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Review

Malignancy in the Lung Transplant Population

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Abstract

The risk for developing a variety of malignancies is significantly elevated in the setting of lung transplantation. Malignancy remains among the three major causes of death in post-transplant recipients, and the relatively high risk of cancer development as well as metastatic aggression pose special threats to this population due to the need for continued immunosuppression. A variety of risks such as tobacco use and inflammatory lung diseases that led to the lung pathology prompting lung transplantation, in addition to immunosuppression and unique post-transplantat viral infections, introduce particularly high risks for carcinomas of the lung and head-and-neck, skin, endothelium (Kaposi sarcoma), colon and anogenital tracts, liver and kidneys. A uniquely high risk of developing non-hodgkins lymphoma or post-transplant lymphoproliferative disorder remains particularly challenging in this population. In this review, we discuss mechanisms leading to risk, details on malignancy presentation and characteristics, and special points on management and prevention in respective sections. In addition to highlighting key features, a major goal is to stimulate future advancements in the prevention and management of malignancy in this unique clinical setting.

Keywords

malignancy; lung; transplantation; immunosuppression; risks; lymphoma; carcinoma

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Introduction

The development of malignancy in the setting of transplantation is a major contributor to morbidity and mortality in the transplant population. It is characterized by a variety of contributory risks that range from pre-transplant organ pathology that contributes to neoplastic transformation (e.g., in chronic liver, lung, or kidney disease) often associated with chronic inflammation [1] to post-transplant risks such as immunosuppression, infections/inflammatory conditions, and other conditions [2]. A particularly challenging combination is the patient previously treated curatively for malignancy pre-transplant, and the risk of post-transplant immunosuppression induction in the growth/recurrence of occult metastases. This can impose "minimum time intervals" as guidelines for the required gap between treatment of a cancer and transplantation [2-4]. Finally, there is also the risk of transmission of occult cancer from the donor, wherein selective risk-taking is balanced with risk avoidance in donors with a history of remotely treated cancer, and depending on the nature and risk of occult metastasis to the donor organ [5]. In this review, we specifically focus on the spectrum, contributory factors, and approach to malignancy that develops in the post-transplant period in lung transplant recipients. We will begin with risk data as well as mechanisms, expand with a focus on post-transplant lymphoproliferative disorder, and discuss a variety of other malignancies along with management, survival/outcomes issues.

Cancer risk in the post- lung transplant recipient: Epidemiology

Cancer risk in general is significantly elevated in the setting of solid organ transplants. Moreover, malignancy remains among the three major causes of death in the post-transplant population [2]. In a large registry analysis using cohort data from the U.S. Scientific Registry of Transplant Recipients linking data on >175,000 solid organ transplants, the overall standardized incidence ratio (SIR) was 2.1 (95% CI 2.06 – 2.14) and the excess absolute risk of 719 per 100,000 person-years in the setting of an overall incidence of 1375 per 100,000 person-years [6]. Non-Hodgkin lymphoma (NHL), lung cancer, and liver malignancy remain among the solid tumors of highest incidence in this population; and both NHL and lung cancer have a particularly high incidence and risk (SIR 18.7 and 6.1, respectively) among lung transplant recipients [6].

Registry analyses also demonstrated high incidence rates for both infection-related malignancies (dominated by NHL and liver cancer) and non-infection related malignancies (dominated by lung and prostate cancers). In particular, diffuse large B-cell lymphoma remains the highest sub-type of NHL, with detectable EBV in tumor cells in most cases [6, 7]. With regard to the relatively high risk of lung cancer development among lung transplant recipients, while most are single lung transplants (SLT), smoking and COPD likely exert most significant contribution to the risk of transformation, with the majority of lung cancers arising in the remaining native lung [8, 9]. Overall, for patients >10 years post- lung transplantation, neoplastic disease accounts for about 17% of deaths [10]. Beyond NHL and lung cancer, liver and kidney malignancies remained the highest-incident solid tumors in the post lung transplant population.

