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Urinary Tract Infections: Virus

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Introduction

Thousands of human viruses challenge human life daily by affecting virtually any anatomic site or function. The urinary tract is no exception. Urologic practice copes frequently with bacterial urinary tract infections (UTIs), but most Urologists are not familiar with urinary infections of viral origin. These are usually seen in immunocompromised patients, especially in solid organ and stem cell transplantation recipients.

While it is assumed that no bacteria should be found in the urine of healthy people, especially in men, some viruses can be found in healthy, asymptomatic, and immunocompetent patients. For example, the polyomaviruses JC virus (JCV) and BK virus (BKV) infect the majority of humans asymptomatically, but are an increasing cause of morbidity and mortality in immunocompromised patients. The prevalence of BKV and JCV infection ranges from 65% to 90% and from 20% to 60% in the adult population, respectively (Knowles, 2006). Despite this difference in prevalence, JCV is more commonly found in the urine of healthy adults, making BKV excretion a more sensitive indicator of immune status. Therefore, the presence of an identifiable viral organism with inflammatory symptoms is required to define a viral infection.

Viral infections can cause clinical syndromes of the lower (bladder) or upper urinary tract (kidneys, ureters). The most common presentation is hemorrhagic cystitis. The clinical frame and the natural history of UTIs depend on anatomic abnormalities and more importantly on the immunologic status of the host. Whereas mortality among healthy patients with UTIs is extremely low, viral UTIs with high viral load can result in multiorgan failure and high risk of mortality in immune-compromised patients. The kidneys can also be the target of several glomerular syndromes associated with chronic (HBV, HCV, HIV) or acute/subacute (Dengue, Hantavirus, etc.) viral infections through a direct or immune-mediated injury. As a final topic, the involvement of the urinary tract by a SARS-CoV-2 infection is investigated. The aim of this chapter on viral UTIs is to present an overview and to provide a practical approach supporting clinical decisions.

Epidemiology

Recent diagnostic improvements led to identify viruses in many more clinical settings as compared to the past. As such, it was found that viral infections are a common cause of hemorrhagic cystitis. Hemorrhagic cystitis is the most common presenting symptom of viral UTI. Hemorrhagic cystitis is a well-recognized complication of hematopoietic stem cell transplantation (HSCT) with an incidence of 15–25%. It comprises a wide range of symptoms varying between microscopic hematuria and severe hemorrhage.

In a large series of 407 adult patients undergoing allogeneic HSCT, hemorrhagic cystitis was viral-induced in 87.5% (Dosin et al., 2017). Similarly, in a prospective study of more than 102 children undergoing bone marrow transplantation, a viral cause was identified in all children with hemorrhagic cystitis (Gorczynska et al., 2005).

Although the prevalence is lower than in bone marrow transplantation recipients, renal transplantation is another setting for viral UTIs. Human polyomavirus, Adenovirus, and Citomegalovirus, account for the vast majority of viral infections.

Polyomavirus

Polyomaviruses are small, non-enveloped viruses, which are widespread in nature and highly adapted to grow in the species and the tissue they infect. BK and JC viruses are human polyomaviruses infecting most people throughout the world, as shown by the presence of antibodies against viral proteins in about 80% of the human population (Pinto et al., 2014).

BK virus (BKV)

Polyomavirus primary infection occurs during childhood in 60–100% of general population, with approximately 97% of the adult population having antibodies against it (Demeter, 2000). BK Virus (BKV) has a significant homology to JCV, a neurotropic virus causing progressive leukoencephalopathy. It can be acquired through a respiratory or oral route. While the primary infection is usually asymptomatic, the virus seeds the urinary system and the brain, often remaining in a latent form (Shah, 2000). BKV has a urotheliotropic nature and can be identified in the epithelium of the collecting ducts and of the transitional tissue. Extensive experience over the past 3 decades has shown the prevalence and clinical importance of BKV reactivation in patients with bone marrow transplantation (BMT) and solid organ transplantation. The first evidence of BKV in BMT was reported in 1981, with the detection of BKV in the urine of 13 patients, 1 to 6 weeks after transplantation. The typical cytopathologic changes of BKV are often found in a healthy person, and it is believed to represent transient shedding of virions in urine, most likely secondary to stress or decreased immune response. The patient's cytopathologic changes resolve within 3 months, and there seems to be no clinically significant sequelae of BKV-positive cytology in immunocompetent people. Different disease processes have been linked to BKV infection, but the two most important diseases are polyomavirus-associated nephropathy (PyVAN) affecting kidney transplant patients and polyomavirus-associated hemorrhagic cystitis (PyVAN) affecting allogenic hematopoietic stem-cell transplantation (HSCT) patients. Other pathological processes that have been associated with BKV are ureteric stenosis, encephalitis, meningoencephalitis, pneumonia, vasculopathy and bladder cancer. The following sections are dedicated to BKV-related syndromes affecting the urinary tract.

a) *Polyomavirus-associated hemorrhagic cystitis* (*PyVHC*)

Hemorrhagic cystitis (HC) is a frequent complication after HSCT. According to the time of occurrence after HSCT, HC is defined as early- and late-onset. Early-onset HC occurs typically during or within 48 h after the end of conditioning regimen, and it is the result of a direct toxic effect of drug metabolites and radiotherapy on the bladder mucosa. Late-onset HC usually starts around the time of the period of neutrophil engraftment (weeks 2–4) or in second-third month after HSCT (Hirsch and Pergam, 2016a, b). The concurrent presence of prohemorrhagic abnormalities of coagulation, severe thrombocytopenia and mucosal inflammation are predisposing factors for any type of HC.

