Sezary Syndrome: A Case Study of Cutaneous T-Cell Lymphoma

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Cutaneous T-cell lymphomas (CTCLs) are a diverse group of neoplasms that affect the skin. Mycosis fungoides and Sezary syndrome are the most common forms of CTCL, with Sezary syndrome being the more aggressive type (Leukemia and Lymphoma Society, 2008). A total of 4,783 new cases of CTCL were identified from 1973–2002; 72% were mycosis fungoides and 25% were Sezary syndrome (Criscione & Weinstock, 2007). The incidence of CTCL is increasing by 2.9 cases per million people per decade; the increase could be a result of changes in classification or improvements in diagnosis. CTCL incidence is about 50% greater in African Americans than Caucasians, and men are affected twice as often as women (see Figure 1). Unlike other forms of CTCL, the incidence of Sezary syndrome is higher among Caucasians than African Americans (Criscione & Weinstock). CTCL incidence increases with age, with the greatest increase occurring at age 70 or older (Criscione & Weinstock) (see Figure 2). This column will use a case study of a patient with Sezary syndrome to focus on the background of the syndrome, signs and symptoms, and new approaches to treatment.

Signs and Symptoms

The initial onset of CTCL often is difficult to diagnose because of its similarity to many other nonmalignant skin pathologies (Trautinger et al., 2006). Sezary syndrome is characterized by an extensive red pruritic rash and, sometimes, sloughing of the skin (Leukemia and Lymphoma Society, 2008). Palms and soles often are thickened, scaly, and fissured. In addition, patients with advanced disease may develop alopecia, nail dystrophy, and eye changes (Hwang, Janik, Jaffe, & Wilson, 2008). Sezary syndrome also has been characterized by the presence of 5% or more malignant T cells with cerebriform nuclei or Sezary cells of peripheral blood lymphocytes. In May 2007, the International Society for Cutaneous Lymphoma proposed that the diagnosis of Sezary syndrome should be made with molecular and flow cytometry based on a large clonal population of abnormal T cells in the blood in addition to erythroderma of 80% of the body or more (Hwang et al.).

Treatment

CTCL treatment is determined by the type and stage of the disease. Treatments are divided into two types: skin-directed and systemic treatments. Options include phototherapy, radiation, topical therapy, systemic single-agent chemotherapy, combination chemotherapy, and combined therapies. Commonly used topical therapies include chemotherapeutic agents (e.g., nitrogen mustard, retinoids). Topical treatments such as phototherapy and corticosteroids generally are used in early stages; systemic treatments, combination therapies, and chemotherapy are reserved for advanced-stage disease. The U.S. Food and Drug Administration has approved the following systemic agents for treatment of CTCL: denileukin, bexarotene, and vorinostat. Patients with localized early-stage disease typically are treated with topical agents, skin-softening agents, anti-itch agents, and phototherapy (Trautinger et al., 2006). Clinical trials should be considered for patients with CTCL.

Case Study

M.O., a 28-year-old African American woman, presented to the National Cancer Institute (NCI) with a history of stage IV CTCL. Her symptoms began in 2003 when she experienced itching on her hands and feet during her second pregnancy. Each week, more skin became affected and progressed to peeling, with increased edema and scalp alopecia. In September 2003, M.O. was given a high-dose steroid regimen by her family practitioner to resolve the edema of her hands and feet. Her symptoms increased when the steroids were tapered, so the steroid dose was escalated. Two months later, M.O. developed significant edema to the hands and feet. She then consulted a dermatologist and was diagnosed and treated for severe eczema. Treatment proved ineffective, as M.O. developed staphylococcal infections. The infections caused oozing ulcerations that were localized to her hands and feet but soon spread to the legs, causing widespread bright-red skin and edema. Multiple skin biopsies were inconclusive. Despite her condition, M.O. successfully delivered a full-term baby by cesarean section in 2004.

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About a year later, M.O. developed lymphadenopathy and bilateral pulmonary emboli. A right inguinal biopsy revealed non-Hodgkin lymphoma. M.O. had several skin biopsies, which showed infiltrating T lymphocytes consistent with mycosis fungoides. M.O. then received three cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) over a five-month period in 2005, with an initial stable response by computed tomography (CT) scan measurement. The treatment was discontinued after the third cycle because of multiple treatment-related side effects, including left ear hearing loss. At that time, M.O. was treated with gemcitabine. She received only one cycle before Sezary cells were detected with peripheral blood cytometry and progressive disease was diagnosed by CT scan. An additional right inguinal biopsy showed involvement of T-cell lymphoma with Sezary syndrome. M.O. then was referred to NCI for additional investigational drug treatment options. She was enrolled and treated on three different protocols over nine months in 2006. Treatment included a bexarotene standard-of-care regimen, a phase II immunotoxin trial with a mixed response. M.O. then was referred to the NCI Developmental Therapeutics Section phase I trial clinic for additional treatment options.

