CMV post kidney transplant

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Introduction

Cmv is a globally widespread virus that becomes latent following primary infection but reactivates frequently and causes disease in kidney transplant recipients in the setting of immunocompromise.

After kidney transplantation, active CMV infection and disease are associated with increased risk of allograft failure and death; thus CMV prevention strategies are commonly used in such patients.

Preventive therapy decreases reactivation in the setting of latent infection in the transplant recipient and/or acquisition of acute infection in CMV seronegative recipients of seropositive grafts.

CMV disease may still occur despite preventive therapies, especially when they are not dosed adequately.

It also occurs following discontinuation of preventive therapy.

cmv establishes latent infection after the resolution of acute (or primary) infection.

Patients who are CMV seropositive have latent infection.

Symptomatic disease may present later:

1-Reactivation of latent cmv

or less commonly

2-Reinfection with a novel exogenous strain.

The risk of CMV reactivation is highest in the setting of systemic immunosuppression. CMV can present in kidney transplant recipients as either cmv infection or cmv disease.

Active CMV infection is defined as the presence of CMV replication in blood regardless of whether signs or symptoms are present.

CMV disease is defined as the presence of detectable CMV in a clinical specimen accompanied by other clinical manifestation.

CMV disease may manifest as either:

1-CMV syndrome or

2-tissue-invasive CMV disease.

EPIDEMIOLOGY

Both CMV D+/R- and CMV R+ patients are at substantial risk of CMV reactivation, but CMV D+/ R- patients are at higher risk of developing CMV disease than CMV R+ patients.

among those with CMV reactivation, peak CMV loads are highest among CMV D+/R- patients.

CMV disease remains common among transplant recipients but typically occurs after preventive therapy is stopped.

In a single-center study of 176 CMV D+/R- patients who received prophylactic ganciclovir or valganciclovir for three months, 29 percent of patients developed CMV disease at a median of 61 days after stopping antiviral prophylaxis, of which 49 percent were CMV syndrome and 51 percent were tissue-invasive CMV disease .

In a multicenter study of 15,848 United States kidney transplant recipients, CMV disease occurring >100 days posttransplant was identified in 4 percent of patients, whereas CMV disease occurring <100 days posttransplant was identified in only 1.2 percent of patients .

CLINICAL MANIFESTATIONS

Active CMV infection in kidney transplant recipients can manifest as CMV syndrome or tissue-invasive CMV disease .

1-**CMV syndrome** is defined as the presence of detectable viral replication in blood accompanied by attributable symptoms and signs (eg, fever, malaise, arthralgia, leukopenia, thrombocytopenia) in the absence of tissue-invasive disease.

2-Patients with **tissue-invasive CMV disease** have clinical symptoms and signs of end-organ disease (eg, enteritis, colitis, hepatitis, nephritis, pneumonitis, meningitis, encephalitis, retinitis).

The most common clinical manifestation of tissue-invasive CMV disease in kidney transplant recipients is gastrointestinal disease .

Among 26 CMV D+/R- kidney transplant recipients who developed CMV disease after completing three months of CMV prophylaxis, 21 (81 percent) had gastrointestinal disease, including one patient who had concurrent pneumonitis . Two patients (8 percent) had CMV nephritis, and there was one case (4 percent) each of retinitis, pancreatitis, and hepatitis.

Patients with tissue-invasive CMV disease may present with any of the following syndromes:

Enteritis and/or colitis – Nausea, vomiting, diarrhea, and/or abdominal pain. In a study of 26 solid organ transplant recipients (including 13 kidney transplant recipients) with CMV gastrointestinal disease, 7 (27 percent) had upper gastrointestinal disease, 16 (62 percent) had lower gastrointestinal disease, and 3 (12 percent) had both .

Hepatitis – Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevation with CMV viremia in the absence of any other cause.

Pancreatitis – Abdominal pain with elevated amylase and lipase in the setting of CMV viremia.

Pneumonitis – Cough, shortness of breath, and pulmonary infiltrates on radiographic imaging plus CMV in bronchoalveolar lavage fluid.

Meningoencephalitis – Headache, nuchal rigidity, mental status changes, or paralysis, plus CMV in cerebrospinal fluid.

Retinitis – Retinal edema or hemorrhage as reported by an ophthalmologist. CMV retinitis can present with one or more discrete foci of retinal edema or necrosis, with or without retinal hemorrhage or inflammatory sheathing of retinal vessels on funduscopic examination .

Nephritis – Kidney dysfunction in the presence of microbiologic and histologic features of CMV infection in a kidney biopsy specimen.

DIAGNOSIS

the clinical manifestations of CMV are nonspecific and overlap with many infectious and noninfectious illnesses. Thus, among all transplant recipients, laboratory confirmation is required to establish the diagnosis. Occasionally, a biopsy with histopathologic examination of tissue is necessary to diagnose tissue-invasive CMV disease .

