Malignancy After Solid Organ Transplantation: An Overview

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Disclosure: This article discusses the use of acitretin (manufactured by Connetics) for prophylaxis of non-melanoma skin cancers; cyclophosphamide* (Bristol-Myers Squibb), adriamycin* (Pharmacia), prednisone* (Pfizer), vindesine (Lilly/EG Labo; not available in the U.S.), rituximab* (Genentech), and monoclonal anti-IL-6-antibody (multiple manufacturers) for post-transplant lymphoproliferative disorder (PTLD) (clinical trial); vincristine* (Lilly/Gensia Sicor) and bleomycin* (Bristol-Myers Squibb) for PTLD and Kaposi's sarcoma (KS); liposomal daunorubicin (Gilead) for KS (indicated for HIV-associated KS); paclitaxel (Bristol-Myers Squibb) for KS (indicated for AIDS-associated KS); imatinib (Novartis) and bevacizumab (Genentech) for KS; and matrix metalloproteinase inhibitor COL-3 (CollaGenex) for KS (clinical trial). (*Drugs marked with asterisks are indicated for use in malignant lymphomas generally, but no specific mention is made of PTLD.) No potential conflicts of interest were reported by the authors, planners, reviewers, or staff managers of this article.

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the most common malignancies encountered after solid organ transplantation.
2. Discuss the pathogenesis of malignancy after solid organ transplantation.

The patient underwent an open-lung biopsy that confirmed the diagnosis of idiopathic pulmonary fibrosis. He was assessed for lung transplantation. An extensive pretransplant

CASE PRESENTATION

A 49-year-old man with no prior medical history initially presented with severe dyspnea progressive over 6 months.

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evaluation included a negative HIV antibody test and a negative cytomegalovirus quantitative polymerase chain reaction (PCR). The patient’s Epstein-Barr virus (EBV) antibody profile was consistent with previous EBV infection (viral capsid antigen [VCA] IgG positive, VCA IgM negative, Epstein-Barr nuclear antigen positive, early antigen IgG positive). The patient underwent bilateral orthotopic lung transplantation.

Immediately post-transplantation, the patient’s dyspnea resolved, and he was started on azathioprine, prednisone, and tacrolimus for immunosuppression. Five months following transplantation the patient’s dyspnea recurred. A computed tomography scan revealed new, bilateral pulmonary nodules (Fig. 1). A thorascopic wedge biopsy of the right lung was obtained with pathology revealing tumor nodules composed of numerous, irregular vascular spaces with spindle cells displaying abundant mitoses (Fig. 2A, B). The tumor cells stained positive for CD31 (Fig. 2C) and human herpesvirus 8 (HHV-8) (Fig. 2D) by the immunoperoxidase method. A serum assay for HHV-8 by PCR was positive, but PCR for EBV was negative. The patient was diagnosed with Kaposi’s sarcoma (KS). This is the second reported case of a patient with lung transplantation who developed KS in the lung graft.

INTRODUCTION
Over 27,000 solid organs were transplanted in 2005 in the U.S., and 94,000 patients were waiting for solid organ transplantation [1]. The number of transplants has been steadily increasing over the past 10 years. With more patients surviving longer after solid organ transplantation, clinicians must be aware of long-term, post-transplant complications, including malignancy after transplantation. The U.S. Organ Procurement and Transplantation Network (OPTN) and the Scientific Registry of Transplant Recipients reported a 0.4% incidence of de novo post-transplant solid tumors in 2005, though the actual incidence is likely higher because of a lack of complete follow-up, limitations of voluntary reporting, and exclusion of post-transplant lymphoproliferative disorder (PTLD) reporting [1]. Studies have reported the cancer incidence in the kidney transplant population to be as high as 40% in patients 20 years after transplant; this is compared with a 6% cumulative risk for cancer in an age-matched, nontransplanted control population [2]. Malignancy is the reported cause of death in up to 26% of kidney transplant recipients who survive for at least 10 years [3]. The most common malignancies encountered in the post-transplant setting—and those on which this review focuses—are nonmelanoma skin cancers (NMSCs) (up to 82% of transplant recipients), PTLD (1%–11%), and KS (6%) [4–6]. Others, including non-Kaposi’s sarcomas and gastrointestinal, urogenital, and thoracic tumors, have also been reported [7–10].