The pathogenesis of BKV is not well understood as similarly high urine BKV loads are found in kidney transplant patients, most of whom do not develop cystitis or gross hematuria (Funk et al., 2008; Leboeuf et al., 2017). Rather, a sequence of events has been suggested, starting with subclinical urothelial damage by the conditioning regimen, high-level BKV replication leading to viral denudation of the pre-damaged regeneration-impaired urothelial lining and urinary leakage in the submucosa followed by hemorrhagic exacerbation with abundant inflammatory cell infiltrates following allogenic stem cell engraftment (Bedi et al., 1995; Li et al., 2013). Indeed, conditioning involving cyclophosphamide, busulfan and total body irradiation has been implicated, and the pronounced toxic, inflammatory properties of cyclophosphamide and its metabolite acrolein are supported by clinical and experimental studies (Romih et al., 2001).

Adenovirus, JCV, citomegalovirus (CMV) and other infectious (bacteria, parasite) and non-infectious etiologies (bleeding disorders with or without low platelet count, primary or metastatic neoplasia, vesical catheter or ureteric stenting) may also cause hemorrhagic cystitis, and must be excluded for appropriate diagnosis and management (Hirsch and Pergam, 2016a, b). The severity of hematuria is commonly described as microscopic (grade 1); macroscopic (grade 2); macroscopic with clots (grade 3); or macroscopic with clots and postrenal failure secondary to urinary tract obstruction (grade 4).

b) *Polyomavirus-associated nephropathy (PyVAN)*

The first reports describing disease resembling polyomavirus-associated nephropathy (PyVAN) in kidney transplant patients, came as early as 1978 (Coleman et al., 1978). However, it was not until the late 1990s that PyVAN emerged and that BKV was found to be its etiologic agent (Binet et al., 1999). At that time, new and more potent immunosuppressive regimens were being taken into use, capable of decreasing the rejection rates at the expense of increased risk of opportunistic infections like BKV. PyVAN affects between 1 and 10% of kidney transplant patients during the first 2 years post-transplantation. PyVAN rarely affects patients other than kidney transplant recipients, and so far only 26 cases of biopsy confirmed PyVAN, in native kidneys of other immunocompromised patients, have been reported (Sharma et al., 2013). This clearly suggests that there must be risk factors associated with the allograft and not only with the suppressed immune status. Prognostication is complicated by the many putative risk factors, including HLA-mismatch, donor gender (female) and age (high), recipient of male gender, type and dose of immunosuppressive medication and transplantation events such as ureteric stents, steroid exposure and acute rejection (Brennan et al., 2013). The pathogenesis of PyVAN is characterized by high-level BKV replication in the renal-tubular epithelial cells of the transplanted kidney leading to cytopathogenic loss and thereby denudation of the epithelial monolayer in the allograft tubulus. As a consequence, the virus leaks into the tissue and bloodstream and inflammatory cells infiltrate the interstitium leading to tubular atrophy and interstitial fibrosis. This reduces the graft function and increases the risk of graft loss. Of note, the urothelial cells may also play an important role in PyVAN. Mathematical modeling of BKV replication in kidney transplant patients with PyVAN suggests that viral replication starts in the renal tubular epithelial cells but is then carried to the urothelial cell compartment where more than 90% of urine BKV loads are generated (Funk et al., 2008). This is supported by histopathologic data revealing extensively infected urothelial cells in the bladder of patients with PyVAN. In agreement with this, primary human urothelial cells from bladder were found to be very permissive to BKV infection.

c) *Ureteric stenosis*

BKV was first identified in the urine of a renal transplantation recipient with the initials B.K. by Dr. Sylvia Gardner in 1971: the kidney transplant patient from whom BKV was initially isolated, was suffering from ureteric stenosis (Gardner et al., 1971). Since then, there have been several reports on BKV-associated ureteric stenosis, usually in kidney transplant patients, both pediatric (Rajpoot et al., 2007) and adult (Coleman et al., 1978) but also in allogenic HSCT patients (Hwang et al., 2013). The pathogenesis of ureteric stenosis is still not completely resolved. Coleman suggested in 1978 that high-dose steroids, given to kidney transplant patients post-transplantation, permitted reactivation of BKV (Coleman et al., 1978). The ureteric epithelium which was damaged by ischemia or inflammation supported infection and was replaced with granulation tissue. In a study of kidney transplanted cynomolgus monkeys receiving immunosuppression, a reactivation of a new polyomavirus called cynomolgus polyomavirus occurred in 12–57 monkeys (Van Gorder et al., 1999). The virus was detected in the urothelium of graft ureters in association with inflammation and in the smooth muscle cells of the ureteric wall showing signs of apoptosis. A significant incidence of late onset stenosis was seen. Apparently, ureteric stenosis is now less frequently reported, possibly due to better surgical techniques and a decline in the use of ureteral stents (Hirsch, 2005).

JC virus (JCV)

BKV and JCV have been shown to establish latency in several tissues including the urinary system. In renal transplant patients and more generally in those suffering from immune system impairments, human polyomaviruses can on rare occasions cause tubulo-interstitial nephritis. Nevertheless, data regarding the ability of JCV to induce ureteral and bladder damage are very scarce (Di Maida et al., 2021). The triggering mechanisms for JC virus reactivation are not well defined yet. It has recently been suggested that there is a higher risk of JC virus reactivation in immunocompromised patients and those treated with immunomodulatory drugs for chronic inflammatory disorders, hematological malignancies, or following organ transplantation (Kartau et al., 2019). However, drug specific causality is difficult to assess, since most patients receive multiple immunomodulatory medications concomitantly or sequentially, or present with several immunocompromising factors related to their underlying disease. At the level of the urinary tract, the association between patient immune status and JCV pathogenicity appears even more ambiguous, due to the limited available evidence. Moreover, low levels of JC viruria can also occur in approximately 13–20% of healthy individuals (Boukoum et al., 2016), making the interpretation of data even more difficult.

