Complications of Immunosuppressive Therapy in Solid Organ Transplantation

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KEYWORDS

• Immunosuppression • Complications • Transplantation • Infections • Malignancy • Computed tomography • Posttransplant lymphoproliferative disorder (PTLD) • MR imaging

KEY POINTS

- Three drugs are commonly used in clinical practice to achieve immunosuppression (corticosteroids, mycophenolate mofetil, and tacrolimus/cyclosporine); mammalian target of rapamycin inhibitors and other novel drugs with more favorable adverse effect profiles and increased potency are increasingly being used.
- Drug-related metabolic side effects are commonly diagnosed from clinical and laboratory findings; imaging is pivotal in the detection and management of posttransplant infections and malignancies.
- A wide spectrum of opportunistic infections occurs in transplant cohorts because of associated immunosuppression. A high index of clinical suspicion, supportive laboratory findings, and imaging features, as well as imaging-guided biopsy/aspiration are invaluable in establishing the correct diagnosis and instituting timely treatment.
- There is an increased tendency for transplant cohorts to develop unique de novo malignancies, including human papillomavirus–associated squamous cell carcinomas and anogenital carcinomas, Epstein-Barr virus–related posttransplant lymphoproliferative disorder, and other virally induced cancers. Transplant cancers are generally associated with aggressive biology, poor response to chemotherapy, and resultant poor prognosis.
- Recent advances in immunology, virology, molecular genetics, and therapeutics have enabled better understanding of complications of immunosuppression, and have also facilitated development of so-called designer drugs to achieve adequate graft function and decrease the risks associated with lifelong immunosuppression.

INTRODUCTION

Solid organ transplantation (SOT) is the treatment of choice for patients with end-stage organ failure. More than 29,000 transplants are performed in the United States each year, with kidney being the most commonly transplanted organ, followed by liver, heart, and lung.[1] The ongoing success of transplantation, with graft survival rates approaching 90% at 1 year and 75% at 5 years, is mainly

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attributable to the availability of potent immunosuppressive drugs that prevent allograft rejection. However, long-term survivals following SOT have not improved because of several factors, including chronic rejection, cardiovascular diseases, and complications of chronic immunosuppression, such as infections and malignancies. The chronic use of immunosuppressive drugs in this cohort of patients leads to 2 categories of complications: (1) drug-related adverse effects such as renal dysfunction, hypertension, hyperlipidemia, and diabetes mellitus; and (2) infections and malignancies.[2] Common posttransplant opportunistic infections secondary to depressed immune system include viral (cytomegalovirus [CMV], herpes simplex virus [HSV], varicella-zoster virus [VZV], and Epstein-Barr virus [EBV]), fungal (*Candida* species, *Aspergillus* species, *Pneumocystis jiroveci*, *Cryptococcus neoformans*, and mucormycosis), bacterial (*Nocardia* species, *Legionella pneumophila*, *Listeria monocytogenes*, and mycobacteria), and parasitic (*Toxoplasma gondii* and strongyloidiasis). Nonmelanoma skin cancer, posttransplant lymphoproliferative disorder (PTLD), Kaposi sarcoma, anogenital cancer, lung cancer, renal cell carcinoma (RCC), and hepatocellular carcinoma (HCC) are the most common malignancies that develop secondary to chronic immunosuppression (**Box 1**). Although clinical features and laboratory findings are essential in diagnosing most drug-related metabolic side effects, cross-sectional imaging techniques such as ultrasonography, computed tomography (CT), 18-fluorodeoxyglucose (FDG) PET, and MR imaging play important roles in the initial diagnosis, treatment follow-up, and long-term surveillance of posttransplant infections and malignancies.

This article first describes mechanisms of action and side effects of commonly used immunosuppressive drugs in SOT. It then reviews the pathogenesis and cross-sectional imaging findings of common posttransplant infections and cancers and discusses the role of imaging in screening, diagnosis, and surveillance of these conditions.

Box 1
Complications of immunosuppressive therapy in SOT

Drug-related side effects

Renal dysfunction

Hypertension

Hyperlipidemia

Diabetes mellitus

Infections

Viral: CMV, HSV, VZV, and EBV

Fungal: *Candida* species, *Aspergillus* species, *P jiroveci*, *C neoformans*, and mucormycosis

Bacterial: *Nocardia* species, *L pneumophila*, *L monocytogenes*, and mycobacteria.

Parasitic: *T gondii* and strongyloidiasis.

Malignancies

RCC

HCC

Skin cancers

Posttransplant lymphoproliferative disorder

Anogenital cancer

Lung carcinoma

IMMUNOSUPPRESSIVE DRUGS IN SOLID ORGAN TRANSPLANTATION

Antigen-presenting cells (APCs) such as B lymphocytes, macrophages, and dendritic cells, along with T lymphocytes, play a central role in the process of alloimmune response and transplant rejection.[3] Initiation of immune response is triggered by T-cell recognition of foreign antigens presented by APCs. This recognition leads to activation of multiple signal transduction pathways in the T cells, including the calcium-calcineurin pathway.[2,3] These pathways stimulate production of new molecules, including interleukin (IL)-2, which is a major stimulator of T-cell proliferation. IL-2 binds to CD 25 (IL-2 receptor) present on the surface of the activated T cells, which leads to proliferation and differentiation of effector T cells, resulting in tissue rejection (**Fig. 1**).[3] In addition, activated B cells synthesize alloantibodies against donor antigens.[3,4] Several immunosuppressive drug combinations are used in SOT with the goal of providing adequate immunosuppression with minimum side effects (**Box 2**).[4,5] Given the critical role of T cells in the rejection process, most available drugs target T-cell activation and proliferation, thereby affecting overall production of T cells. However, drugs targeting B lymphocytes with downstream effects on alloantibody production and components of the innate immune system (complement and macrophages) are also being investigated (see **Fig. 1**).[5] Current regimens include at least 3 drugs that work at different parts of the immune system; this allows dose optimization of each drug with lower side effect profiles while increasing synergistic