NMSC

Epidemiology
NMSC is the most common malignancy to develop after solid organ transplant, especially after kidney transplantation [11–13]. Squamous cell cancer (SCC) is the most common subtype, with an incidence 65–250 times higher than that of the general population [5, 11, 14–16]. The incidence of SCC increases with the length of post-transplant follow-up, thereby supporting the argument that the development of SCC is associated with cumulative exposure to immunosuppressive agents [17]. SCC is an aggressive disease in transplant recipients [18, 19]. Half of those who develop NMSC are likely to develop a second NMSC within 3.5 years, with men having a significantly higher risk for recurrence than women [14]. A poor prognosis is associated with the presence of multiple tumors, tumors on the head, extracutaneous tumors, older age, poor histologic differentiation, tumor thickness of >5 mm, and invasion of underlying tissue [5].

Pathophysiology
Greater sun exposure and fair skin type play an important role in skin cancers after transplant, because UV-induced p53 tumor-suppressor gene mutations have been demonstrated in NMSC tissue from transplanted patients [11, 20, 21]. As with most tumor types arising after solid organ transplantation, immunosuppression is often cited as the primary culprit because immunosuppressed patients are susceptible to infection with viruses such as EBV, herpes simplex, herpes zoster, and polyoma, all of which have been implicated in oncogenesis [22].

Prevention and Treatment
Transplant recipients should be warned as to the dangers of sun exposure. They should undergo full skin exams by their transplant care provider. Studies have demonstrated a benefit to systemic retinoid chemoprophylaxis in transplant recipients. One such randomized, controlled study investigated the effect of 6 months of acitretin in 44 renal transplant recipients [23]. A relative decrease in keratotic skin lesions of 13.4% was seen in the acitretin group, compared with a 28.2% increase in the placebo group. Kovach et al. [24] reviewed nine studies describing 111 solid organ transplant recipients who received oral retinoids as chemoprevention for post-transplant skin cancers. Although significantly fewer skin cancers were reported while patients received oral retinoids, a rebound effect of a higher number of NMSCs and...
keratotic lesions shortly after oral retinoid therapy was discontinued was seen in multiple studies. Larger studies are needed to determine the doses, length of therapy, and long-term effects of oral retinoids.

After development of skin cancer, patients should be treated aggressively because of the high risk for metastasis, recurrence, and death. Standard therapies include Mohs micrographic surgery, superficial ablative therapy, cryotherapy, and photodynamic therapy [25]. As with most other transplant-related malignancies, attenuation of the immunosuppressive regimen is useful for controlling tumor progression. Consensus guidelines for immunosuppression reduction have been developed by the International Transplant Skin Cancer Collaborative and Skin Cancer for Organ Transplant Patients Europe Reduction of Immunosuppression Task Force [26]. These guidelines present several scenarios in which mild, moderate, or severe immunosuppression reduction would be appropriate [26].

PTLD

Epidemiology

The term PTLD refers to a disease spectrum ranging from infectious mononucleosis to malignant lymphoma and resulting from uncontrolled lymphoid growth in an immunosuppressed transplant recipient [27, 28]. In adult solid organ recipients, PTLD has been reported in up to 2.3% of kidney transplants, 2.8% of liver transplants, 6.3% of heart transplants, 5.8% of heart–lung transplants, and 20% of small bowel transplants [27]. PTLD is the most common post-transplant malignancy among pediatric transplant recipients [29]. Indeed, transplantation at <18 years of age and male gender are independent risk factors for developing the disease [30]. In a study of >200,000 transplant recipients included in the Collaborative Transplant Study international database, the incidence of lymphoma was highest in the first year post-transplant, particularly for patients receiving lung or heart–lung transplants [31].