General considerations on risk and mechanisms

In the post lung transplant setting, the most important general reasons for increased cancer risk include the presence of an immunosuppressive regimen (load and duration), the presence of oncogenic viral infections, the organ transplanted, and the summation of accumulated risks in the recipient. The variation in risk according to organ transplanted exists essentially in a pattern dominated by the organ transplanted: Thus, post-transplant kidney cancer has the highest risk in kidney recipients (i.e., ~ 8-fold risk relative to population background), and the analogous applies to lung or liver recipients. While for NHL or post-transplant lymphoproliferative disorder (PTLD; discussed further below), a many-fold risk over the background population applies to all solid organ recipients, greatest risks appear to be among heart and lung recipients [2].

In terms of immunosuppression, there are impairments in cellular immunity as well as an altered balance of humoral factors that may impair effector anti-tumor mechanisms. Impairment in T-cell surveillance and T effector mechanisms may be particularly important, whether in the presence or absence of contributions by oncogenic viruses (that may further promote tumor initiation and progression). Certain regimen-specific effects may also be unique, such as specific inhibition in DNA repair combined with increased TGFβ as well as endothelial growth stimulation in classical calcineurin inhibitors such as cyclosporine [11-13]. Anti-proliferative agents such as those inhibiting mammalian target of rapamycin (mTOR), including sirolimus or everolimus, might also have inhibitory growth effects on tumors once neoplastic transformation has taken place, and there is evidence of lower malignancy risk with such regimens [14-16]. Tacrolimus, on the other hand, is a more potent calcineurin inhibitor that inhibits cytokines such as IL-2 as well as T cell proliferation; and this common effect on cellular immunity imparts a tumor-suppressive milieu by all such agents.

Viral transformation is an important mechanism of malignancy induction during lung transplant immunosuppression. Unchecked viral replication may be linked to the initiation of immunosuppression as well, and evident in the rapidity with which certain viral-oncogenesis associated malignancies develop after transplantation [2, 17]. Those viruses include Epstein-Barr virus (EBV) involved in the pathogenesis of PTLD, Human Herpesvirus 8 (HHV-8), associated with Kaposi's sarcoma, Human Papillomavirus (HPV), associated with anogenital cancers as well as squamous skin cancers. In addition, hepatitis B and C pose additional risks for hepatocellular carcinoma in the post-transplant period.

Various humoral factors play roles in modulating cancer initiation and progression. Those involved in innate anti-tumor responses may include interleukins and interferons as well as complement; while important humoral factors in acquired anti-tumor immunity include antibodies against specific tumor antigens. The latter may kill tumor cells via complement activation or through antibody-dependent cell-mediated cytotoxicity (ADCC), whereby the antibody's Fc portion bridges with receptors on NK cells or macrophages that effect tumor-cell killing [18]. Often, tumor complex carbohydrate antigens may be the targets of such processes [19]. Cellular T-cell immunity probably plays a more robust role than that of humoral immunity in anti-tumor responses by the immune system: As such, inhibition in cellular immunity by immunosuppressive regimens may account for the development of malignancies (including viral-driven neoplasia) following lung transplantation, while the role of transplant immunosuppression in limiting anti-tumor humoral immunity in this setting is less well understood. Nevertheless, it is important to consider the

possibility that novel efforts to limit antibody-mediated rejection (AMR) and donor-specific antibody (DSA) responses in the post-transplant period [20] stand the possibility of interfering with acquired humoral responses against carcinomas in post-transplant recipients.