Among transplant recipients, we confirm the diagnosis of CMV infection or disease with nucleic acid testing (NAT). NAT using the polymerase chain reaction (PCR) for the detection of CMV DNA is the diagnostic modality of choice for most transplant clinicians. PCR has broad linear range, low limits of detection, and low risk of contamination . PCR is primarily used to evaluate blood, cerebrospinal fluid, or, among patients who have a funduscopic exam that is compatible with CMV retinitis, ocular or vitreal fluid . However, various clinical specimens can be subjected to PCR.

Standardized assay results are reported as international units/mL, whereas nonstandardized assay results are reported as copies/mL.

In general, there are no widely accepted PCR thresholds that differentiate among latent infection, low-level active infection, and CMV disease.
Clinical judgment must be used when evaluating PCR results.
In general, viral loads are highest among patients with tissue-invasive CMV disease.
In a study using a standardized CMV assay, patients with CMV syndrome had mean baseline viral loads of 9120 international units/mL, whereas patients with tissue-invasive CMV disease had mean baseline viral loads of 20,893 international units/mL.

Other noninvasive tests are less helpful in the diagnosis of CMV infection or disease. Shell vial and plaque assay cultures are occasionally used to detect CMV in bronchoalveolar lavage specimens in transplant centers where validation of molecular assays on respiratory samples has not yet been performed.

Shell vial viral culture consists of the detection of viral infection of human fibroblast cells using monoclonal antibodies against immediate-early antigens .

Traditional viral cultures are rarely used to diagnose CMV. Viral culture has low sensitivity, long turnaround time, and high cost.

histopathologic examination of biopsied tissue may be necessary to diagnose tissue-invasive CMV disease in patients who have localizing signs or symptoms and negative CMV assays .

CMV disease can occasionally be localized to the gastrointestinal tract in a patient who has negative assays for CMV in the blood or other compartments .

We only perform a biopsy when it is critical to distinguish CMV disease from other conditions or co-pathogens.

Tissue invasion is indicated by cellular and nuclear enlargement and the presence of amphophilic or basophilic cytoplasmic inclusions, which signify aggregates of CMV nucleoproteins produced during viral replication .

The sensitivity and specificity of histopathologic testing may be increased by in situ hybridization with CMV-specific complementary DNA probes and immunohistochemical testing with antibodies against early CMV antigen .

Some transplant centers use assays that evaluate CMV-specific T cell responses to help predict which patients may develop CMV disease posttransplantation.

In a cohort study evaluating 583 adult kidney transplant recipients across 43 centers in the United States, rates of CMV viremia and disease were lower in patients with positive CMV enzyme-linked immunospot (ELISPOT) assay results (measured serially posttransplantation following completion of antiviral therapy) compared with those without (3 versus 19.5 percent) .

While these results are compelling, further study is needed to validate these findings and determine which type of CMV-specific T cell assay has the greatest predictive value.

MANAGEMENT

CMV infection and disease is associated with morbidity, allograft failure, and death in kidney transplant recipients . Timely diagnosis and appropriate treatment are essential to optimizing outcomes. Our approach to treatment depends upon whether the patient has active CMV infection or CMV disease.

Active CMV infection — Active CMV infection is defined as the presence of detectable CMV replication in blood regardless of whether signs or symptoms are present. Active CMV infection is detected by screening for CMV viremia.

An important goal of treating active CMV infection in the absence of signs and symptoms is to decrease progression to CMV syndrome and tissue-invasive organ disease, so-called preemptive therapy. Strategies to control virus progression include decreasing immunosuppression, adding antivirals, and a combination of both.

Many centers add an antiviral agent upon recognition of CMV reactivation (even in asymptomatic patients), especially in high-risk patients, although cut-offs to trigger therapy in this setting are not well defined and likely vary according to methods of PCR testing.

Our practice is to stop the antimetabolite immunosuppressant (ie, mycophenolate or azathioprine) first, before adding the antiviral drug in patients who are without symptoms of disease or syndrome. We repeat the polymerase chain reaction (PCR) one week after stopping the antimetabolite to assess response and add an antiviral if there is continued evidence of viremia. If the patient continues to have evidence of active viral replication, we start antiviral treatment even in the absence of symptoms. PCR should be checked weekly.

there are centers that are more aggressive with antiviral therapy in the setting with active viremia, even without symptoms of disease. Decision points to dictate aggressiveness in this setting should include :
1-consideration of the intensity of immunosuppression (especially with cellular-depleting induction immunosuppressive therapies and treatment for rejection) and
2-risks for disease, as dictated by serostatus, with CMV-seronegative (CMV R-) recipients having the highest risk for rapid progression to disease.

While we typically do not restart the antimetabolite upon resolution of viremia, we reintroduce it at a lower dose in patients who are at increased risk of rejection.

We monitor the blood for CMV replication with PCR at weekly intervals for four weeks to ensure that CMV does not reactivate at the lower antimetabolite dose.

If CMV infection recurs, we discontinue the antimetabolite indefinitely.

If CMV reactivation does not occur, we continue the antimetabolite at the reduced dose.