The central nervous system and kidney are considered as the reservoirs of JC virus infection, in which the virus can persist in latency after primary infection. The possible role of JC virus in urinary tract involvement has only recently been recognized. Based on laboratory findings and PCR studies, several authors have long considered BK virus as the only polyomavirus eventually affecting the kidneys and urinary tract. Indeed, although genomic sequences of both JCV and BKV DNA have been detected by PCR in renal biopsies of transplanted patients, combined immunohistochemical and molecular biology studies suggested that renal impairment was secondary to the replication of BK virus, whereas JC virus was usually present as a co-infecting agent in a latent, non-replicative phase (Boldorini et al., 2001). As such, JC virus has long been considered unable to elicit pathological effects.

Nickeleit et al. (2000) proposed that JC viral particles produced after a viral lytic cycle in the renal pelvis or ureter may enter the capillary vessels and infect the tubular cells of the kidney or, alternatively, follow an ascending route of infection from transitional cells to kidney tubular cells. Conversely, Boldorini et al. (2003) first reported morphological evidence of lytic JC virus infection in four renal specimens from AIDS patients, supporting the hypothesis that, in immunocompromised patients, active JC viral replication can also occur in the kidney and urinary tract. JC virus-related nephropathy is now recognized as a rare cause of nephropathy in transplant recipients (Wiegley et al., 2021). Ureteral and bladder involvement is more rarely reported in different types of immunosuppressed patients (Cavallo et al., 2007).

Diagnosis of polyomavirus

As the initial presentation of PyVAN is insidious, it is strongly recommended to screen kidney transplant patients regularly for early diagnosis (Hirsch, 2005). Screening should be performed at least every 3 months the first 2 years after transplantation and then annually until the fifth year of post-transplantation. Screening is usually accomplished by quantitative PCR of urine and/or plasma for detection of high-level BKV viruria $\geq$7 log10 copies/mL or viremia $\geq$4 log10 copies/mL (Randhawa et al., 2004). Alternatively, cytological examination of urine in search of decoy cells (Mackenzie et al., 1978) or electron microscopy in search of viral aggregates can be performed (Singh et al., 2009). Plasma PCR has a higher positive predictive value than urine PCR as episodic viruria is quite frequent in this patient group, while viremia is less common and usually precedes PyVAN. Usually the diagnosis of PyVAN requires a histological demonstration of BKV replication (Purighalla et al., 1995). However, due to the focal nature of PyVAN, a negative biopsy result cannot rule it out (Hirsch and Pergam, 2016a, b; Brennan et al., 2013). To distinguish PyVHC from the more frequent early-onset hemorrhagic cystitis occurring prior to the engraftment due to urotoxic conditioning or total body irradiation, the triad of cystitis, hematuria (grade II or more) and high-level BKV replication with urine loads of $\geq$7 log10 GEq/mL, must be present.

Treatment of polyomavirus

No specific anti-viral therapy has been developed to treat PyVAN. Thus, early treatment before the development of irreversible histopathological damage are important to ensure a favorable prognosis. The AST (American Society of Transplantation) guideline recommends starting interventions at the high-level BK viremia stage, which is indicative of probable or presumptive PyVAN (Hirsch et al., 2019). Since no BKV-specific antiviral therapy has been developed, reducing the level of maintenance immunosuppression is the most common and effective treatment for BK viremia or PYVAN. Currently, the AST guideline recommends two strategies (Hirsch et al., 2019): (1) first reduce the dose of the calcineurin inhibitor by 25–50% in one or two steps, and then reduce by 50% and ultimately discontinue the antimetabolites; (2) first reduce the antimetabolites by 50%, and then reduce the calcineurin inhibitors by 25–50% and discontinue the antimetabolites. At this time, the "calcineurin inhibitor first" and "antimetabolite first" approaches (as the first step) are considered largely equivalent (Hirsch et al., 2019; Bischof et al., 2019; Hardinger et al., 2010).

In addition, several medical treatments have been tried, including intravenous immunoglobulin (Piburn and Al-Akash, 2020), cidofovir (Kuten et al., 2014), and fluoroquinolone (Gabardi et al., 2010). Cidofovir (Vistide®, Gilead, Foster City, CA, USA), is an intravenously administered nucleoside analog of deoxycytidine monophosphate that is licensed by the U.S. Food & Drug Administration for the treatment of cytomegalovirus (CMV) retinitis in AIDS patients. In 2000, a patient with PyVHC and simultaneous CMV infection was successfully treated with cidofovir and shortly after it was reported to be useful in the treatment of one patient with PyVAN (Bjorang et al., 2002). The drug is taken up via the organic anion transporters (OAT1), which are mainly expressed on the basolateral side of renal tubular epithelial cells. Cidofovir is nephrotoxic and has less potent anti-BKV activity than the other therapies. Intravenous immunoglobulin through osmotic injury causes vacuolation in proximal tubular epithelial cells, in turn leading to acute kidney injury (Levy and Pusey, 2000). Fluoroquinolones are synthetic broadspectrum antimicrobial agents targeting the bacterial enzymes topoisomerase II and IV (158) and are also suggested to interfere with the helicase activity of BKV LTag (Ali et al., 2007). Critical aspects of Fluoroquinolone in this setting are related to their gastrointestinal and central nervous system side effects, given the lack of significant effects on BKV replication and hemorrhagic cystitis severity, and the selection of antibiotic resistance (Walker, 1999). None of these treatments have sufficient clinical data supporting their use as standard practices. PyVAN sometimes accompanies acute rejection; these cases are difficult to treat. Due to the lack of effective anti-viral drugs, the main therapeutic strategy is to reduce immunosuppression; at the same time, clinicians must pay attention to the risk of allograft rejection.

