

A Case of Adult T-cell Leukemia Masquerading as Mycosis Fungoides

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Citation

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Abstract

INTRODUCTION AND INITIAL PRESENTATION

This 81 year old Japanese American male presented 9 years ago with a rash that was diagnosed as psoriasis and was treated with 14 weeks of light therapy. Shortly after this therapy a skin biopsy of the right buttock revealed an atypical T-cell infiltrate consistent with mycosis fungoides with the malignant cells positive for CD 2,3,4, and 5 but negative for CD7 and 8. The epidermis showed hyperkeratosis, hyperparakeratosis, and acanthosis and there was a band-like lymphocytic infiltrate in the superficial dermis. Epidermotropism and Pautrier microabscesses with atypical lymphocytes with convoluted nuclei and occasional large cells were noted. T-cell gene rearrangement and HTLV-1 serology were positive. Bone marrow examination was unrevealing. While the patient had not ever been in Japan, his father came from Kyushu.

The patient received therapy with PUVA with an initial response, then experienced progression in skin. Treatment with topical BCNU and extracorporeal photopheresis were also rendered; again with initial short-lived responses, then progression of the skin rash. Two years after the initial diagnostic skin biopsy, the patient had a PET scan showing right hilar, axillary, and inguinal adenopathy.

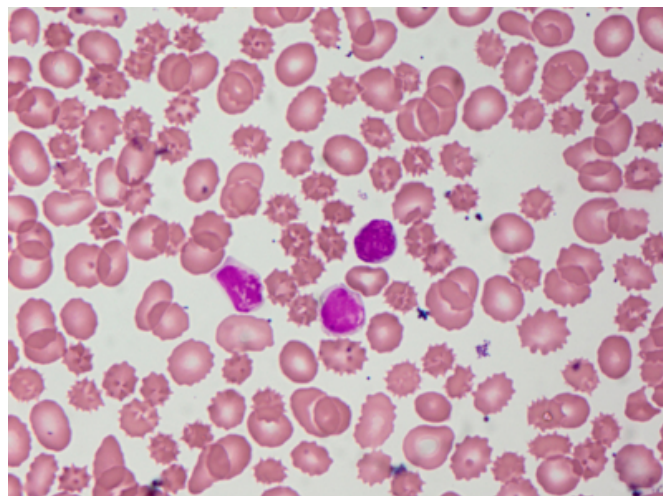
The patient began therapy with bexarotene with a complete response in skin and continued on bexarotene in good health for 3 years. He then presented with a hemoglobin of 8.9 and white blood cells of 12,800. CT scanning showed bilateral perihilar alveolar infiltrates, a 1.5 cm density at the right apex of the lung, mediastinal and right hilar adenopathy and splenomegaly with peripheral hypodensities.

DIAGNOSTIC WORK-UP

At this time, he was referred to a tertiary center. On physical examination the patient was a frail, ill-appearing elderly man

who had no skin lesions, and no palpable adenopathy. The liver was 10 cm below the right costal margin and the spleen was 8 cm below the left costal margin in the mid-clavicular line. Flow cytometry of his blood showed that 8% of lymphocytes were abnormal T-cells with positive CD 2,3,4,5,25 and 52 and a T-cell gene rearrangement was present. Human T-cell leukemia type 1 serology was positive by ELISA screen with Western blot confirmation.

Figure 1



Soon after his initial evaluation, the patient developed hypoxia and was admitted to the hospital where he underwent bronchoscopy which was unrevealing. A large left pleural effusion was tapped with smear showing an atypical lymphocytosis with similar morphologic and flow cytometry characteristics as the abnormal cells in the peripheral blood. CT scans showed patchy and confluent ground glass opacities in the left upper lobe and diffuse ground glass opacities and consolidation in the right lung. Mediastinal nodes were noted with the largest a subcarinal node of 3.9 cm. Hepatomegaly, marked splenomegaly and a

2.9 portacaval node was noted.