CMV disease management

We treat all transplant recipients with CMV disease (either CMV syndrome or tissue-invasive disease) by decreasing immunosuppression and by providing antiviral therapy.

The selection of antiviral treatment is determined by the severity of illness, initial viral load, ability to tolerate oral medication, and the ability to administer intravenous (IV) therapies at home.

The selection of antiviral therapy is **not** stratified depending upon whether the patient has CMV syndrome or tissue-invasive CMV disease . Both CMV syndrome and tissue-invasive disease may be associated with significant clinical manifestations and high viral loads.

When disease involves the gastrointestinal tract, it is necessary to start induction therapy with IV ganciclovir as metabolism of the oral drug (valganciclovir) relies on metabolism of the prodrug.

Reduction of immunosuppression

We recommend stopping the antimetabolite immunosuppressant (ie, mycophenolate or azathioprine) when treating CMV disease.

We usually do not restart it at the conclusion of CMV treatment (ie, when symptoms have resolved and PCR is negative), since we believe that CMV viremia is a sign of excessive immunosuppression.

However, occasionally, among patients who are at increased risk of rejection, we reintroduce the antimetabolite at a lower dose. We monitor the blood for CMV replication with PCR at weekly intervals for four weeks to ensure that CMV does not reactivate at the lower antimetabolite dose.

If CMV recurs, we discontinue the antimetabolite indefinitely and restart treatment with antivirals. If CMV reactivation does not occur, we continue the antimetabolite at the reduced dose.

Antiviral therapy

Available anti-CMV drugs include IV ganciclovir, oral valganciclovir, IV foscarnet, and IV cidofovir. These drugs interfere with viral replication by targeting CMV DNA polymerase. Our selection of agent depends on the severity of the clinical manifestations and the level of viremia and, among some patients, patterns of drug resistance.

Initial therapy

We treat all patients with life-threatening illness (eg, pneumonitis, meningoencephalitis), high viral loads, or moderate to severe gastrointestinal disease (with either diarrhea or nausea and vomiting) with full treatment doses of antiviral therapy with ganciclovir, 5 mg/kg IV every 12 hours (adjusted for kidney function) .

IV ganciclovir has been shown to be effective against CMV infection in randomized trials including kidney transplant recipients with severe CMV disease .

Side effects of ganciclovir include leukopenia, thrombocytopenia, and diarrhea.

Risk of bloodstream infection with a central venous catheter is also a concern. We perform weekly complete blood counts and basic metabolic panels to monitor for adverse effects and to reassess kidney function.

For patients with mild CMV disease (ie, those with minimal signs and symptoms) who are expected to have good absorption of oral medications, we use full treatment doses of valganciclovir, 900 mg orally twice daily (adjusted for kidney function).
Oral valganciclovir has good oral bioavailability and spares patients from the risks and cost of central venous access;
however, the drug's absorption relies on enterocyte metabolism of the prodrug, which can be variable in people with gastrointestinal tract disease, resulting in low or variable levels.

In a randomized, controlled trial of 321 solid organ transplant recipients with mild to moderate CMV disease assigned to either 900 mg of oral valganciclovir or 5 mg/kg of IV ganciclovir twice daily for 21 days, valganciclovir was found to be noninferior to ganciclovir, with equivalent rates of viremia eradication (45.1 versus 48.4 percent) and treatment success (77.4 versus 80.3 percent) .However, the study excluded patients with life-threatening illness, extremely high viral loads, or severe tissue-invasive gastrointestinal disease. Moreover, most patients were CMV seropositive (CMV R+) and therefore had pre-existing anti-CMV immunity, which may have resulted in less severe disease.

Patients who do not respond to reduction of immunosuppression and to antiviral therapy may require an alternative regimen, further reduction of immunosuppression, and/or adjunctive treatment with cytomegalovirus immune globulin (CytoGam, CMV Ig) or intravenous immune globulin (IVIG).

Duration of therapy

The duration of therapy depends on the severity of disease, as well as the clinical and virologic response to treatment. We generally treat with one of the antiviral regimens at the full treatment doses described above until the clinical signs and symptoms of CMV disease are completely resolved and there is no evidence of CMV viremia in two blood PCRs performed at least one week apart.

The typical duration of therapy is 21 days but can range from 14 to 28 days or longer.

The longer time period is typically required in people with gastrointestinal tract disease.

Once symptoms and viremia are resolved, we treat all patients with a one- to three-month course of oral valganciclovir at 900 mg once daily (adjusted for kidney function) to prevent relapse .this reduced dose of valganciclovir is sometimes referred to as secondary prophylaxis. No randomized trials have evaluated the efficacy of secondary prophylaxis.

However, in a retrospective cohort study evaluating 170 solid organ transplant recipients (including 79 kidney transplant recipients), secondary prophylaxis was associated with decreased relapse rates when compared with no prophylaxis (21.7 versus 26 percent) .
The benefit of secondary prophylaxis did not extend beyond six weeks of antiviral prophylaxis use.