M.O. presented with a complex medical history, including bilateral pulmonary emboli, methicillin-resistant staphylococcus aureus and vancomycin-resistant enterococcus colonization, clostridium, colitis, sepsis, bacteremia, gastroesophageal reflux disease, and nausea and vomiting from prior chemotherapies. She also had bilateral lower-extremity skin infections, hydrocortisone-mediated adrenal insufficiency, and a history of left ear conductive hearing loss induced after treatment with CHOP. Other symptoms included depression, hypersensitivities, and insomnia; M.O. reported a nightly average of about four hours of sleep.

M.O. was enrolled in the multi-institutional adult phase I investigational study of IV fenretinide (4-HPR). The agent is a synthetic insoluble retinoid compound that is suspended in a fat emulsion and administered as a continuous IV infusion via a central venous catheter or peripherally inserted central catheter. Fenretinide is cytotoxic in various cancer cell lines, including neuroblastoma, leukemia, and lymphoma, as well as colorectal, head and neck, breast, prostate, lung, ovarian, cervical, and pancreatic cancer (Mohrbacher et al., 2007). In this trial, fenretinide was given as a continuous IV infusion over five days on a 21-day cycle.

Prior to therapy, M.O.’s baseline tests included CT scan, dermatologic staging and evaluation, and peripheral blood flow cytometry. M.O.’s initial dermatologic staging indicated that she had
100% diffuse total body erythema, with significant scaling and pruritis throughout the trunk, face, and upper extremities as well as fissuring and malodorous drainage to the lower extremities. Her baseline CT scan showed hepatosplenomegaly and significant cervical, axillary, and inguinal adenopathy. Peripheral blood flow cytometry was positive for Sezary cells.

M.O. began the first therapy cycle, and a CT scan of the chest, abdomen, and pelvis was repeated at the end of every two cycles. Peripheral blood flow cytometry and dermatologic physical evaluation were performed and photographs were taken at the completion of every two cycles.

After two treatment cycles (42 days), M.O. achieved an unconfirmed partial tumor response by CT scan. A partial response is defined as a reduction of more than 50% of measurable lesions. M.O.’s peripheral blood flow cytometry also showed no immunophenotypical evidence of CTCL. Dermatologic evaluation showed dramatically decreased erythroderma with a few patches of normal-colored facial skin and finer generalized scaling. M.O. also reported a significant improvement in pruritic symptoms.

Subsequent treatment cycles showed additional improvement. After four cycles, M.O. achieved a 75% decrease in the diameter of measurable lymph node lesions compared to baseline. Per protocol, the percentage reduction qualified her with an unconfirmed complete response. M.O. obtained a confirmed tumor response with the completion of the sixth treatment cycle. As of 2008, M.O.’s dermatologic examination showed an overall smooth skin surface with no evidence of pruritic plaques or erythema (see Figure 3).

Skin lesion immunohistochemical stains also showed no definitive evidence suggestive of CTCL. The findings and those of the CT scan were consistent with complete tumor response. After receiving a total of 26 treatment cycles, M.O. was taken off study treatment in June 2008. M.O. reported a dramatic improvement since the start of treatment; she currently is a stay-at-home mother who is planning to re-enter the workforce. M.O. feels healthy and has resumed all normal activities. She was encouraged to contact the research team at the first sign of any dermatologic symptoms. M.O. remains on study for quality of life for patients with Sezary syndrome.

**Conclusion**

Sezary syndrome is a complex disease that presents a substantial diagnostic challenge because of its similarity to other dermatologic processes (Leukemia and Lymphoma Society, 2008). Much progress has been made in pathologic classification and identification of the syndrome since 1998 (Trautinger et al., 2006). In addition, recent innovations in novel, targeted, and biologic therapies are showing promise for the treatment of the disease. The importance of participating in clinical trials should not be underestimated, as demonstrated by this case presentation. Increased understanding of the disease coupled with improved treatment modalities may translate into improved disease control and quality of life for patients with Sezary syndrome.

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**References**


**Additional Resources**

To learn more about workup and suggested treatment regimens for Sezary syndrome, visit www.nccn.org/professionals/physician_gls/PDF/nhl.pdf.