Therapy for PyVHC is purely supportive, involving symptom relief by analgesia, hyperhydration to increase diuresis and continuous bladder irrigation to prevent clot formation and urinary tract obstruction (Hirsch et al., 2019). Moreover, lost platelets and erythrocytes are substituted. Other treatments of PyVHC aim at repair and regeneration of the urothelial mucosa through hyperbaric oxygen therapy or by topical application of fibrin glue. The main drawback of hyperbaric oxygen is its limited availability on a larger scale, the requirements for dedicated hyperbaric room facilities, the risk of ear barotrauma/pressure intolerance and claustrophobia linked to the procedure (Hosokawa et al., 2014). Finally, topical applications to the damaged bladder mucosa to achieve hemostasis through cystoscopy have been reported in single-center retrospective series of 35 patients. The complete response rate was 83% (Tirindelli et al., 2014). Similarly, several compounds to reduce bleeding have been used in case studies and small series, e.g. FXIII concentrate (Demesmay et al., 2002), intravesical sodium hyaluronate (Cipe et al., 2009), estrogens (Ordemann et al., 2000) or choreito extract granules (Kawashima et al., 2015). The same adjuvant treatments have been tried for PyVHC as for PyVAN again without any documented benefit.

As the understanding regarding the pathogenesis of PyVHC is evolving, new potential therapeutic targets are expected to emerge. Recently, Schneidewind et al. reported the successful use of an innovative three-dimensional (3D) organotypic cell culture model for studying BKV life cycle. Such culture methods will highlight the interactions between BKV and human urothelial cells which might unveil the unknown nuances associated with BKV pathogenesis. Furthermore, they might facilitate the in vitro testing of antiviral drugs against new potential therapeutic targets (Schneidewind et al., 2020a, b).

In a recent experimental study, a novel 3D cell culture approach was used to study BKV pathogenesis and potential new therapeutic targets. The results favored the involvement of the STAT3 pathway in the pathogenesis of BKV infection, and IL-11 was recognized as the potential therapeutic target. The utilization of antibody against IL-11 showed promising in vitro activity against

BKV. Although tocilizumab (an anti-IL-6 antibody) did not yield significant results in this study, its role in the treatment of BKV infection will need detailed further exploration, as IL-6 is an important component of the STAT3 pathway (Schneidewind et al., 2020a, b). Likewise, it may be expected that further experimental studies focussed on the STAT3 pathway in BKV infection might unveil more potential therapeutic targets.

Synopsis and current recommendations on BKV management

Polyomavirus BK persistently infects the majority of people at an early age, usually without causing disease. Pathological consequences appear mainly in immunodeficient individuals, an expanding patient group due to transplantations, use of immunosuppressive therapy and the increasing average age of the population. However, the management of PyVAN and PyVHC differs.

Safe and effective antiviral treatment of BKV diseases is still lacking and for patients with PyVAN, the only treatment strategy with documented effect is reduction of immunosuppressive therapy. On the other side, PyVHC remains a challenging complication after allogeneic HSCT with average rates of 13%. Its diagnosis requires the clinical and laboratory triad of cystitis, gross hematuria and high urine BKV loads 7 log10 copies/mL, but a significant role of other etiologies must be excluded. Plasma BKV loads 1000 copies/mL has a role for the management and follow-up of triad positive allogeneic HSCT recipients. Screening of asymptomatic HSCT patients at risk remains an area of investigation and is presently not recommended, as pre-emptive therapy is not established (DII). Specific antiviral prophylaxis is not available and fluoroquinolones are not recommended. PyVHC treatment is based on the best supportive therapy, such as hyperhydration, bladder irrigation, platelet transfusions as needed to reduce bleeding, and pain treatment, particularly when using myeloablative conditioning based on cyclophosphamide, busulfan and total body irradiation. The risk/benefit ratio of reduction of immunosuppression is not clear in PyVHC and must be balanced with the risk of worsening or triggering an acute graft-versus-host disease. Antiviral treatment with intravenous cidofovir is controversial due to the absence of randomized controlled studies. Until the availability of safe and effective antivirals, the use of cidofovir may be an option although there is uncertainty of efficacy, the best dose schedule and the need to balance any benefit against its renal side effects. Non-specific measures aimed at speeding the healing process of the damaged urothelial lining such as hyperbaric oxygen therapy or urologic fibrin glue application have been successful in a limited number of uncontrolled studies. No recommendation is possible for several other treatments such as the administration of intravesical sodium hyaluronate, intravenous FXIII concentrate, leflunomide, estrogens, mesenchymal cells and cellular immune therapy because these treatments have only been used sporadically in a very limited number of patients or are still experimental. These evidence-based recommendations are applicable for both pediatric and adult patients. In conclusion, despite much progress in understanding the pathogenesis, epidemiology and risk factors of PyVHC, this complication still represents a disabling unmet clinical need with limited prophylactic and therapeutic options. To overcome this deficiency will require novel antiviral treatment approaches supported by proper clinical trials.

Our institutional BKV protocol in transplanted patients

BKV PCR-based search is performed every 3 months in the first year post-transplantation, every 6 months in the second year, and annually thereafter.