Over a 10-year period, the transplant recipient’s risk of developing lymphoma is 11.8 times that of the general population [31].

Pathophysiology

PTLD has been grouped by the World Health Organization into morphological categories (Table 1) [32]. Early lesions are most often seen in children or young adults and usually occur within the first year post-transplantation, while the second and third groups are seen later post-transplantation [27].

Immunosuppression is an important risk factor in the development of PTLD, though questions remain as to whether the specific immunosuppressive drug or immunosuppression, per se, is to blame. For instance, an Italian study found that HIV-infected patients demonstrated a similar pattern of cancer risk as solid organ transplant recipients [33]. Impaired immune function might lead to the proliferation of abnormal cells that might have otherwise been eliminated with normal immune surveillance [22]. Immunosuppressive drugs such as cyclosporine might further contribute to this process. A study by Libertiny et al. [34] examined the incidence of PTLD among 1,537 renal transplant patients. In 1975–1984, prior to the widespread use of
cyclosporine as immunosuppressive therapy, only one patient was diagnosed with PTLD. In 1984–1998, when the use of cyclosporine became more prevalent, 34 patients were diagnosed with PTLD, indicating a link between the drug and the development of malignancy. Multiple studies have demonstrated an association between the onset of lymphoma and the use of OKT3, tacrolimus, and high-dose cyclosporine [6, 31, 35, 36].

The molecular pathogenesis of PTLD is most likely a result of the combined effects of immunosuppressive agents and infection by oncogenic viruses such as the EBV [37]. In an uncompromised host, EBV-infected cells are killed by EBV-specific cytotoxic T lymphocytes (CTLs). In an immunosuppressed transplant recipient, however, EBV-infected cells may proliferate beyond the ability of CTLs to clear them [27]. Subsequently, constant lymphocytic stimulation in the setting of a foreign allograft, either in the presence or absence of EBV, may be important in the development of mutations and eventual malignancy [22].

In addition to EBV, the presence of genetic or epigenetic mutations can also lead to the development of PTLD: molecular alterations of BCL-6, c-MYC, and p53, DNA hypermethylation, and aberrant somatic hypermutation have been implicated in PTLD [37].

EBV infection also appears to play a temporal role in PTLD outcomes. Early, polymorphic lymphomas are usually EBV positive and respond well to immunosuppression reduction [31, 37]. Late-onset, monomorphic disease is usually EBV negative, unresponsive to immunosuppression reduction, and associated with a worse prognosis [31, 38]. The pathophysiology for such late cases is unclear, but they may be a result of unidentified viral agents, loss of EBV, or incomplete diagnostic techniques [38, 39]. The increased division of lymphocytes caused by EBV infections yields an increased rate of new mutations. One of these mutations may lead to the replication of the cell independent of the presence of EBV. Over time, the EBV virus is lost, and the non-EBV–driven cells replicate in an unregulated manner.

Of note, donor-derived PTLD has also been reported, particularly in the setting of disease localized to the allograft. The pathophysiology behind this mode of transmission is not completely clear. Healthy donor lymphocytes might be infected by an EBV-positive organ donor, or EBV-infected donor lymphocytes might enter the immunosuppressed host via the graft and proliferate [40]. Patients with donor-derived PTLD may have a better outcome than those with recipient-derived PTLD [41].

**Clinical Presentation and Diagnosis**

Clinically, PTLD has variable presentations not clearly dependent on subtype (Table 1). As with nontransplant-related lymphoma, the most common symptoms are nonspecific, including fever, lymphadenopathy, weight loss, abdominal pain, and splenomegaly [42, 43]. Rarely, patients present with multiorgan failure [43]. PTLD usually presents at extranodal sites, with the gastrointestinal tract being the most common site aside from the allograft itself [44]. As with most lymphomas, excisional biopsies should be obtained to allow for examination of architecture, and fine-needle biopsy should be avoided whenever possible.