Adverse effects

Hematologic suppression, in particular leukopenia (including neutropenia), appears to be the most significant and common adverse event associated with ganciclovir and valganciclovir. When leukopenia occurs, dose reduction of these agents should be avoided, given the risk of promoting resistance .

Patients should be evaluated for other potential causes of leukopenia (eg, mycophenolate, trimethoprim-sulfamethoxazole).

It is also important to note that CMV itself can cause leukopenia and thrombocytopenia and that these abnormalities often improve with antiviral therapy.

The addition of granulocyte colony-stimulating factor should be considered before discontinuing ganciclovir or valganciclovir.

Laboratory monitoring for treatment response

Among all patients with active CMV infection or disease, we monitor virologic response to treatment with weekly PCR in order to identify refractory disease, which is often due to virologic resistance. A decrease in the viral load generally correlates with a clinical response to treatment .

In one study that included 267 solid organ transplant recipients with CMV disease, weekly decreases in viral load every week were demonstrated in most patients receiving antiviral therapy; however, a baseline viral load greater than 18,200 international units/mL and detectable viremia after 21 days of treatment were associated with delayed resolution of CMV disease .These findings may not be generalizable, since patients with severe tissue-invasive CMV disease or high baseline viremia were excluded.

Either whole blood or plasma can be used for baseline measurements and monitoring of CMV load, but the same sample and assay should be used to ensure comparability.

As noted above, we transition patients from full treatment doses of antiviral therapy to reduced doses of antiviral therapy (ie, secondary prophylaxis) upon clinical resolution and the absence of CMV viremia in two blood PCRs performed at least one week apart.

Resistance testing

Monitoring CMV load is a useful approach for assessing the likelihood of drug resistance. Markers suggestive of CMV resistance include a rising viral load, rebounding viral load, and a persistently elevated viral load in the setting of adequate doses of antiviral therapy. When antiviral drug-resistant CMV infection or disease is suspected, a

genotypic assay for drug resistance should be performed [30].

Genotypic assays are done directly from clinical specimens (plasma, cerebrospinal fluid, bronchoalveolar lavage) and usually require a viral load of >1000 copies/mL.

Genotypic assays have replaced phenotypic antiviral drug-resistance testing assays, which were used in the past. However, genotypic assays are referenced against drug resistance mutations defined by phenotypic methods.

Drug-resistant CMV

Refractory CMV disease progresses despite antiviral agents and reduction of immunosuppressive agents. Refractory CMV disease is often due to ganciclovir resistance. Ganciclovir resistance should be suspected in the presence of rising or persistently elevated viral loads despite treatment with appropriately dosed ganciclovir for more than two weeks. Ganciclovir resistance occurs in 1 to 2 percent of kidney transplant recipients with CMV infection or disease and typically develops in CMV D+/R- patients .

Ganciclovir resistance is a spectrum and ranges from 2- to 10-fold increases in CMV inhibitory concentrations depending on the mechanism(s) of resistance.

Both CMV prophylaxis and preemptive treatment increase the risk of ganciclovir resistance.

In general, resistance occurs when chronic immunosuppression and inadequate exposure to ganciclovir allow for prominent emergence of virions that have mutations in DNA polymerase genes .

As these mutated virions are typically less "fit" than wild-type CMV, resistance usually occurs in people who have inadequate immunologic control of the virus and long-term low serum concentrations of ganciclovir, frequently due to inadequate dosing in settings of fluctuating kidney function.

▪In a retrospective, single-center, cohort study of 225 CMV D+/R- solid organ transplant recipients who received prophylactic valganciclovir at a dose of 900 mg once daily, 29 percent of patients developed CMV disease after stopping prophylaxis, of whom 6 percent had ganciclovir-resistant virus.

.In a larger, retrospective study of 1244 kidney transplant recipients who received preemptive treatment with valganciclovir, 2.2 percent later developed ganciclovir-resistant CMV, of whom 96 percent were CMV D+/R- .

No controlled trials exist to support the use of specific therapeutic strategies for ganciclovir-resistant CMV disease.

Drug-resistant or refractory CMV disease is usually treated with foscarnet but occasionally responds to an increased dose of ganciclovir.

The preferred anti-CMV regimen depends on the mutation that confers ganciclovir resistance. We perform genotype testing on all patients with ganciclovir-refractory CMV disease in order to identify whether a mutation in either UL97 or UL54 exists.

Common resistance mutations include those in the genes that encode UL97 phosphotransferase, which performs the initial phosphorylation of ganciclovir (which is required for its antiviral activity), and the viral DNA polymerase gene UL54:

- More than 80 percent of resistant isolates have UL97 mutations clustered at codons 460, 520, and 590 to 607 . These "canonical" UL97 mutations are M460V/I, H520Q, C592G, A594V, L595S, and C603W.
  UL97 mutations confer 5- to 10-fold increases in CMV inhibitory concentrations.
  Occasionally, UL97 mutations that confer low-grade resistance occur.
  . UL54 mutations are much less common and confer various patterns of cross-resistance depending on the specific mutation . UL54 mutations located in the exonuclease domains and region V confer dual ganciclovir-cidofovir resistance.
  UL54 mutations that are located at and between regions II and III confer foscarnet resistance

  .Unlike UL97 mutations, UL54 mutations are not limited to a short list of "canonical" mutations and therefore require more extensive sequencing for elucidation.
  .A significant number of patients with clinically ganciclovir-refractory CMV disease have no detectable mutation.