The spectrum of PTLD post lung transplant

The majority (>80%) of PTLD is comprised of a group of B cell lymphoproliferative disorders with variable clonal involvement and lymph node preservation versus destruction, while a much lesser incidence of the disease originates from T cells (~15%) or NK cells (~1%) [21]. Most adults have been EBV exposed, and thus most donor organs are EBV positive [22, 23]. In the setting of a relatively aggressive immunosuppressive regimen required post- lung transplantation, the development of EBV mediated transformation of B cells with progression to PTLD is particularly significant, especially in the relatively uncommon EBV-naïve host [24]. The major immunologic arm of protection from PTLD development in the immunocompetent EBV-infected host results from EBV-specific cytotoxic T cells; and the setting of altered T cell immunity following lung transplantation is thus a fertile microenvironment for the uncontrolled growth of EBV-infected B cells. Overall rates of PTLD following lung transplantation have improved to ~5% in more recent years [25-27]; however, this depends on factors such as improved prolonged anti-viral prophylaxis and viremia DNA detection assays, and immunomodulatory regimens [23]. Nevertheless, overall mortality from PTLD may still approach 50%, especially in the setting of late-presenting PTLD.

PTLD spectrum of presentation and prognosis

Four histologic variants of PTLD may be distinguished in the most recent (2008 WHO) classification [21]: In one variant, early plasmacytic hyperplasia, lymph node architecture remains preserved; while destruction of architecture is noted with polymorphic PTLD, characterized by a polyclonal infiltrate with cellular atypia. Monomorphic PTLD resembles NHL, with clonal B cells, T cells, and NK cells. On the other hand, classical Hodgkin's lymphoma has been described.

Early-onset PTLD (within first year post-transplant) typically occurs in the allograft; and pulmonary nodules, masses, or infiltrates may occur in the presence or absence of abdominal, CNS, or even cutaneous involvement. Early presentation is associated with primary EBV infection, CMV infection, increased rejection frequency, and induction agents at time of transplant [23, 28, 29]. Late onset PTLD (>1 year post-transplant) is more likely to present as extrathoracic disease, especially in the gastrointestinal tract. Diagnosis of PTLD requires sufficient tissue in a biopsy or surgical sample to evaluate histologic architecture, which is often sufficient in transbronchial or needle-core biopsies. Analyses of clonality and lineage tracing may be carried out with flow cytometry, while levels of plasma EBV assayed from whole blood appear to correlate with risk of disease and treatment response in established disease [21, 30].

Evolution in the management of PTLD

Immunosuppression adjustments and standard cytotoxic/ablative treatment: The first modality in the treatment of PTLD is reduced immunosuppression (RI), whereby calcineurin inhibitors may be reduced from 25-50% while low-dose prednisone is maintained in the absence of mycophenolate and azathioprine [21, 23]. While the majority of cases without multiorgan disease

or allograft dysfunction will remit within weeks, the risk of acute and chronic rejection is significant and requires tight monitoring [21, 31]. Occasionally, chemotherapy (typically CHOP regimen) +/- radiation (especially in CNS disease) may be required, and surgical tumor de-bulking may be required for obstruction (e.g., bulky chest- or colonic-obstructive disease) or bleeding. In CD20+ PTLD, rituximab is an effective option in those unresponsive to RI or showing progression; and thus CHOP or multi-agent therapy is often reserved for CD20- or EBV- disease or for aggressive PTLD sub-types [32, 33]. While the Ann Arbor system for lymphoma staging as well as the International Prognostic Index may be applied to PTLD to assist in prognosis, disseminated disease and presentation >6 months after transplant are predictors of mortality [34]. Nevertheless, for rituximab treated patients, remissions have been generally >50 - 60%, with median survivals of around 3 years [35, 36].

Therapies more recently under development include viral gene induction or infusion of cytotoxic T lymphocytes (CTLs). With particular regard to EBV-specific cytotoxic T cell approaches, targeting EBV-positive tumor cells may be achieved through infusion of CTLs from EBV-experienced donors, thus transferred adoptively. Potential off-target effects of the adoptive response, however, may impose challenges [23, 37]. Treatment with a proteosome inhibitor such as bortezomib, which also targets B cell lymphoma cells, is another strategy where pairing with rituximab has been considered [23]: More work is needed to assess the full efficacy of this combination over the individual drugs. Finally, it is also important to consider technology for early detection of PTLD, and possibly for recurrence of disease, wherein CD30 antibodies may be used as a monitoring tool; while measuring light chains to detect early B cell dysfunction/progression may be quantified in the circulation [38, 39].