<table>
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<tr>
<th>Classification</th>
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<td>Early lesions</td>
<td>Reactive plasmacytic hyperplasia</td>
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<td>Polymorphic PTLD</td>
<td>Infectious mononucleosis-like</td>
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<td>Monomophic PTLD (classify according to lymphoma classification)</td>
<td>B-cell lymphomas</td>
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<td>Diffuse large B-cell lymphoma (immunoblastic, centroblastic, anaplastic)</td>
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<td>Hodgkin's</td>
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<td>Hodgkin's</td>
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<td>Hodgkin's</td>
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<td>Hodgkin's</td>
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possible. Immunohistologic staining for EBV is vital for diagnosis [45].

Prevention
Because EBV has been implicated in the pathogenesis of PTLD, monitoring for the virus in serum has been considered as a means of prevention. Much of the work in this area has been done in the pediatric liver transplant population, because about 50% of these young patients are EBV seronegative at the time of listing [46]. A single-institution study prospectively compared the rates of PTLD in pediatric liver transplant patients before and after reverse transcription PCR EBV viral-load monitoring was instituted [47]. Prior to the monitoring of EBV levels, the institution’s incidence of PTLD was 16%. After 2001, patients who developed EBV loads >4,000 copies/µg DNA were treated with immunosuppression reduction. After immunosuppression reduction was instituted for increasing EBV load, the PTLD rate decreased to 2% (p < .05). Studies have used varying cut points of EBV load, and a value truly predictive of PTLD development has yet to be determined. Importantly, all patients who have elevated viral loads do not go on to develop PTLD [27, 48]. Antiviral therapies may be helpful in preventing PTLD. A multicenter case–control study matched 100 biopsy-confirmed, PTLD-positive renal transplant recipients to 375 healthy renal transplant recipient controls. In the first year post-transplant, the study found a 38% lower PTLD risk (odds ratio, 0.62; 95% confidence interval, 0.38–1.0) for every 30 days of ganciclovir treatment [49].

Treatment
The initial treatment for PTLD involves immunosuppression modification. In a report of 274 cardiac transplant recipients from the Israel Penn International Transplant Tumor Registry (IPITTR), the largest proportion of PTLD patients (42%) were solely treated with immunosuppression reduction [50]. Any patient who received immunosuppression reduction as a component of treatment had better survival than those who did not (32.3% versus 10.8%; p < .001). Survival was better yet for patients who received immunosuppression reduction in combination with surgery for localized disease [50]. Case reports suggest that using or changing immunosuppression to sirolimus, an inhibitor to the mammalian target of rapamycin, can induce complete responses (CRs) [42, 51]. Localized radiotherapy for PTLD has been reported in the form of adult and pediatric case studies, though no randomized data are available [52–54].

Chemotherapy forms the backbone of therapy when the tumor progresses through immunosuppression reduction, and the most frequently used regimen has consisted of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). In 2005, the IPITTR published their experience with 193 solid organ transplant patients who received chemotherapy for PTLD [55]. Forty-seven percent of the patients received CHOP, while 12% received single-agent therapy. The 5-year survival rate was 24% for those receiving CHOP and 5% for those receiving single-agent therapy [55]. A more recent—though much smaller—case series from 2007 reported a median follow-up of >8 years for 26 adults with PTLD treated with CHOP after initial progression [56]. The overall response rate (ORR) was 65%, the median overall survival time was 13.9 months, and the progression-free survival time was 42 months.

Because of this high rate of treatment-related morbidity and mortality, the use of less-toxic agents such as rituximab, an anti-CD20 monoclonal antibody, has become more common. Case series have described response rates with single-agent rituximab of around 60%, with multiple case reports demonstrating CRs [57–60]. A 2005 phase II study gave 11 patients with PTLD a weekly rituximab dose of 375 mg/m² for 4 weeks [61]. All patients had progressed through immunosuppression reduction. The ORR was 64%, similar to that of CHOP reported in other studies. Six patients obtained a CR with the median CR lasting 8 months. The treatment was well tolerated. Cytokine-based therapies with interferon-α and interleukin-6 antagonist have also been used to treat PTLD, though evidence is limited to studies treating <15 patients [62, 63].

