anasarca, asterixis, hyporeflexia, and lethargy. A lumbar puncture was performed which revealed no evidence of central nervous system involvement by the lymphoma or leukemia, or CNS infection. Lactulose therapy for hepatic encephalopathy was initiated. The following day the patient's mental status improved and the white blood cell count decreased to 50,000. On the fifth night of admission the patient's temperature rose to 100.7 F and Ceftazidime 1gm IV q8hrs was administered. He developed an allergic reaction so the antibiotic was changed to Imipenem 500 mg IV q6hrs. Administration of 4 liters per nasal canulae of oxygen was required to maintain 92% saturation by pulse oximetry.

On the sixth hospital day AZT was discontinued because of progressive elevation in liver enzymes and liver failure. By the seventh day oliguria developed and IV Furosemide failed to increase urine output. Low grade disseminated intravascular coagulopathy, nonoliguric renal failure with creatinine increasing to 2.0 mg/dl, and possible hepatorenal syndrome evolved and the patient became progressively more somnolent. The patient decided not to continue treatment and he died on the eleventh day of his admission. Despite the development of multiorgan system failure his white blood cell count reached a nadir of 23.5 x 10(9)/L and an absolute lymphocyte count 18.1 x 10(9)/L with treatment.

Table 1.—Lab Values

	In Majuro	In Honolulu
White Blood Cell	52 x 10(9)/L	54.3 x 10(9)/L
Hemoglobin	14 g/dl	15 g/dl
Hematocrit	39%	44%
Platelets	78 x 10(9)/L	66 x 10(9)/L
Absolute Granulocyte Count	8.32 x 10(9)/L	4.3 x 10(9)/L
Absolute Lymphocyte Count	42.1 x 10(0)/L	4.3 x 10(9)/L
Prothrombin Time	13 seconds	19.6 seconds
Partila Thromboplastin Time	36 seconds	52 seconds
Total Protein	7.0 g/dl	6.7 g/dl
Albumin	3.1 g/dl	2.7 g/dl
Aspartate Aminotrasferase	394 U/L	426/U/L
Alanine Aminotransferase	160 U/L	146
Alkaline Phosphatase	243 U/L	202 U/L
Total Bilirubin	9.4 mg/dl	15 mg/dl

Table 2.—Peripheral Blood Flow Cytometry

Cell Markers	Percentage of Cells Positive
CD2	96
CD3	94
CD4	92
CD5	95
CD7	4
CD8	2
Myeloperoxidase	2
Tdt	0
CD34	1
CD45	98
CD56	1
HL-DR	17

Pathology

Examination of the patient's admission hemogram and peripheral smear disclosed normal red cell parameters and an atypical lymphocytosis (white count 64,900; lymphocytes 90%) comprising moderately sized cells with immature chromatin, one to several variably conspicuous nucleoli, and variably folded to overtly convoluted and multilobulated nuclear configurations. Cytoplasm was scant to moderate in quantity and non-granular. A conspicuous minority of cells manifested a "hand-mirror" appearance (Fig 1) due to the presence of a cytoplasmic uropod. Platelets were decreased (60,000).

Bone marrow aspirate smears and core biopsy sections revealed cellularity of 50% with a predominance of normal appearing hematopoietic elements. Aspirate smears showed 30% and core biopsy sections 20% of nucleated cells to be lymphoid with immature cytologic features and folded nuclear contours. In core biopsy sections these lymphocytes formed aggregates which occupied nonparatrabecular foci.