In case a billion copies/mL is found in the urine, BKV is searched in the blood. The threshold for an active treatment is a BKV plasma level of 5 log10 copies/mL. The search for SV40 on renal tissue is also performed in order to quantify the renal injury.

Our strategy in case of clinically significant BKV infection is based on three progressive steps:

1) reduction or suspension of antimetabolite therapy (mycophenolate)
2) switch calcineurin-inhibitor therapy from tacrolimus to everolimus
3) antiviral therapy with levoflunamide, in case the above steps were ineffective

Adenovirus

Adenoviruses (ADV) are double-strand DNA viruses with at least 51 serologic subtypes. They are known to cause upper respiratory, gastrointestinal, and conjunctival infections in healthy people and children; however, their pathogenicity is altered by the immunologic status of the host, and in immunocompromised patients, ADV can affect many other systems (Ison, 2006). Human ADV are classified into 7 species (A–G) and 67 types (1–67). Types 1–51 were identified by serotyping, whereas types 52–67 were identified by genomic sequencing and bioinformatic analysis. As the assay for ADV detection covers only a proportion of the currently known virus types, the occurrence of ADV infection of the urinary tract may have been underestimated. In addition, ADV has been identified as the causative agent of various diseases, including acute upper respiratory inflammation, pneumonia, pharynx conjunctivitis, gastroenteritis, hepatitis, and myocarditis (Echavarria, 2008). Normally, ADV causes asymptomatic infection of lymphoepithelial tissues, but in the immunocompromised patient, they can reactivate the latent infection or cause de novo infection. The adenoviral infections are more common in stem cell transplantation and solid organ transplantations. ADV can be detected in 10% of urine samples after transplantation, and over 12 months of follow-up, adenoviral UTIs occurred in 9% of patients (Runde et al., 2001). ADV are ubiquitous infectious agents that cause significant morbidity and even loss of life, particularly in select groups of at-risk individuals. Troubling outbreaks of ADV infection occur far too frequently, and these can also affect otherwise healthy individuals not normally at risk for serious infection.

Diagnosis

Adenoviral cystitis can present as gross or microscopic hematuria in up to 20% of patients (Allen and Alexander, 2005). History of solid organ or bone marrow transplantation and use of immunosuppressants aids in diagnosis because ADV cystitis occurs almost exclusively in immunocompromised patients. Most cases of ADV-related hemorrhagic cystitis occur within 12 months of transplantation (Hofland et al., 2004). The adenoviral infection can often coexist with Aspergillosis and CMV in immunocompromised patients, and broad cultures should be obtained. A urine bacteriological culture, urine cytology, and the presence of urine ADV and BKV DNA were examined in those with a diagnosis of urinary tract infection based on symptoms of macrohematuria and dysuria (i.e., urinary frequency, urgency, and micturition pain). A definitive diagnosis of ADV infection of the urinary tract should confirmed by positive results for the presence of ADV DNA in the urine. In addition, blood culture and the presence of ADV DNA in the blood were examined in patients with fever. ADV DNA in the urine and blood is detected using a qualitative polymerase chain reaction assay (Lion, 2014) for ADV types 1–6, 8, 19, and 37; types 7 and 11 were also included because of hemorrhagic cystitis. BKV DNA in the urine is also detected using a qualitative polymerase chain reaction assay. Furthermore, it is necessary to perform a cystoscopy, computed tomography (CT), and/or magnetic resonance imaging (MRI) of the abdomen and pelvis in cases of prolonged hematuria, and renal graft biopsy in cases of renal graft dysfunction.

Treatment

Unfortunately, until recently there was no single antiviral drug that would be potent and devoid of drug toxicity. For treatment of ADV infection of the urinary tract after renal transplantation, reduction in immunosuppression is necessary, similar to other viral infections (Asim et al., 2003). Both B and T lymphocytes play an important role in recovery from ADV infection. Therefore, if clinical improvement cannot be achieved by the reduction or discontinuation of mycophenolate only, dosages of calcineurin inhibitors, such as tacrolimus or cyclosporine, should be reduced. Moreover, an antiviral effect can be expected following intravenous immunoglobulin administration, particularly in cases of hypogammaglobulinemia. Antiviral therapies include CDV, ganciclovir, ribavirin, and brincidofovir. The primary anti-viral agent for the treatment of ADV infections is CDV. Cidofovir can display a doselimiting nephrotoxicity, and the incidence is relatively low (6.9%). Intravesical administration of cidofovir achieved favorable outcomes in case of non-response to intravenous cidofovir or renal failure.

The findings also suggested that this method could be an alternative to intravenous administration of cidofovir to reduce nephrotoxicity. Owing to less nephrotoxicity and high potency against all clinically significant ADV subtypes, brincidofovir is an attractive antiviral therapy for the management of ADV disease (Painter et al., 2012). However, given the small sample size, more studies are expected to provide important evidence for the efficacy of brincidofovir (Lion et al., 2010). An appreciable benefit among patients with various manifestations of ADV disease was found to be associated with ribavirin, although the small number of cases in the studies limits these conclusion. Based on current data, there is no recommendation regarding the use of ganciclovir for ADV systemic infection but there is possible benefit of ganciclovir against urinary tract infection. Previous study observed that hemorrhagic cystitis and nephritis probably can generally be treated only with reduction in immunosuppression without specific antiviral therapy (Florescu et al., 2013).