The patient received a course of dose-adjusted EPOCH but represented two weeks later febrile and was readmitted. CT scan showed decreased mediastinal adenopathy, but he had reaccumulation of his left pleural effusion and had a right lower lobe consolidation. The patient had evidence of disseminated intravascular coagulation on laboratory examination requiring transfusion. He had oral herpes simplex virus infection. He eventually required placement of a permanent chest tube for his rapidly recurrent pleural effusion and was begun on recombinant alpha interferon 2 million units three times weekly and zidovudine 1 gram daily.

TREATMENT COURSE AND RESPONSE

While on this therapy, the patient felt tired and had a continued anemia requiring erythropoietic stimulating agents (ESA) and transfusion. After three weeks of treatment he had no spleen palpable on examination and a normal white blood count. By two months after treatment his chest tube could be removed.

He did well until 7 months after interferon and zidovudine was first initiated. He presented with a fever, hypotension and recurrent oral herpes simplex virus. His white blood count was 48,000 with 92% lymphocytes again with morphology and flow cytometry characteristics of his malignant cells. He began denileukin diftitox treatment at 9 micrograms/kg/day for five days every 21 days. The patient received a total of 12 months of therapy, receiving no further ESA or transfusion therapy and with a gain of 20 kilograms. His ECOG performance status was 0 with the patient enjoying gardening 2 hours daily. With both his flow cytometry and PET/CT scans negative, the denileukin diftitox was stopped.

Eight months later the patient was seen in clinic with normal laboratory examination and a good performance status but was noted to have erythematous patches and plaques on his skin which were asymptomatic. A skin biopsy of his posterior torso had similar findings to that seen at initial diagnosis. Treatment with denileukin diftitox was resumed and by the fourth cycle the skin was clear. Unfortunately, two months later the patient was admitted to an outside hospital with weight loss and altered mental status. He was found to have cryptococcal meningitis and while he briefly improved, finally expired from this infection.

DISCUSSION

The World Health Organization defines Adult T-cell leukemia/lymphoma (ATLL) has a “peripheral T-cell neoplasm...caused by the human retrovirus known as human T-cell leukemia virus type 1 (HTLV-1)” (1). HTLV-1 is estimated to have infected 1-2 million people worldwide (2). It is endemic in several regions of the world most notably Southwest Japan, the Caribbean basin (Jamaica, Trinidad), parts of central Africa, Peru and the Southeast of the US. The virus may be transmitted in breast milk, by exposure to blood or blood products or thru sexual encounters. While the cumulative incidence of ATLL is estimated to be between 2-5% of HTLV-1 carriers, there is a long latency until disease presentation. Thus, ATLL occurs only in adults with an age of onset between 20-80 years of age with an average of 58 years; in men slightly higher than women (1.5:1).

Although ATLL is considered one of the aggressive T-cell lymphomas, the disease course is variable and can sometimes be indolent depending on the form that the disease takes. Four forms of ATLL have been classified (3): the acute, lymphomatous, chronic and smoldering forms. Skin is the most common extranodal site of involvement occurring more than 50% of the time, and in all forms of the disease. Skin lesions can be clinically diverse ranging from erythematous rashes, papules and/or nodules with or without ulceration to an exfoliative skin rash.

The acute form is the most common presentation of the disease occurring 60% of the time and presenting with lymphocytosis with abnormal lymphoid cells sometimes called “flower” cells because of their polylobated appearance in the peripheral blood and eosinophilia. Additionally, patients with the acute form may have constitutional symptoms such as fever, sweats and weight loss, elevated LDH, hypercalcemia with or without lytic bone lesions, lymphadenopathy, hepatosplenomegaly and bone marrow infiltration. Besides involvement of spleen, skin or liver, lung, stomach and central nervous system can be involved. Prognostic indicators found in multivariate analysis for survival in the acute phase include performance status, LDH, age > 40 years, greater than three areas of involvement and hypercalcemia (4). The lymphomatous form occurs 20% of the time and is characterized by nodal enlargement and involvement with no blood involvement. Despite the use of aggressive combination chemotherapy, median survival is less than 12 months in both the acute and lymphomatous forms.