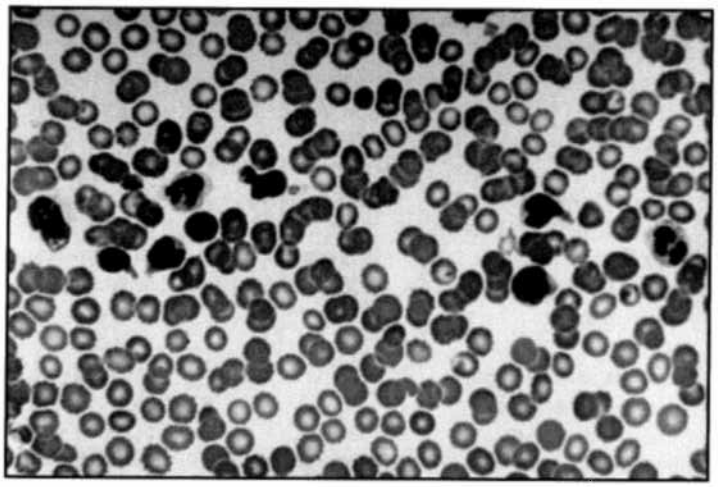
Peripheral blood lymphocytes were studied by flow cytometric analysis. Approximately 95% of lymphocytes manifested a mature T helper cell phenotype and were Tdt negative (Table 2).

Bone marrow cytogenetics study disclosed chromosomal abnormalities in 19 out of 20 cells examined, involving complex rearrangements of chromosomes 1, 9, 12, and 15 [46, XY, del (9) (q12), der (12) t (1;12) (q21; q24), add (15)(q24)]. Peripheral blood analysis disclosed a Western Blot pattern which was positive for HTLV-I antibodies.

The aggregate of these findings was diagnostic of Adult T-Cell Leukemia Lymphoma related to HTLV-1 infection.

Discussion

Human T-cell lymphotropic virus type I (HTLV-I) is the first human retrovirus isolated and one of the first viruses to be confirmed as causing human cancer.[4] In addition to adult T-Cell Leukemia/Lymphoma it has been implicated in Tropical Spastic Paraparesis/HTLV-I-Associated Myelopathy (TSP/HAM), a chronic, progressive degenerative disease of the spinal cord.[5] Because the virus is endemic in parts of Japan, T-Cell leukemia/lymphoma is the most common type of lymphoma in that country.[6] The virus apparently infects Cd4+ human T-cells and integrates its proviral DNA into the cell's own genome.[7] There is genetic variability in viruses from different geographical locations which does not appear to play a role in the clinical presentation of the infection.[8,9] Major genetic differences exist between viral isolates from Japan, Africa and Melanesia, and the rare isolate from a Polynesian patient has been reported to be virtually identical to the Japanese strain.[2] Prior reported cases of



Peripheral Blood Smear (600x orginal magnification)
Atypical Leukemic Lymphocytes with scattered hand mirror cells.

HTLV-I infection in Hawaii were associated with TSP/HAM and occurred in Japanese-American patients whose parents had lived in regions of Japan that were endemic for the virus.[10] This patient represents the first case reported in the English language medical literature of HTLV-I associated T-cell leukemia from Micronesia.

It is unclear how our patient acquired his HTLV-I infection. Since HTLV-1 is known to be transmitted by blood products, and contact with body fluids he could have become infected at the same time as his Hepatitis B was acquired. It is not certain how the patient developed Hepatitis B, however, he denied blood transfusions, even during his nephrectomy. During his work in the Marshall Islands the patient was frequently exposed to blood products. Since HTLV-1 has not been previously documented in Marshallese patients, the presumed extremely low prevalence of the virus in that population makes it unlikely that he acquired it through occupational exposure.

Since much of the tertiary health care provided to the Micronesian population occurs at various civilian and military medical institutions in Hawaii, all practitioners should be aware of this first case from that region. While a rare disease, recent publications suggest that significant palliation and even cure is possible with aggressive chemoimmunotherapy using alpha-interferon and zidovudine.[11] Investigation of seroprevalence rates of HTLV-1 infection in the Republic of the Marshall Islands and other Micronesian populations may provide a window of opportunity to further elucidate the mode(s) of transmission, infectivity, and carcinogenicity of this retrovirus.

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Editor's Note:

This is our first "Case of the Month." This new feature honors our late editor Harry L. Arnold Jr. MD. Benjamin W. Berg MD will serve as editor and facilitator for this new and unique series of case reports from our Medical Ohana. Manuscripts for the "Case of the Month" may be sent to LTC Benjamin W. Berg, MC, Chief Pulmonary/Critical Care at Tripler Army Medical Center, HI 96859 and a copy to the Journal office.