If genotypic testing identifies UL97 mutations that confer a 5- to 10-fold increase in ganciclovir resistance, then we administer IV foscarnet at 60 mg/kg every 8 hours or 90 mg/kg every 12 hours (adjusted for kidney function), particularly among patients with uncontrolled disease or high and increasing viral loads . Foscarnet is highly nephrotoxic and warrants very close laboratory monitoring and aggressive hydration.

If genotyping identifies a UL97 mutation that confers only low-grade resistance, we continue ganciclovir rather than starting foscarnet; however, we increase the ganciclovir dose to 10 mg/kg IV every 12 hours . If this high dose is used, the complete blood count and kidney function should be followed especially closely.

Cidofovir may be given in cases in which ganciclovir and foscarnet resistance is documented, but it is relatively contraindicated in kidney transplant recipients given its intense nephrotoxicity.

We only administer cidofovir when its benefits exceed its considerable risks. We recommend not using cidofovir when UL54 mutations are identified, since CMV strains harboring this mutation are often resistant to cidofovir as well as ganciclovir.

If cidofovir is used, it should be given with aggressive hydration, and probenecid use should be considered.

An alternative approach is to use letermovir, a CMV-specific antiviral compound that inhibits the formation and release of infectious CMV virions by targeting the viral terminase complex encoded by UL56. Letermovir is US Food and Drug Administration (FDA) approved for CMV prevention in allogeneic hematopoietic cell transplant recipients and has both oral and IV formulations Resistance is readily inducible in vitro , however, and studies need to be performed to determine its efficacy in treating active CMV infection or disease.

A phase III trial for letermovir prophylaxis in kidney transplant recipients is ongoing.

Resistance testing

For patients with drug-resistant CMV, we reduce antirejection immunosuppression more stringently than among patients without drug resistance. In addition to stopping the antimetabolite (ie, mycophenolate or azathioprine), we lower the doses of both the calcineurin inhibitor and prednisone.

Patients with life-threatening disease (such as CMV pneumonitis) that progresses despite antiviral agents and reduction of immunosuppression agents may be treated with cytomegalovirus immune globulin (CytoGam, CMV Ig) and intravenous immune globulin (IVIG) irrespective of the mutation that is identified and even if no mutation is identified. Among such patients, the potential benefits may outweigh potential harms (infusion reactions, kidney failure, fluid overload, aseptic meningitis) and cost.

Two antiviral drugs are undergoing clinical development for the management of CMV infection and may have roles in the treatment of multidrug-resistant CMV disease. The following agents have been used in clinical trials and for compassionate use:

Maribavir is an oral drug that inhibits UL97 kinase and stops viral maturation and egress. It has a good safety profile with no evidence of myelosuppression or nephrotoxicity .

In a randomized trial comparing varying doses of maribavir in 120 hematopoietic cell transplant and solid organ transplant recipients with refractory or resistant CMV infection, 67 percent of patients achieved undetectable CMV viral loads with maribavir treatment . Subsequent recurrent viremia occurred in 35 percent of those who achieved undetectable viral loads, with de novo mutations conferring maribavir resistance in approximately one-half. Four patients died from CMV disease during the study period. No difference in outcomes were detected when comparing 400, 800, and 1200 mg twice-daily doses.

Brincidofovir is an orally bioavailable lipid conjugate of cidofovir that has not been associated with kidney or bone marrow toxicity . It has broad antiviral efficacy and inhibits DNA polymerase. It has not been evaluated in kidney transplant recipients, and its use has not yet been approved by the US FDA. In trials evaluating hematopoietic stem cell recipients, brincidofovir use has not been shown to reduce clinically significant disease but has been associated with increased adverse events

PROGNOSIS

CMV disease increases allograft loss and mortality:

In a single-center study of 51 CMV D+/R- patients who developed CMV disease after stopping antiviral prophylaxis (49 percent with CMV syndrome and 51 percent with tissueinvasive CMV disease), CMV disease was associated with a 2.8-fold increased risk of allograft loss or death, whereas CMV syndrome was not .

In a multicenter study of 15,848 United States kidney transplant recipients assembled using large administrative data, CMV disease occurring >100 days posttransplant was identified in 4 percent of patients, and CMV disease occurring <100 days posttransplant was identified in 1.2 percent of patients. In multivariable analysis, CMV disease occurring 101 to 365 days posttransplant, and CMV disease occurring >365 days posttransplant were associated with a 1.5- and 2.1-fold increased risk of death, respectively .

