Infections in Oncology

INFECTIOUS COMPLICATIONS OF CUTANEOUS T-CELL LYMPHOMA

Petros E. Tsambiras, MD, Salil Patel, MD, John N. Greene, MD, Ramon L. Sandin, MD, MS, and Albert L. Vincent, PhD

From the Department of Medicine, Division of Infectious and Tropical Diseases (PET, SP, JNG, ALV) and the Department of Pathology (RLS) at the University of South Florida College of Medicine and the M. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla.

Introduction

Cutaneous T-cell lymphoma (CTCL) is the most common primary lymphoma of the skin. As with most cancers, survival depends on the stage of disease. Infection is a common complication of CTCL, contributing significant morbidity and mortality. We report a patient with severe, generalized mycosis fungoides (MF) complicated by recurrent skin infections, and we review the infectious complications of patients with CTCL.

Patient Report

A 52-year-old woman was diagnosed with MF after a 7-year history of granulomatous lesions of the skin. She was treated in the past with topical medications and intermittent courses of prednisone. At our center, a new pathologic diagnosis was confirmed by histopathology that showed the characteristic epidermotropism of CTCL, specifically, stage III MF. She had extensive plaque-like lesions and nodular lesions involving much of the skin. Extensive, thick, keratotic lesions were present on the bilateral soles (Figs 1 and 2) and palms. Foot involvement was severe, prohibiting normal ambulation. At diagnosis, the patient was hospitalized for ulcerations and foul-smelling discharge from many of her skin lesions that had not responded to treatment with oral ciprofloxacin and metronidazole at an outside hospital. Group B streptococcus was cultured from the lesions, which improved after treatment with 3 g of intravenous ampicillin/sulbactam given every 6 hours and 2 g of ceftazidime given every 8 hours. The patient also had no evidence of visceral disease. Radiation therapy was initiated using whole-body external beam radiotherapy. Over the next few months, she received 30 Gy to her left hand and both feet and 24 Gy to her hip and back lesions.

Four months after the initial infection with group B streptococcus, the patient presented with crusting and weeping of purulent fluid from multiple skin lesions. She also had a fever of 100.5°F. Wound cultures revealed methi-
cillin-resistant *Staphylococcus aureus* (MRSA). Following 5 days of treatment with 1 g of intravenous vancomycin every 12 hours and 500 mg of imipenem/cilastatin every 6 hours, the patient received 100 mg of oral minocycline twice daily for an additional 14 days with some improvement of her symptoms. During this admission, chemotherapy as treatment of MF was not used due to moderate to severe anemia and the inability of the patient to receive blood transfusions due to her religious beliefs.

One month later, the patient returned with a fever of 101.7°F and an increase in pain and drainage from multiple lesions. She had multiple ulcerated lesions on her hand, chest wall, back, inguinal region, and feet. The average lesion measured 2 × 3 cm with serosanguineous to purulent discharge. MRSA was grown again from cutaneous lesions. Treatment with 1 g of vancomycin every 12 hours and 600 mg of oral rifampin daily was begun. Intravenous vancomycin after several days was replaced by 1 double-strength tablet of oral trimethoprim/sulfamethoxazole taken twice daily. Though the patient was taking erythropoietin, she remained severely anemic with a hemoglobin level of 6.9 g/dL, and chemotherapy was still not a good option. During this hospitalization, her vital signs remained stable, and she underwent whole-body electron beam therapy. The patient also received whirlpool treatments and Domeboro soaks to help treat the lesions topically. With the chronicity of her disease and the inability to implement chemotherapy or further radiation therapy, the patient was discharged with home health supportive care and conservative treatment.

The patient returned 16 days later with a 1-day history of excruciating body pain and oozing lesions over her entire body. Her pain and symptoms were managed aggressively, but she became hypothermic with worsening respiratory status. She died a few days after admission.

**Discussion**

CTCL is the most common primary lymphoma of the skin, representing approximately 65% of all primary cutaneous lymphomas. CTCL affects men twice as often as women. It is composed of multiple variants, of which MF and Sezary syndrome are the most common. The majority of MF cases are diagnosed in the fifth and sixth decades, often following ambiguous symptoms that occur over the course of a few months to several years. With lack of strong scientific evidence linking retroviral or other viral causes, the etiology of CTCL as a whole is uncertain. Early skin lesions may mimic benign dermatitis, eczema, or psoriatic processes, delaying the diagnosis of the true neoplastic condition. Early patches are often located in a bathing-trunk distribution and may be pruritic or asymptomatic. Plaque lesions are often red to brown, well demarcated, and pruritic. Inflammatory infiltration leads to exfoliative dermatitis or erythroderma. Tumor lesions are violaceous, exophytic masses that are often described as mushroom-shaped. Tumors commonly undergo necrosis and ulcerate, leading to disfigurement and secondary infection.

The Sezary syndrome variant of CTCL, which is considered by some to be a leukemic variant of MF, is characterized by the classic triad of generalized erythroderma, lymphadenopathy, and leukemia.

The diagnosis of CTCL is based on a combination of clinical and histologic features. Light microscopy of skin sections remains the diagnostic gold standard. Although nonspecific changes may be noticed during the early patch phase, the characteristic histologic epidermotropism (atypical mononuclear cells in the epidermis) is more consistently observed in later plaque stages. Immunophenotyping often supports the diagnosis.
by revealing the loss of mature T-cell antigens (eg, CD7) in CD4+ cells. T-cell receptor gene rearrangement analysis via polymerase chain reaction identifies clonal gene rearrangement and is an important tool in early diagnosis of CTCL and its variants. To diagnose Sezary syndrome, atypical lymphocyte counts in the peripheral blood of greater than 5% are used, though some centers use up to 20% for their diagnostic criteria.