Finally, adoptive T-cell immunotherapy, via infusion of EBV-specific CTLs in patients with EBV-positive PTLD, has shown promise as a therapeutic modality. A phase II study of 33 patients demonstrated a 52% 6-month ORR (14 CRs) with no treatment-related toxicity [64]. Other studies have shown similar promising results for both prevention and treatment, but no multicenter, randomized trial has yet been reported [65, 66].

KS

Epidemiology
Prior to the AIDS epidemic and the increase in solid organ transplantation, KS was rare, comprising only 0.02%–0.06% of malignancies [67]. However, the incidence of KS among solid organ transplant recipients is up to 500 times higher than that of the general population and has been calculated to affect 6% of solid organ recipients based on IPITTR data [4], though recent OPTN data demonstrate a lower overall incidence of 8.8 cases of KS per 100,000 person-years (54-fold higher than the general population) [68]. In the U.S. population, risk factors associated
with developing KS after solid organ transplantation include male gender, older age at transplantation, Hispanic race, and non-U.S. citizenship [68]. The median time from transplantation to diagnosis of KS is almost 1.5 years [68]. Cutaneous-only involvement is seen in 80% of cases, while visceral involvement is only seen 20% of the time [68].

**Pathogenesis**

The pathogenesis of KS is most likely related to viral infection. The first association between an infectious agent and the development of KS was made when HHV-8, also called KS-associated herpesvirus, was isolated from KS tissue obtained from AIDS patients [69]. Since then, in situ hybridization has localized HHV-8 viral gene expression to the KS spindle cell, thereby supporting the direct link between the virus and KS [70]. In the transplant population, a study of 400 renal transplant recipients showed that 32 had anti-HHV-8 antibodies at the time of transplantation. Among these 32 patients, 28% developed KS after 3 years while none of the patients without anti–HHV-8 antibodies developed KS [71]. In patients who are HHV-8 negative prior to transplantation, the means of HHV-8 transmission and infection are not completely clear. One study examined 100 transplant recipients who experienced HHV-8 new seropositivity from pre- to post-transplantation. Among those whose donor blood was available, none of the organ donors were seropositive for HHV-8, suggesting that the higher rate of seropositivity seen in the recipients was not a result of the graft [72]. Blood product transfusions and intimate contact have been implicated as means of transmission [72–75].

The mechanism by which HHV-8 induces oncogenesis has not been completely elucidated. HHV-8’s proinflammatory proteins might directly inhibit apoptosis and thereby promote cell transformation [76]. The virus might also modulate the major histocompatibility class I antigen-presentation pathway, making infected host cells invisible to CTL surveillance [76]. Finally, vascular endothelial growth factor (VEGF) and its receptors are known to be highly expressed in KS lesions and are likely growth factors for the KS cell [77]. An HHV-8 nuclear antigen has been shown to upregulate VEGF receptors, thereby promoting proliferation [78]. These effects, among others, likely contribute to HHV-8’s oncogenic potential in the already immunosuppressed transplant recipient.

**Treatment**

Surgical resection might be useful with isolated KS lesions [79, 80]. However, immunosuppression reduction is the most common primary therapy, with consistent reports of CRs resulting from this intervention alone [81, 82]. However, loss of grafts secondary to chronic rejection was also reported, thereby highlighting the delicate balance between risk and benefit associated with immunosuppression reduction.

The replacement of immunosuppressive drugs has also shown some promise. As with PTLD, cyclosporine has been associated with a higher risk of developing KS [81, 83, 84]. Switching to sirolimus might provide a useful alternative. An Italian study enrolled 15 renal transplant patients with biopsy-proven KS of the skin who were receiving cyclosporine [4]. The patients’ regimens were switched from cyclosporine to sirolimus. All the patients experienced a CR of the cutaneous KS lesions after 3 months of sirolimus therapy, and no acute rejection was observed. Other reports have supported the utility of sirolimus, though longer-term follow-up demonstrates disease recurrence despite continued sirolimus therapy [85–88]. To date, immunosuppression reduction has only improved outcomes for patients with cutaneous disease.