Acute post-renal kidney graft dysfunction due to cytomegalovirus-positive nephrogenic adenoma—case report and review of the literature

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2024

We present the case of a kidney transplant recipient with acute post-renal kidney graft dysfunction due to CMV-positive nephrogenic adenoma of the ureter. To the best of our knowledge, this is the second described case of ureteral nephrogenic adenoma with CMV superinfection to date.

CMV ureteritis is a rare manifestation of CMV-related tissue-invasive disease that has been increasingly recognized in kidney transplant recipients during the last decades and been linked to the progressive use of mycophenolate in the transplant setting . Its main manifestations include mild fever, urinary obstruction and kidney impairment. Risk factors for the development of CMV ureteritis are acute allograft rejection, the use of depleting immunosuppression or MMF as well as the absence of prophylactic antiviral therapy . In our patient, use of an MMF-based immunosuppression and lack of antiviral prophylaxis following the preemptive therapy approach might have favored the occurrence of CMV-associated tissue-invasive disease.

Nephrogenic adenoma of the urinary tract may present with various symptoms. According to a single center retrospective analysis of 32 cases of nephrogenic adenoma, symptoms were present in 72% of patients including hematuria, urinary symptoms or incontinence, flank pain and hydronephrosis .

In our patient, new-onset microhematuria was retrospectively noted 1 week before acute worsening of graft function together with the finding of hydronephrosis. There were no urinary symptoms nor painful graft site.

Until now, the pathogenesis of the development of nephrogenic adenoma remains incompletely understood. Several hypotheses have been put forward including the development from remnant mesonephric tissue, the development as metaplastic response to local trauma, irritation, inflammation or immunosuppression as well as the development from shed, secondarily implanted renal tubular cells.

Indeed, in a landmark study in 24 kidney transplant recipients, bladder nephrogenic adenoma has been shown to derive from the kidney graft (i.e., donor) using fluorescence *in situ* hybridization studies of sex chromosomes .I
n our patient, nephrogenic adenoma of the ureter was found to be CMV-positive. We are aware of four previously reported cases of CMV-positive nephrogenic adenomas in kidney transplant recipients; while three of them affected the bladder, only one case involving the transplant ureter has been described so far.

Author	Time after kidney transplantation	Symptoms	Location	Detection of CMV	Therapy
Beaudry 1983 (18)	5.33 years	Gross hematuria	Over 50% of bladder surface including the site of the reimplanted ureter	Biopsy and serum	Withdrawal of azathioprine
Buzelin 1988 (19)	2.4 years	Gross hematuria, dysuria	Bladder	Biopsy	Resection
Redman 2000 (20)	1 year	Vesical calculi	Bladder next to the ureteroneo-cystostomy	Biopsy	Resection
Hung 2001 (21)	3 months	Ureteral obstruction, gross hematuria	Ureter	Biopsy	Resection, Valganciclovir, withdrawal of azathioprine
Our case	2 months	Ureteral obstruction, hematuria	Ureter	Biopsy and serum	Valganciclovir and resection