The chronic form, occurring 15% of the time, is characterized by an abnormal lymphocytosis but no or mild lymphadenopathy, organomegaly, or elevation in LDH; and no hypercalcemia. The smoldering form, the least common at 5%, is characterized by more than 5% abnormal T-lymphocytes in the peripheral blood confirmed by cytology and immunophenotyping or flow cytometry. As in all the other forms, skin involvement may be present. Median survival in the smoldering form can be greater than five years. Progression from the chronic or smoldering forms to the acute form occurs 25% of the time at a median time of 38 months.

Biopsy of the skin may show epidermal infiltrates with Pautrier-like microabscesses which are common. The cells are mostly CD 4+, and CD25+ with CD2,3,5 positivity and loss of CD7. Monoclonal integration of HTLV-1 virus genome is seen in the malignant cells. The differential diagnoses include T-Prolymphocytic leukemia, Mycosis fungoides/Sezary syndrome, other Peripheral T-cell lymphomas, the healthy carrier of HTLV-1, and occasionally Hodgkin lymphoma.

Observation has been advocated for patients with the chronic or smoldering forms of the disease; while multi-agent combination chemotherapy as per other advanced, aggressive non-Hodgkin lymphomas is utilized in the acute and lymphomatous forms though these patients usually progress after an initial, brief response and median survival does not appear to be significantly improved. Antiviral agents such as zidovudine along with interferon (AZT/IFN) are among the most accepted treatments (5). A phase II trial demonstrated 92% response rate (58% CR and 33% PR) in patients who received AZT/IFN as initial treatment, with mean event free survival of 11 months, and side effects were largely tolerable, mainly hematological. However, approximately 80% of patients relapsed (6). Arsenic trioxide with interferon- γ have also been studied in a small phase II trial. Allogeneic bone marrow transplantation appears to be the only hope for cure, but with the accompanying morbidity and mortality associated with that procedure.

Denileukin diftitox is a cytotoxic fusion protein composed of interleukin-2 (IL-2) sequences fused with diphtheria toxin. It has been approved for the treatment of recurrent or persistent, CD25 positive, cutaneous T cell lymphoma (CTCL). Three cases have been reported with using denileukin diftitox to treat ATLL in the literature but this treatment has not been prospectively studied in the treatment of this disease.

As patients with ATLL have an associated T-cell immunodeficiency, death often is caused as in this patient by infectious complications such as *Pneumocystis carinii* pneumonia, cryptococcal meningitis, disseminated Herpes zoster infection, or disseminated strongyloides infection. Some advocate sulfamethoxazole/trimethoprim prophylaxis in all patients; with antifungal prophylaxis to be considered in patients receiving chemotherapy.

SUMMARY AND CONCLUSIONS

This is a case of a frail elderly Japanese-American male who was diagnosed with mycosis fungoides, stage I and HTLV-1 positive serology who most likely had the smoldering form of ATLL at diagnosis. After a 5-6 year period, he presented with the acute form of ATLL, unresponsive to multi-agent chemotherapy, and with a clinical response with AZT/IFN that lasted seven months but with a significant impairment of quality of life. He attained a complete clinical response with an excellent quality of life during treatment with denileukin diftitox that lasted greater than two years; unfortunately he expired due to infection most likely related to immunoincompetence from his underlying disease.

The diagnosis of ATLL should be considered in those with connections to an HTLV-1 endemic area whose pathology resembles those changes seen in mycosis fungoides and HTLV-1 serologic testing performed. Though patients presenting with the smoldering or chronic forms of ATLL may resemble patients with early stage mycosis fungoides or even Sezary's syndrome and may initially fare well, 25% may progress to the acute form of ATLL. Optimal treatment for patients with ATLL remains unclear; prospective studies of denileukin diftitox in the treatment of such patients may be warranted. As death is often caused by infectious agents due to an underlying immunoincompetence, prophylaxis of such patients with sulfamethoxazole/trimethoprim, antifungal agents such as fluconazole and evaluation for strongyloides in patients coming from endemic areas may be appropriate even in the absence of the use of multiagent chemotherapy.

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