Special considerations on the diagnosis of lung cancer following lung transplantation

As introduced, the risk of lung cancer remains significantly elevated in lung transplant recipients (with an incidence range of ~ 0.25% to as high as 4%). Smoking, older age, and underlying diagnoses of COPD or IPF are known to increase risk, with the vast majority of bronchogenic carcinomas (>90% non-small cell lung cancer) in single-lung transplant series developing in the native lung [21]. Bronchogenic carcinoma has been described in the explanted lung (incidence as high as 1.4% in one series [40]). Given the incidence, and since prognosis is especially poor (especially at clinical stage II or greater), it is important to screen at regular intervals in high-risk transplant candidates. Several forms of infection in post- lung transplant patients may commonly present with heralding symptoms, nodules, infiltrates, and other manifestations that can mask a primary lung malignancy (or metastatic disease) during workup. Given the elevated risk, it is thus especially important to consider malignancy with a high index of suspicion upon encountering such lesions in this population. Often, such lesions may be missed due to other radiographic factors such as postoperative changes or existing disease in the native lung [21].

Treatment for lung cancer in the post- lung transplant patient follows the state-of-the-art approach according to stage under the most current IASLC/AJCC recommendations [41]. A reduction in immunosuppression, however, is commonly applied; although this is without data to guide specific adjustment(s) and timing. Lesions are occasionally discovered at the time of

transplant, with surgical margin decisions and appropriate surgical correction with adjuvant adjustments made in the peri-transplant period.

Skin malignancies in the post lung transplant recipient

Cutaneous carcinomas develop with increased incidence in post-transplant population, with risk-ratios for squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) many-fold above that of immunocompetent hosts. In one study, malignant melanoma rates were 2.6 fold higher than the expected rate in the reference population [42]. Beyond sunlight exposure, cumulative voriconazole exposure, and previous cutaneous malignancy, risks factors include the nature and level of immunosuppression as well as some viral infections (including human papillomavirus (SCC), human herpesvirus 8 (Kaposi's sarcoma), and Merckel cell polyomavirus (Merckel cell carcinoma) (reviewed in [21]). It should be highlighted that a personal history of melanoma may be a strong relative contraindication to transplantation; with approximately 1/3 of post-transplant melanomas developing at the site of pre-existing nevi [43]. Beyond prevention with appropriate sun and UVA/B exposure reduction measures, the discovery of even early-appearing SCC-type (e.g., actinic keratosis) lesions in this population may require a biopsy to ensure invasive SCC is ruled out.

For SCC or BCC, treatment recommendations follow guidelines for the immunocompetent population, with excision +/- Mohs approaches, depending on risk, margins, and recurrence history; along with lymph node biopsy/staging and metastasis workup as appropriate examination reveals. While radiation may be used for invasive lesions and/or nerve involvement, chemotherapy is considered sparingly given risk/benefit concerns for adverse effects in the setting of post-transplant immunosuppression. Pre-cancerous lesions in single organ transplant patients in general may be approached with cryotherapy or electrocautery, or with topical (e.g. 5-FU, imiquimod) or photodynamic strategies [44-47].

Kaposi's sarcoma in the setting of lung transplantation

Kaposi's Sarcoma (KS) is a mesenchymal tumor originating from the cells of blood and lymphatic vessels that has been associated with Human herpesvirus 8, which likely contributes to the mechanism of KS in the transplant recipient. The virus can be reactivated from a latent persistent infection during immunosuppression (especially with use of calcineurin inhibitors), or may be transmitted to the recipient via the donor organ itself. KS primarily affects the skin but can cause disease in other parts, including the lung allograft without other systemic involvement. Case reports of KS include presentations with allograft nodules and hemorrhagic pleural effusion, with or without cutaneous involvement [48].