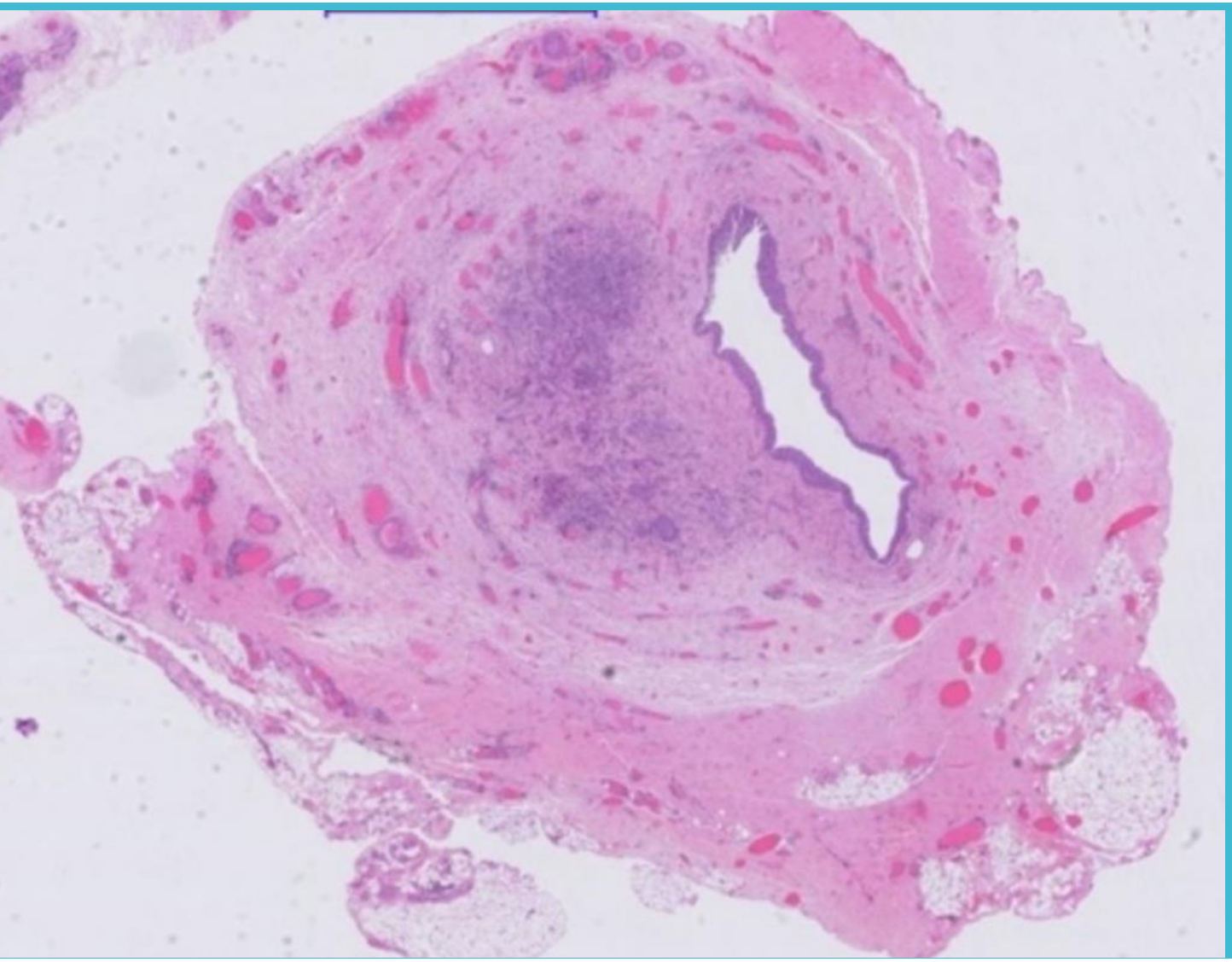


Figure 3. Resected ureter segment. Narrowed lumen in transplant ureter due to the presence of a cellular proliferation (H&E, x 10)

