Folliculotropic Mycosis Fungoides as a Posttransplant Lymphoproliferative Disorder

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Abstract

Posttransplant lymphoproliferative disorder (PTLD) is a known complication of solid organ transplantation. The majority are B cell in origin and related to Epstein-Barr virus infection. T-cell PTLD is much less common; most are Epstein-Barr virus negative and have a worse prognosis. Primary cutaneous T-cell lymphoma (CTCL) as a presentation of PTLD is rare. CTCL has a less favorable prognosis in transplant patients compared with that in immune-competent patients. Herein, we report a case of a 13-year-old boy who developed folliculotropic mycosis fungoides, a rare subtype of CTCL, subsequent to renal transplantation. To our knowledge, this is the first report of this type of PTLD in a pediatric patient.

A 13-year-old Hispanic boy, who underwent renal transplantation 10 years ago, presented with a 2-year history of widespread psoriasiform plaques and a 6-month history of an asymptomatic hyperpigmented patch with numerous overlying comedones on his left chest (Fig 1). He also reported a 5-month history of hair loss consisting of a patch of alopecia with follicular plugging on his occipital scalp and concomitant loss of his left eyebrow and eyelashes. Past medical history was significant for a congenital solitary dysplastic right kidney diagnosed in utero. At age 2, the patient presented to the hospital with acute-on-chronic renal failure with severe hypertension and pulmonary edema requiring initiation of hemodialysis. At age 3, he underwent cadaveric renal transplantation. Epstein-Barr virus (EBV) serology before transplantation was positive. The transplant immunosuppressive regimen consisted of induction with basiliximab, as well as sirolimus, tacrolimus, and prednisone, as per protocol at the time of his transplantation. He continued taking the last 3 medications until presentation for his skin condition.

Lesional skin histopathology from the left chest revealed dilated follicles with an associated dense superficial and deep perifollicular lymphocytic infiltrate (Fig 2) with CD3 positivity. A clonal rearrangement in the T-cell receptor γ-chain gene was detected via polymerase chain reaction analysis of this skin sample.

Because of social issues and financial constraints, the patient was briefly lost to follow-up. Over the subsequent 7 months, the plaque on the chest thickened and ulcerated, and the psoriasiform plaques enlarged and became tender and pruritic (Fig 3). The eyebrow and eyelash alopecia persisted, whereas the occipital scalp lesion had enlarged and developed comedones in addition to the follicular plugging. Histopathologic analysis again revealed a perifollicular and perivascular lymphocytic infiltrate with folliculotropism. The CD3+ T-cell lymphocytes expressed a T-cell helper phenotype (CD4+). Rare scattered CD20+ cells were present.
EBV-encoded RNA staining was negative. T-cell clonality was again detected, and the diagnosis of folliculotropic mycosis fungoides (MF) was rendered. No extracutaneous disease was detected through computed tomography imaging or peripheral blood flow cytometry.

Immunosuppression was reduced secondary to the diagnosis of posttransplant lymphoproliferative disorder (PTLD). The decision was made to initially discontinue sirolimus in the short term because the patient had ulcerations, and sirolimus has been shown to impede wound healing compared with tacrolimus.1 Although sirolimus has antiangiogenic and antitumor properties mostly associated with inhibition of the growth of EBV-transformed B lymphocytes in vitro,2 there have been no conclusive prospective studies addressing the use of sirolimus in the treatment or prevention of PTLD. In this patient, the approach to reduce immunosuppression was individualized and, given that his PTLD was non–EBV-related, along with the existing significant social and financial barriers, the decision was made to continue the more affordable tacrolimus and prednisone. Photochemotherapy with UV-A and psoralen was initiated, along with bexarotene 1% gel for the plaques. The patient has been followed for 37 months. He has maintained partial clinical remission, with resolution of the chest ulceration and psoriasiform plaques (Fig 4), but he continues to experience occasional follicular papules. Although his skin has improved, the clinical course has been complicated by episodes of graft rejection (grade IB histologically), manifesting as elevations in creatinine and a positive donor-specific antibody. He has been treated with pulse methylprednisolone and monthly intravenous immunoglobulin. The most recent renal biopsy revealed no evidence of cellular or humoral rejection but showed signs of chronic damage likely secondary to chronic allograft nephropathy.

**FIGURE 1**

**DISCUSSION**
Although infrequently encountered, PTLD is the most common malignancy in pediatric solid organ transplant recipients, occurring in 2% to 4% of renal transplant patients.3,4 PTLD most commonly presents with lymph node involvement followed by the gastrointestinal tract, kidney allograft, and the central nervous system.4 Graft dysfunction is a rare but known manifestation of systemic PTLD, especially if PTLD involves the allograft or causes compression of the graft or surrounding structures. Renal transplant recipients with allograft involvement of PTLD often present with renal dysfunction, hydronephrosis secondary to obstruction, and increased serum creatinine.

Cutaneous presentation of PTLD is extraordinarily rare, with <100 cases published in the literature to date.5 The risk of developing PTLD increases with duration and degree of immunosuppression, but data on the risk posed by individual immunosuppressive drugs are conflicting.6,7 PTLDs have 2 peaks of onset after organ transplantation: early and late. The majority of PTLDs are B cell in origin, related to EBV infection, and present early, usually
within the first year posttransplantation. Early PTLD is more likely to be polymorphic and have a higher likelihood for allograft involvement and has a better response to immunosuppression reduction. T-cell and T-/natural killer–cell PTLDs are much less common; most of these present as late PTLD, which is more commonly EBV-negative, and occur after the first year after transplantation. Late PTLD is usually monoclonal and widespread, responds poorly to immunosuppression reduction, and has a worse prognosis. In 1 review, T-cell PTLD was found to be more common in renal transplant patients: 69% of the 130 cases of T-/natural killer–cell PTLD reviewed were in kidney transplant recipients.