The realization that we need more effective and safer antiviral drugs for HAdV infection seems to have passed a critical threshold in recent years, and the surge of studies in the field of anti-ADV development is encouraging. The past decade has seen exponential growth in the field of ADV antivirals. However, there is still ground to be covered before an effective therapy is clinically available. Progress in this field is intimately related to the strength and power of the tools available. Specifically, drug screening platforms and model organism systems for preclinical testing are critical tools to advance research on ADV antivirals (Mackenzie et al., 2021). In conclusion, although urinary tract infection is a common complication after renal transplantation, a differential diagnosis of ADV infection should be considered. ADV infection can cured, although nephritis or viremia might be developed. Hence, the possibility of exacerbation should always be considered. After a definitive diagnosis of ADV infection of the urinary tract, adequate follow-up observation should be conducted, and diligent and aggressive therapeutic intervention is required before the condition worsens.

Citomegalovirus

Citomegalovirus (CMV) infection is common, and more than 60% of adults are seropositive. CMV belongs to a large group of herpes viruses with limited pathologic significance in immunocompetent patients. CMV reactivation or new infection is common in transplantation patients, and it can cause significant mortality and morbidity; hence CMV prophylaxis is commonly employed in patients after transplantation. CMV is a relatively rare cause of lower UTIs; however, circumferential evidence supports the association between CMV and hemorrhagic cystitis (Spach et al., 1993). Although rare, CMV cystitis can also occur in immunocompetent patients (Basquiera et al., 2003). Hemorrhagic cystitis has been clearly associated with reactivation of CMV (Childs et al., 1998). CMV is also believed to cause ureteritis and ureteral stenosis (Mueller et al., 1995).

Cytomegalovirus (CMV) is the most common viral infection following kidney transplantation. Without prophylaxis, CMV disease occurred in 45% of recipients with high-risk CMV serostatus (donor CMV seropositive and recipient CMV seronegative) (Lowance et al., 1999). CMV infection has been associated with reduced renal allograft function and survival (Kliem et al., 2008; Helanterä et al., 2006). However, invasive CMV disease involving the renal allograft is apparently uncommon. This may be

attributed to the rarity of detecting CMV inclusion in renal allograft biopsies (<1%) despite the presence of concurrent renal dysfunction and CMV disease. The spectrum of renal allograft pathology caused by CMV can demonstrate tubulointerstitial changes or glomerular involvement. Tubulointerstitial nephritis caused by CMV is the more common manifestation in renal allograft. CMV glomerulopathy, which can occur with or without concomitant tubulointerstitial disease, has been reported (Rane et al., 2012). A case of CMV-induced necrotizing and crescentic glomerulonephritis in renal transplant patient has been described (Detwiler et al., 1998).

Diagnosis

CMV can be detected by seroconversion in a previously negative host and increase in IgM and IgG antibodies titers (Kalil et al., 2005), but a high prevalence of latent CMV infection makes serologic diagnosis difficult, and detection of CMV antigen (pp65), RNA, or DNA is commonly used. The pp65 antigenemia and real-time PCR have been compared with each other, and real-time PCR seems to correlate better with the clinical picture (Mengoli et al., 2004).

Treatment

Letermovir has been shown in a placebo-controlled randomized trial to decrease the risk for clinically significant CMV infection (need for preemptive antiviral therapy and/or CMV disease) and also decrease all cause mortality in CMV (+) patients. Most patients receive prophylaxis with ganciclovir after solid organ transplantation; however, in active diseases, other drugs, such as foscarnet, 60 mg/kg IV twice daily for 14 days, can be used because they are active against CMV (Bielorai et al., 2001). Ganciclovir can reduce the risk for CMV disease but is associated with significant toxicity. High-dose acyclovir/valaciclovir can reduce the risk for CMV replication. The data regarding prophylactic Ig is conflicting and its use is currently not recommended.

Ganciclovir (valganciclovir) and foscarnet are the most used drugs for CMV disease. The addition of high-dose Ig for treatment of CMV pneumonia has been commonly used, but the data supporting this combination is limited. There is no data supporting the addition of Ig to antiviral treatment for other types of CMV disease. Cidofovir is also a possibility for second- or third-line antiviral therapy (Ljungman et al., 2019), whose duration has to be decided on a case-by-case basis, but normally longer therapy is needed compared to preemptive therapy (6–8 weeks). Cidofovir is active against both BKV and CMV and has been used if both viruses are detected. For this reason, cidofovir may become a drug of choice in patients who present with hemorrhagic cystitis after solid organ or bone marrow transplantation. New antiviral drugs are in development but have not been proven efficacious on this indication. Leflunomide and artesunate have been tested, but data supporting their use is very limited.

Several groups have tried to prevent or treat CMV infection and disease following allo-HSCT by the transfer of CMV-specific T-cells. The transfer of these cells was shown to reconstitute virus-specific T-cell immunity. When given therapeutically to patients with chemotherapyrefractory CMV infection, a drop in the viral load after an increase in the number of CMV-specific T-cells could be documented. In patients with chemotherapy-refractory CMV infection postHSCT, adoptive T-cell therapy is a valid therapeutic option (Ljungman et al., 2019).

Human papilloma virus

Recently, human papillomavirus (HPV) has been suggested as a causative agent for squamous cell carcinoma (SCC) of the urinary bladder (Kim et al., 2014). Whether HPV also plays a significant role as etiological factor in other urinary cancers is less clear.