**Treatment**

The treatment plan for CTCL and its variants depend on the clinical stage of the disease. For limited patch/plaque disease, local treatment with topical agents, psoralen–UV-A (PUVA) therapy, or even local electron-beam therapy is preferred. In generalized disease, total skin electron-beam therapy is usually part of the treatment regimen, combined with other modalities such as topical therapies, interferon-α, photopheresis, and retinoids. Systemic chemotherapy with multiple agents (ie, cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]) is considered in patients with refractory disease or in those with severe extracutaneous or extranodal disease. Many centers now have a multidisciplinary approach that lends itself to more standardized approaches toward treatment.

**Infectious Association**

The infectious complications of CTCL are of paramount importance since they are involved in over 50% of deaths in patients with CTCL. The increased susceptibility to infection by patients with CTCL is partially due to disruption of the normal skin barrier. Immunosuppression in CTCL can be partly quantified by a progressive fall in the absolute numbers of residual normal circulating T cells. There is a marked increase in the CD4/CD8 ratio secondary to expansion of the malignant CD4+ cell population and a reduction in the normal residual CD8+ T cells. Disruptions in the integument occur with tumor infiltration and are often accompanied by ulceration, necrosis, and invasion of pathogenic bacteria. Hospital-related procedures such as skin or node biopsies and intravenous catheter placements are frequently identified as infectious portals.

In a retrospective study of 356 CTCL patients, 478 infections were documented, with the skin being the most commonly infected site by far, followed by blood and lungs. In addition to being most frequently infected, the integument has been reported as the source of sepsis in up to 80% of cases. Bacteremia and bacterial pneumonias have been described as the most common infectious causes of death in CTCL patients.

S. aureus has been consistently identified as the most common pathogenic organism recovered in cutaneous infections and bacteremias in CTCL patients. The long-standing opinion is that S. aureus infections result from profound immunosuppression; however, some researchers hypothesize that S. aureus superantigen may provide enough T-cell stimulation to lead to clonal expansion and may play a role in initiating and maintaining the CTCL disease process. This opinion has been clinically associated with the observation that in some patients, antibiotic treatment for S. aureus infection leads to decreased erythroderma and tumor size without other adjunct treatment. A high incidence of colonization with S. aureus similarly appears in many of the dermatologic conditions that often confuse the early diagnosis of CTCL (eg, benign dermatitis, psoriasis, and eczema). The preponderance of S. aureus infection in septicemia and cutaneous infection make its identification and treatment essential in CTCL patients.

With compromise of the immune system, blunted fever response may occur during presentation of sepsis and pneumonia, the most serious infectious complications in CTCL. In a retrospective study, 59% of bacteremias and 62% of pneumonias were associated with nosocomial etiology. In addition to S. aureus, Enterobacteriaceae and Pseudomonas aeruginosa have been reported as important pathogens causing pneumonias in patients with CTCL. This strengthens the observance that many CTCL pneumonias are nosocomial. Although sepsis by S. aureus is most frequent, the mortality associated with Gram-negative sepsis remains higher. In an early study by Posner et al, 4 out of 5 CTCL patients with Gram-negative bacillary sepsis (P. aeruginosa or Serratia marcescens) died within 48 hours compared to none of 20
patients with Gram-positive sepsis. The risk of death from bacteremia by Gram-negative bacilli compared with staphylococcus or streptococcus infections has been reported as 88% and 22%, respectively.

Beta-hemolytic streptococcus has also been frequently implicated in cutaneous infections in CTCL patients. Skin infections with herpes simplex and herpes zoster were the second most common overall cutaneous infection in a study by Axelrod et al. Disseminated cutaneous herpes infection occurs more frequently in advanced stages of CTCL. A common finding in CTCL is dermatophytes, though they rarely lead to widespread infection and disability in patients with CTCL. There have also been reports of cutaneous infection with Histoplasma capsulatum and Candida in CTCL patients.

Due to the depletion of normal circulating T cells, patients with CTCL have been reported on occasion to have patterns of infection and secondary complications similar to patients with AIDS. Increases in secondary malignancy and Kaposi’s varicelliform eruptions have been reported. Also, Pneumocystis carinii, Cryptococcus, Aspergillus, and Toxoplasma infections have been infrequently encountered in the literature. Grossman et al. reported leprosy in a MF patient, where the authors posed the question of whether the MF in the patient was actually an epidermotropic T-cell response against Mycobacterium leprae bacilli antigens.

If addressed early, the majority of community-acquired infectious complications in patients with CTCL generally respond to oral antibiotics. With the segregation of complicated disease processes to specialized, tertiary referral centers, the likelihood of infection with antibiotic-resistant organisms (MRSA in this patient) is higher and thus makes treatment of infections more difficult. Our patient’s symptomatic disease, coupled with the recurrence of resistant bacteria, highlights the need for a multidisciplinary approach to patient care. With hospitalization, the rate of nosocomial infections has been shown to correlate with invasive procedures. Many of the cutaneous complications are located at procedure sites. Since the mortality rate in CTCL patients is highest following sepsis, identification and treatment of common infections (e.g., cutaneous infection) are key in preventing progression. Vigilance in the preparation and maintenance of intravenous catheter sites and circulating T cells in patients with CTCL have been reported on occasion to have patterns of infection and secondary complications similar to patients with AIDS. Increases in secondary malignancy and Kaposi’s varicelliform eruptions have been reported. Also, Pneumocystis carinii, Cryptococcus, Aspergillus, and Toxoplasma infections have been infrequently encountered in the literature. Grossman et al. reported leprosy in a MF patient, where the authors posed the question of whether the MF in the patient was actually an epidermotropic T-cell response against Mycobacterium leprae bacilli antigens.

References