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VIRAL INFECTIONS IN SOLID ORGAN TRANSPLANTS: HITTING A MOVING TARGET

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Viral infections cause a wide variety of complications in solid organ transplant recipients, some of them life threatening. Direct infection of allografts by viral pathogens is common, and can cause extensive damage to graft tissue. In some cases, such infections may also potentiate other complications such as acute or chronic rejection. The maintenance immunosuppression required to prevent rejection also predisposes transplant recipients to systemic infections with a range of pathogens. Some of these, including cytomegalovirus (CMV) and adenovirus, can also infect the allograft, while others, such as parvovirus B19, have tropisms (in this case, for bone marrow cells) that typically do not involve the transplant itself. Finally, for renal transplants, infections with a variety of organisms, including viruses such as hepatitis C virus, are associated with a spectrum of glomerulonephritides, many mediated by immune complexes.

Though many of these infections and complications are caused by common, well-studied pathogens, their prevalence and patterns have fluctuated considerably over the past decade. The reasons for this are unclear, but may include novel immunosuppressive regimens, alterations in infection prophylaxis, new virus strains, and changes in the spectrum of diseases necessitating transplantation. In some cases, the overall incidence of a particular pathogen in a given organ site has waxed or waned over time. For at least one virus, adenovirus, the incidence of infection in our practice has increased in renal transplants while decreasing in lung transplants. In other instances, the pattern of infection within a given organ parenchyma has shifted from one tissue to another. On rare occasions, truly novel pathogens may emerge.

The prevalence of several forms of allograft virus infection has shifted considerably over the last ten years. Since the mid-1990's, BK polyomavirus interstitial nephritis, previously rare, has become an important cause of renal transplant dysfunction and loss [1]. Severe renal transplant infections with adenovirus are also being reported with increasing frequency [2]. In contrast, adenovirus pneumonitis in lung transplant recipients, an often-fatal complication [3], has become less common. Allograft infections with cytomegalovirus have also become uncommon except in the setting of lung transplantation [4]. (Systemic infections with this pathogen continue to be a relatively frequent problem in all transplant populations.)

In many cases, viral tissue tropisms and patterns of infection within a given organ or system have shifted as well. Cytomegalovirus infection in lung transplants is often histologically subtle, without classic Cowdry A viral inclusions, and may have unusual manifestations (e.g., bronchial polyps or tumor-like masses). Cytomegalovirus infection in renal transplants, when it occurs, now often takes the form of a glomerulitis, though tubular epithelial infections predominated in years past [5]. In contrast, while polyomavirus and adenovirus infections in the urinary tract have classically been focused primarily on the transitional epithelium lining the bladder, ureters, and renal pelvis, the recently described infections of renal transplants by these agents have centered on the tubules. Epstein Barr virus-driven post-transplant lymphoproliferative disorder has remained an occasional problem in solid organ transplants, but it has been recognized

recently that the proliferating cells may be of either host or donor origin, with possible prognostic implications [6]. Recurrent viral hepatitis in patients transplanted for hepatitis B or C occasionally takes novel forms (fibrosing cholestatic hepatitis, acute lobular hepatitis C).

A possible example of a novel pathogen affecting transplant patients is provided by trichodysplasia spinulosa, a new folliculocentric skin disorder caused by an as yet uncharacterized papovavirus [7]. This unusual disease, first described in a kidney-pancreas transplant recipient in 1999, has now been reported in several additional transplant recipients as well as one patient with a hematologic malignancy [8]. Transplanted organs have also served on rare occasions as vectors for established or emerging pathogens such as rabies and West Nile virus [9].

Infection-associated glomerulonephritis is an unusual but potentially serious complication of renal transplantation, where it can occur as either a recurrent or de novo process [5]. Recognition of this problem is crucial to avoid unnecessary therapy for other conditions with which it can be confused, such as allograft rejection. If a specific treatment for the underlying infection is available, it may also arrest or reverse the glomerulonephritis. The most common disorder in this category is membranoproliferative glomerulonephritis type I associated with hepatitis C. Post-infectious glomerulonephritis can be seen in conjunction with a wide range of infections, however, including anecdotal cases of CMV-associated immune complex glomerulonephritis that responded to antiviral therapy.

Recognizing these fluctuating infectious complications is a challenge for the diagnostic pathologist. Successful diagnosis is often facilitated by a multidisciplinary approach, including various forms of microscopy, histochemical and immunohistochemical staining, and molecular diagnostic methods. Electron microscopy plays a specialized but often vital role in the diagnostic armamentarium. It is a useful means for detecting viral pathogens both in tissue specimens and, with the negative staining technique, in fluid specimens such as urine. The latter method is particularly desirable due to its rapidity and the fact that the specimens to which it is applied can generally be obtained non-invasively. Ultrastructural examination is particularly useful in cases where the clinical scenario is not sufficiently clear to allow informed selection of analyte-specific diagnostic reagents. Electron microscopy is also central to the diagnosis and classification of transplant glomerulonephritis,

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