Although EBV-seronegative recipient status is a reported risk factor for developing PTLD, a review of PTLD in pediatric kidney transplant recipients found that T-cell PTLD occurred only in patients who were EBV-seropositive before transplantation as in our case patient. Organ transplant recipients are at increased risk of skin cancer due to chronic immunosuppression. The incidence of nonmelanoma skin cancer, melanoma, and Kaposi sarcoma is significantly increased in the renal transplant population relative to the general population. Primary cutaneous lymphoma (CL) as a presentation of PTLD, however, is extremely rare, with conflicting data regarding which subtype (B cell or T cell) predominates. According to a recent multicenter case series by Seçkin et al, cutaneous T-cell lymphoma (CTCL) was found to be more common than primary cutaneous B-cell lymphoma, representing 68.6% of cases of primary cutaneous PTLD. This finding conflicts with a previous report suggesting that cutaneous B-cell lymphoma is more common. A review by Ravat et al of 23 cases of posttransplant CTCL found that a majority were in kidney transplant recipients. The youngest patient in their review was 15 years of age. On the basis of these few reports, the prognosis for PTLD CTCL is considered less favorable than for CTCL of comparable stage and subtype in immunocompetent patients. Specifically in transplant patients, prognosis has been reported to be similar to that for systemic T-cell lymphoma.

MF is the most common type of CTCL and accounts for 44% of all primary CL cases. Folliculotropic MF is a rare subtype, accounting for ~4% of primary CLs. There has been only 1 previous report from the United States, by Vlassova et al, of

FIGURE 2
A. Dilated follicular infundibula with large orthokeratotic plugs and associated dense superficial and deep perifollicular lymphocytic infiltrate (hematoxylin and eosin staining; original magnification ×4). B. Extension of lymphocytes into the follicular epithelium (hematoxylin and eosin staining; original magnification ×10).

FIGURE 3
Seven months after presentation. A and B, Ulceration of the plaque on the chest. C, Enlargement of the psoriasiform plaques (leg). D, Worsening scalp alopecia with follicular plugging.
Folliculotropic MF in a 46-year-old man diagnosed 2 years after receiving an unrelated living-donor renal transplant. Unlike our patient, EBV staining was detected in the lymphocytic infiltrate of lesional skin. A more recent multicenter European series reported that 4 of 35 (11.4%) cases of primary cutaneous PTLD presented as folliculotropic MF; these patients ranged in age from 43 to 69 years. These data suggest that folliculotropic MF may occur at a higher frequency in posttransplant patients than in the general population.

Folliculotropic MF has been identified as a distinct variant of MF in the most recent World Health Organization/European Organization for Research and Treatment of Cancer classification for CLs because of distinct clinical, pathologic, and prognostic outcomes. Skin findings include grouped follicular or acniform papules, including clustered comedones, nodulocystic lesions, pustules, and milia, as well as indurated plaques or tumors. Representative skin lesions typically involve the head and neck, unlike classic MF, which usually affects the sun protected areas of the trunk and buttocks (“bathing suit distribution”). Eyebrow involvement with plaques and alopecia is particularly representative, as is severe pruritus. One review of 43 patients with folliculotropic MF found that if truncal involvement was present, follicular accentuation and follicular papules and nodules were frequently seen. Our patient’s clinical findings were consistent with the described presentations of this rare disease.

Histologically, several patterns have been recognized and reported. Folliculotropism with atypical CD3+, CD4+, CD8+ T lymphocytes is most typically observed. Mucinous degeneration of the follicle is often present; however, the presence or absence of mucin has been found to have no bearing on the clinical presentation or disease course. Our patient had no histopathologic evidence of follicular mucinosis. It is important to note that given the deep perifollicular location of the atypical lymphocytic infiltrates, folliculotropic MF may be less responsive to skin-targeted therapies. The prognosis has also been reported to be worse than that of classic plaque-stage MF. In fact, it has been suggested that patients with folliculotropic MF of any presentation should all be treated as though they have tumor-stage disease. However, a recent case series found that folliculotropic MF as PTLD has a more indolent course, with all of the patients in the series alive at a median follow-up of 87 months. Our patient has been followed for 37 months and despite near complete remission of his CTCL, his recent course has been complicated by episodes of acute graft rejection. Treatment is challenging due to the need for immunosuppression to prevent graft rejection, with fine adjustments to prevent worsening of his lymphoproliferative disease. Our case is noteworthy because it represents the youngest patient reported in the literature presenting with this rare form of folliculotropic CTCL as a PTLD. Given the less favorable prognosis of T-cell, EBV-negative PTLD, our patient requires continued close follow-up, monitoring, and treatment.

It is important for the general pediatrician who may be caring for posttransplant patients to be vigilant for the detection of malignancies in this at-risk population and to request early evaluation by a dermatologist for any new skin lesions to allow for early diagnosis of PTLD.

**ABBREVIATIONS**

CL: cutaneous lymphoma, CTCL, cutaneous T-cell lymphoma
EBV: Epstein-Barr virus
MF: mycosis fungoides
PTLD: posttransplant lymphoproliferative disorder

**REFERENCES**


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Pediatrics originally published online August 17, 2015;
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Pediatrics originally published online August 17, 2015;

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