HPV is a double-stranded circular DNA virus of approximately 8000 base pairs, containing eight genes; E1, E2, E4, E5, E6, E7, L1, and L2 (Narisawa-Saito and Kiyono, 2007). The L1 gene encodes the principal capsid protein. Today, approximately 120 different genotypes are known. To be classified as a genotype the sequence of the L1 region has to be >10% different from the L1 region in any other HPV genome. The most common types, among women with HPV DNA positive cervical uterine cancer, are in descending order of frequency, HPV 16, 18, 45, 31, 33, 52, 58, and 35. Furthermore, HPV can be classified into low risk (LR), probable high risk (pHR), and high risk (HR) HPV types according to their prevalence in benign and malignant lesions where causality has been established (Munoz et al., 2003). The tumor suppressor p16INK4a (p16) is well known to be associated with HR HPV infection in cervical uterine cancer and oropharyngeal cancer, which is why it has been suggested as a surrogate marker for HPV infection in bladder cancer.

HPV is a common sexually transmitted infection among women and men, with a life-time risk of infection of approximately 80% for sexually active women. The virus is linked to almost 10% of cancers worldwide, especially a subset of squamous cell carcinoma of the cervix uteri, vulva, penis, anus, and oropharynx. It is therefore anticipated that the virus has affinity for squamous cells. In as much as 90% of cases, the HPV infection is cleared spontaneously by an effective cell-mediated immune response. HPV evades the innate immune system, delaying activation of the adaptive immune system which is the agent responsible for removal of the HPV infection The remaining 10% with a persistent infection thus have increased hazard of oncogenic progression in case of an HR HPV infection (Stanley, 2010).

A geographical variety in HPV prevalence exists. The HPV prevalence has been presented to be highest in Asia. Compared with this, a significantly lower prevalence was demonstrated in Europe. Genetic difference, differences in environmental risk factors (including sexual behavior) and other unknown sources may explain such geographical variety. Comparing studies from different regions of the world should be taken into consideration such geographical variety (Li et al., 2011).

Studies investigating the simultaneous presence of HPV DNA and p16 overexpression have shown as high as 94% incidence in bladder cancer and 8.8% in other urinary with squamous cell differentiation. In the latter study on 35 cases with a HPV prevalence of 17.1%, a high p16 overexpression of 45.7% was demonstrated (Kim et al., 2014). A meta-analysis including 37 studies with 2246 cases of bladder cancer focused on the topic of an association between p16 and prognosis or clinicopathology in bladder cancer cases. The meta-analysis showed a downregulation of p16 in bladder cancer (Gan et al., 2016). Consequently, the knowledge on the association of BC, HPV, and p16 is even more uncertain than the association between HPV and bladder cancer.

Association between HPV presence and positive p16 staining seems to be equally unclear and, therefore, negative p16 staining cannot rule out HPV infection in bladder cancer tissue. Although HPV infection has been found in bladder cancer studies, it is important to keep in mind that such an association is not equivalent to causation. Thus, clear etiological association between HPV and bladder cancer development cannot be established at this point.

Viral-induced glomerulonephritis

Viruses are capable of inducing a wide spectrum of glomerular disorders with variable immune response and different histologic forms of glomerular injury. Although emerging data emphasizes the role of occult viral disease in the development of glomerulonephritis (GN), the criteria to define a viral illness should include: the demonstration of active viremia primarily through serologic PCR testing, the identification of viral proteins/nucleic acid residues within renal tissue and/or within immune complexes deposited in the glomerular basement membrane, and the regression of the glomerular lesion concomitant with the host immune clearance of viremia or eradication of viremia through antiviral therapy. The present classification is based on the duration of active viremia, chronic or acute/subacute.

Glomerular syndromes associated with long-term chronic infections

HCV

Similar to HBV, HCV-associated glomerular disease is primarily a consequence of viral antigen – immune complex formation with glomerular basement membrane deposition. The histologic aspect include type 1 membranoproliferative glomerulonephritis (MPGN) as a consequence of type 2 mixed cryoglobulinemia, polyarteritis nodosa from immune complex deposition, mesangial proliferative and focal proliferative GN and IgA nephropathy. It is important to note that most renal diseases in HCV patients with liver disease are a consequence of acute tubular necrosis, hepatorenal syndrome, prerenal azotemia, chronic kidney disease, and not GN. Therefore, it is essential to be aware of the characteristics of acute GN in HCV patients, differentiating them from the more common diagnoses causing acute kidney insufficiency in this population (Kupin, 2017a, b). Oral direct-acting antivirals (DAAs) against HCV replaced Interferon and became the mainstay of treatment, providing long-term successful eradication of HCV and elimination of cryoglobulinemia A variety of drugs in this class have been developed that are used in combination over a 12-week period without Interferon and result in sustained viral remissions of 95% (Sise). It has also been proved that persistent HCV infection was independently associated with chronic kidney disease, and that antiviral treatment with IFN plus ribavirin can improve renal function and reverse chronic kidney disease (Zhang et al., 2019).

HIV

The HIV pandemic involves 37 million active carriers in the world, significantly less than the 240 million carriers of HBV and the 170 million carriers of HCV. The differential diagnosis of glomerular disease in this setting will be influenced by the treatment status in relation to combined Antiretroviral Therapy (cART-naïve versus actively on cART), and by their coinfection status with HBV (5–10%) or with HCV (25–30%). As with HCV, the prerequisite need for ongoing active viremia is essential for the development of HIV-related glomerular syndromes: HIV-associated nephropathy (HIVAN) and HIV immune complex disease of the kidney (HIVICK) (Sise et al., 2016).