Recurrence after reduction or change in immunosuppression has been treated with chemotherapy. Until recently, anthracycline-based therapy comprised the mainstay of treatment. A retrospective study reviewed the efficacy of doxorubicin (20–30 mg/m²), bleomycin (10 mg/m²), and vincristine (2 mg) (ABV) administered every 3 weeks in five solid organ recipients who developed KS [67]. Four of the five patients responded (two partial responses [PRs], two CRs). The median duration of response was >13 months, and minimal toxicity was seen. This trial has been the only one to specifically assess the use of chemotherapy in transplant-related KS. The remainder of the data have been extrapolated from treating AIDS-related KS.

Multiple phase III trials have compared single-agent liposomal formulations of daunorubicin or doxorubicin with the more toxic combination regimens. The first such trial randomized 232 patients with AIDS-related KS to either 40 mg/m² of liposomal daunorubicin or ABV and showed a comparable ORR between the two regimens [89]. ABV patients experienced significantly more alopecia and neuropathy, while liposomal daunorubicin patients had significantly more grade 4 neutropenia. A second study gave liposomal doxorubicin to 53 patients with AIDS-related KS who had progressed through or were intolerant to combination therapy [90]. The study demonstrated a 36% PR rate and a median duration of response >4 months, helping to establish liposomal doxorubicin as a reasonable second-line drug. In 1998, a phase III trial randomized 258 patients with AIDS-related KS to liposomal doxorubicin or ABV, and reported a significant difference in the response rate between liposomal doxorubicin and ABV (45.9% ver-
sus 24.8%, \( p < .001 \), with toxicity profiles favoring the single agent [91]. Paclitaxel has also shown success in two phase II trials as a single agent in both the first and second lines of therapy. However, as with the anthracycline studies, neither studied transplant-associated KS. In the first trial, paclitaxel was initially administered to patients with HIV-associated KS at 135 mg/m² every 3 weeks. Of the 28 assessable patients, 20 had major responses (including one CR). Four responders had been previously treated through anthracycline therapy. Alopecia, grade 2 peripheral neuropathy, and diarrhea were the most common toxicities. In the second trial, 100 mg/m² of paclitaxel was administered every 2 weeks to 56 mostly untreated patients with AIDS-related KS, resulting in a 59% ORR, a 10.4-month median duration of response, and a 15.4-month median survival time [92].

Biologic agents will likely play a role in treating KS. Imatinib, a platelet-derived growth factor/c-Kit inhibitor, has shown promise in a small study [93]. While there are no data using antiangiogenic agents like bevacizumab, such agents are ripe for study because of the high expression of VEGF in KS tissue [88].

**CONCLUSION**

As more people receive organ transplants, the incidence of post-transplant malignancy is increasing. These patients present an even more complicated picture than the usual cancer patient because they bring with them the added burden of immunosuppression and its unwanted consequences. The cancers that develop in transplant recipients are often more aggressive than those that develop in their non–transplant-associated counterparts and thus warrant rapid escalation in therapeutic intervention. Transplant recipients should undergo frequent, regular cancer screening. New advances in immunomodulation and novel agents should continue to improve outcomes for this select group of patients. Table 2 summarizes the authors’ approach to treating these diseases.

**CASE PRESENTATION AND FOLLOW-UP**

After diagnosis of KS, our patient’s immunosuppressive regimen was switched to sirolimus, prednisone, and tacrolimus. The lung nodules progressed 11 months later. He received a single dose of liposomal doxorubicin before treatment was discontinued as a result of a worsening performance status. The patient died approximately 1
year after being diagnosed with KS. He was not tested for HHV-8 prior to transplantation. His somewhat unique presentation of KS in the lung graft raises the question of whether the graft tissue might have harbored latent HHV-8.

REFERENCES