A multicenter, longitudinal study of over 4,700 solid organ transplant recipients in Italy showed that the overall KS risk was 125.3-fold higher than the general Italian population [49]. Indeed, origin from a high HHV8 sero-prevalence area appears to confer the greatest risk for the development of KS in the post-transplant patient [2]. The risk of KS also significantly increased with age (greater than 60 years compared to younger than 40 years), male sex, and lung transplant recipients (2.6-fold increase in incidence compared to kidney recipients). Over time, the incidence of KS decreased with a reduction of 80% after 18 months from transplantation.

Treatment of KS is dependent on the location of the lesions as well as the extent of involvement. Some patients show remission with reduction of immunosuppression alone, which is

typically the first therapeutic step [2]. Local treatments include surgery (ie. local excision), radiation therapy, cryotherapy, laser therapy, topical therapy, and intralesional injection of chemotherapy agents. Systemic treatments include chemotherapy, such as doxorubicin, vinblastine, and bleomycin, which are usually used for widespread and rapidly progressive KS.

Other malignancies and screening

In general, cancers with a particularly high risk in the post- lung transplant population include non-melanoma skin- and lip cancer, KS, NHL, lung, colorectal, and anogenital tract cancers [2, 6]. An Australian study also found a 9.3-fold increase in head and neck cancer incidence in heart and/or lung transplant recipients. A variety of "field-effects" by carcinogens or lung inflammatory conditions may markedly increase the risk for cancers of the lung as well as the head/neck prior to transplantation: This is in the setting of smoking (resulting in COPD) or chronic inflammatory lung disease (e.g., IPF) that result in the host's need for a lung transplant.

In addition to strict adherence to tobacco cessation, measures to screen for a variety of cancers in the post-transplant period are important to adopt during follow-up. One must be cautious in solid-organ transplant recipients, given the greater development of common solid-organ malignancies (including breast, prostate, lung, and colon cancers) in that population [50]. For example, post-transplant cancer screening guidelines (published most recently from the renal transplant literature) [51] include cervical cancer screening on an annual basis, with standard breast cancer screening (annual or biannual for women over 50 yr), and colorectal screening with yearly fecal occult blood testing and endoscopic examinations every 5 years. Skin screening should include monthly self-examination with total body reviews by a dermatologist every 6 to 12 months. Finally, prostate cancer screening with annual PSA and digital rectal examination for male recipients over 50 yr and hepatocellular cancer screening with 6-monthly α-fetoprotein and ultrasound examinations in high-risk individuals should also be included. While there are no formal guidelines for lung cancer screening in lung transplant recipients per se, Grewal and others [52] cite the relatively high risk of lung cancer in the lung transplant recipient and the importance of developing improved guidelines for screening in this area. For now, it is at the very least prudent to follow standard USPHTF recommendations regarding low-dose CT scanning for at-risk individuals based on pre-transplant tobacco exposure [53]. However, post lung transplant imaging schemes should take into account specialized surveillance for this high-risk/high-mortality malignancy. Finally, and more generally, it would be advantageous to have a program of immune-monitoring built into any screening program to facilitate the enrichment of sub-populations with especially high risk (and thus with improved probability of cancer detection).

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Competing Interests

None to declare.

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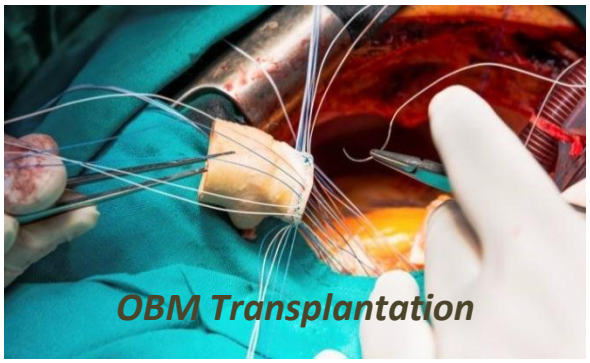

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