HIVAN embraces glomerular injury arising from direct viral infection, particularly the visceral and parietal epithelial cells, without the presence of immune complexes. The lifetime risk of HIVAN in an untreated HIV-infected black patient is 2–10%, rising to 50% in homozygous for the APOL1 variants (Kruzel-Davila et al., 2016). It should be considered in any cART-naïve HIV patient of black race ancestry with any degree of abnormal albuminuria or proteinuria. New emerging therapy for HIVAN includes renin-angiotensin-aldosterone system inhibition, interruption of the mTOR pathway, and retinoic acid derivatives (Kumar et al., 2010).

Unlike HIVAN, HIVICK includes a constellation of histopathologic diseases with a different presentation and prognosis (Booth et al., 2016). It derives from the deposition of immune complexes in the glomerulus and it is a complication of active HIV viremia in a cARTnaïve patient or a patient with cART resistance. Like HIVAN, HIVICK glomerular lesions from coinfected HIV patients with HBV or HCV are not considered HIVICK and are classified separately as secondary lesions due to their individual viruses. Because 50% of the lesions are postinfectious, these would not be expected to improve with cART, whereas the remaining immune complex glomerular diseases should theoretically show benefit depending on their degree of chronicity. However, the heterogeneity of HIVICK and the limited number of studies makes it difficult to make a recommendation on the benefit of cART (Foy et al., 2013).

HBV

Overall, renal disease may occur in 3–5% of patients with chronic HBV infection (Gupta and Quigg, 2015). Immune-complex GN (MPGN and IgA nephropathy) or immune complex–related vasculitis (polyarteritis nodosa) are the histologic manifestations of HBV-associated renal disease. Of note, many patients with chronic HBV may also harbor coexistent HIV (5–10%) and HCV (10–30%). Checking for these viruses in all HBV carriers is essential (Basnayake and Easterbrook, 2016). Antiviral agents and corticosteroids are mainstay of treatment. The Kidney Disease Improving Global Outcomes recommends the use of IFN or oral antiviral agents (tenofovir, adefovir) or nucleoside (lamivudine, entecavir, telbivudine) reverse transcription inhibitors (KDIGO, 2012). Corticosteroids may be given for a period of <6 months without a significant effect on liver disease, HBV viremia, or patient morbidity or mortality as long as concomitant antiviral therapy is used (Zheng et al., 2012). Universal HBV vaccination reduced those childhood cases of HBV membranoproliferative related to horizontal transmission of the virus (Liao et al., 2011).

Glomerular syndromes associated with acute/subacute viral infections

This focus is on individual types of glomerular lesions seen with a variety of acute and subacute viral infections including cytomegalovirus (CMV), parvovirus, Epstein–Barr virus (EBV), hantavirus, and dengue. An accurate differential diagnosis in case of GN should rule out acute or chronic viral infections. Familiarity with the main renal syndromes associated with viral diseases is essential in order to begin accurate testing and therapeutic interventions (Kupin, 2017a, b).

Although any acute viral illness can lead to an immune complex–proliferative glomerulonephritis (GN), a select group of viral syndromes can induce glomerular injury: dengue, hantavirus, and non-HIV viruses associated with collapsing FSGS (cFSGS) (parvovirus, EBV, and cytomegalovirus).

Dengue

Dengue is a worldwide infection with estimated 100 million new per year. It is classified into dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. GN in dengue results not only from immune complex deposition but also from direct viral entry into renal tissue (Lizarraga and Nayer, 2014). Treatment remains supportive in all categories of dengue.

Hantavirus

Hantaviruses are RNA viruses of the *Bunyaviridae* family which are associated with two major syndromes: hanta pulmonary syndrome and hemorrhagic fever with renal syndrome, characterized by diffuse endothelial cell injury as a consequence of direct viral infection. Similar to dengue, no specific therapy is available for hantavirus infection but preventive strategies with widespread vaccination are undergoing clinical trials (Kruger et al., 2015).

Collapsing focal segmental glomerulosclerosis

Viral-induced Collapsing Focal Segmental Glomerulosclerosis (cFSGS) has long been associated with parvovirus B19, CMV, and EBV. These viruses can cause acute immune complex GN especially with vertical transmission and membranous glomerulopathy has been the most common renal histology reported in this setting. In addition, CMV causes a distinct tubulointerstitial nephritis in transplant patients and may play a role in the development of transplant glomerulopathy (Beneck et al., 1986).

Covid-19 and urinary tract involvement

The current pandemic has seen a new character arising from the multitude of human viral pathogens. SARS-CoV-2 has been shown to be a global player, potentially involving any anatomic site or function. Although the abundance of the virus genetic material in both urine (ca. 10^2–10^5 gc/mL) and feces (ca. 10^2–10^7 gc/mL) is much lower than in nasopharyngeal fluids (ca. 10^5–10^{11} gc/mL) (Jones), it is believed that urinary symptoms are caused by a direct action of SARS-CoV-2. Urinary frequency has been identified as an additional symptom of SARS-CoV-2 infection independent of acute renal injury or urinary tract infection in a small series of hospitalized patients (Mumm et al., 2020). It has been also suggested that the urinary tract may become the target of life-threatening involvement by SARS-CoV-2, especially in patients with pre-existing urologic conditions (Luciani et al., 2020). This assumption is based on the finding that the bladder urothelium, as well as the kidney, harbors cells expressing ACE2, the receptor for the viral spike protein (Zou et al., 2020; Sise et al., 2020). In the face of a possible prolonged or recurring waves of the pandemic, clinicians should be aware that a nontypical course of hematuria or other urinary symptoms might be related to a COVID-19 infection. Although the likelihood of infection due to contact with sewage-contaminated water is low, it has also been speculated that a risk of transmission might occur in clinical and care home settings where secondary handling of people and urine/fecal matter occurs (Jones et al., 2020).

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