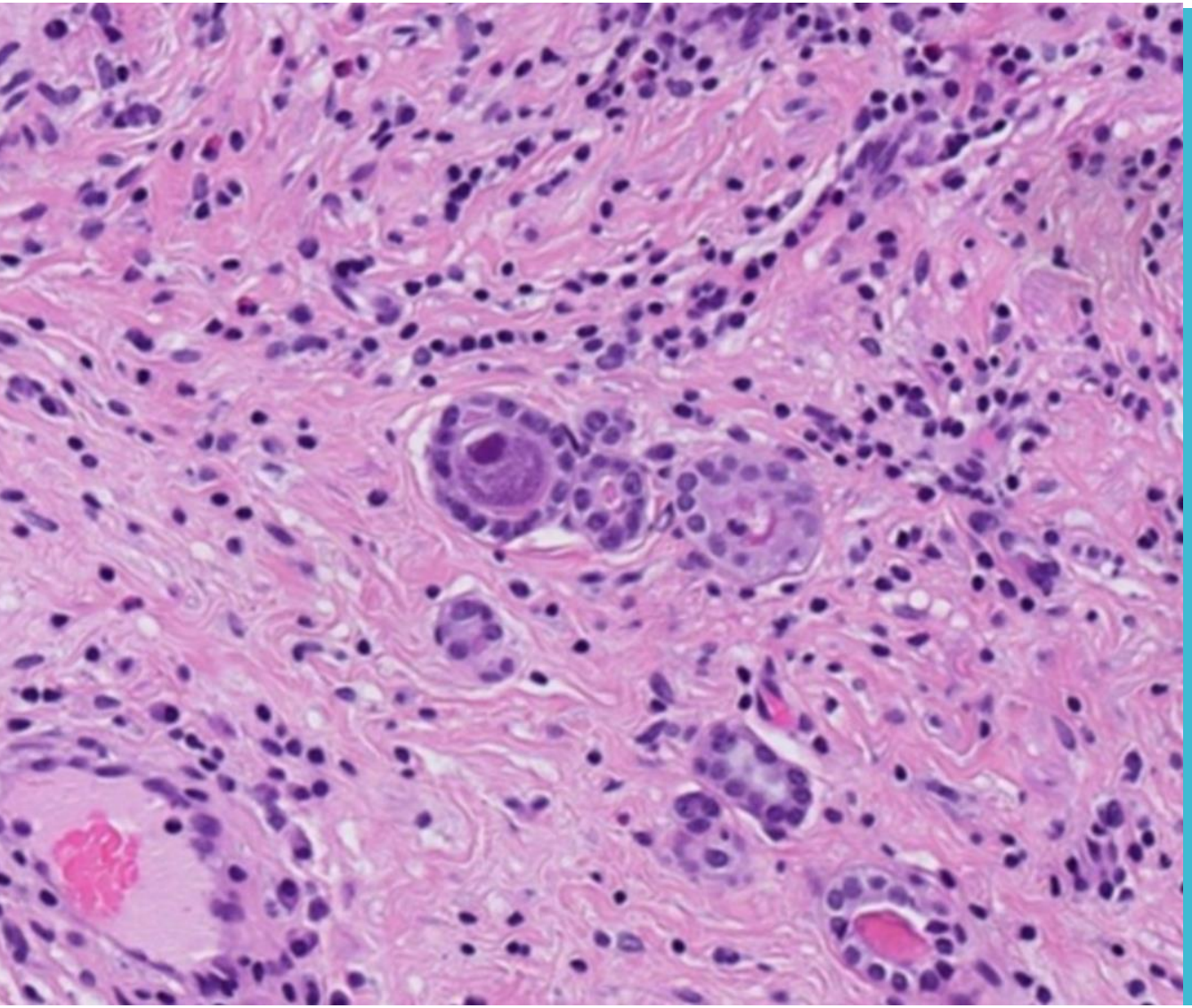


Figure 4. Resected ureter segment. Microglandular proliferation of a nephrogenic adenoma with typical cytopathic appearance of a CMV-infected cell (H&E, x 200).

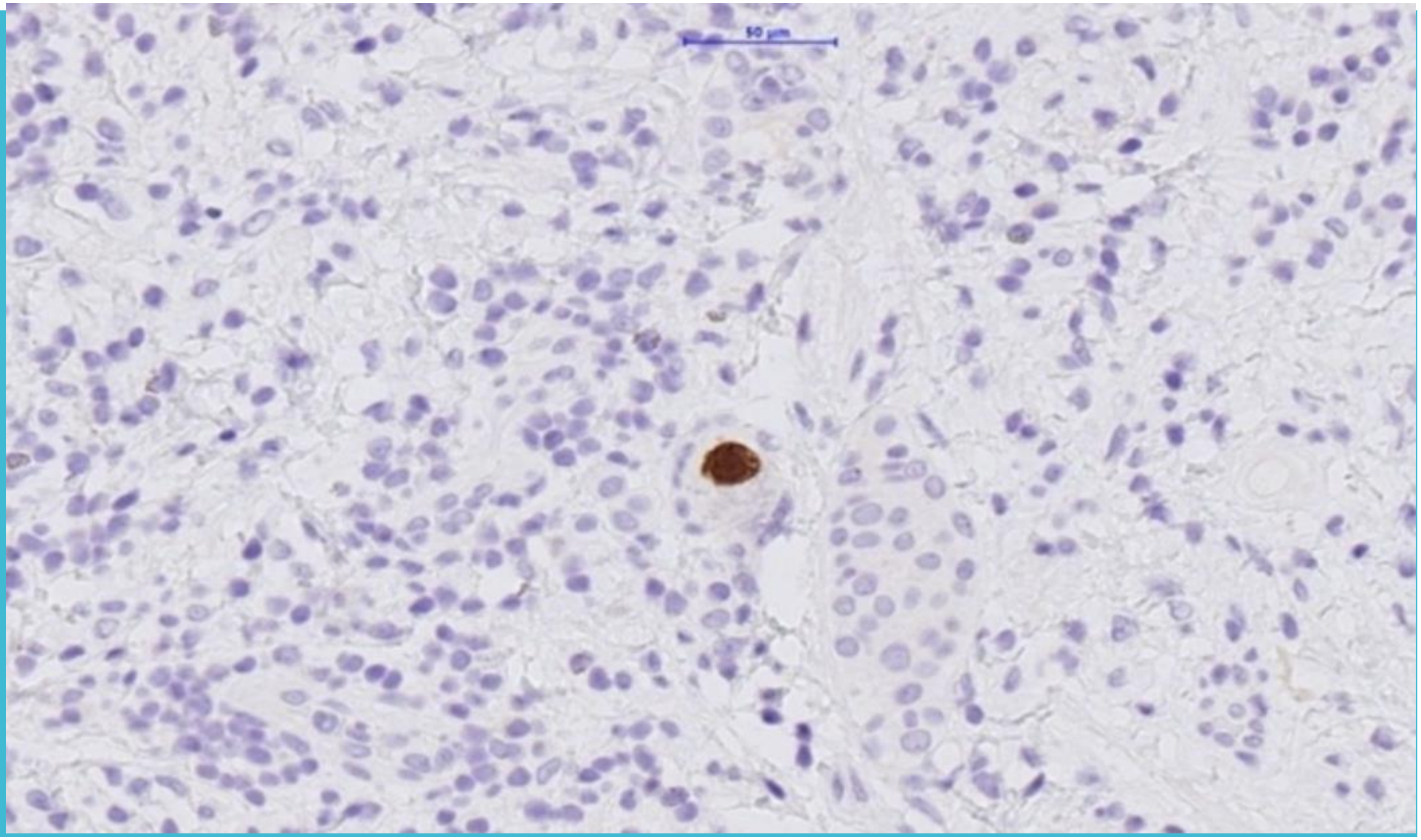


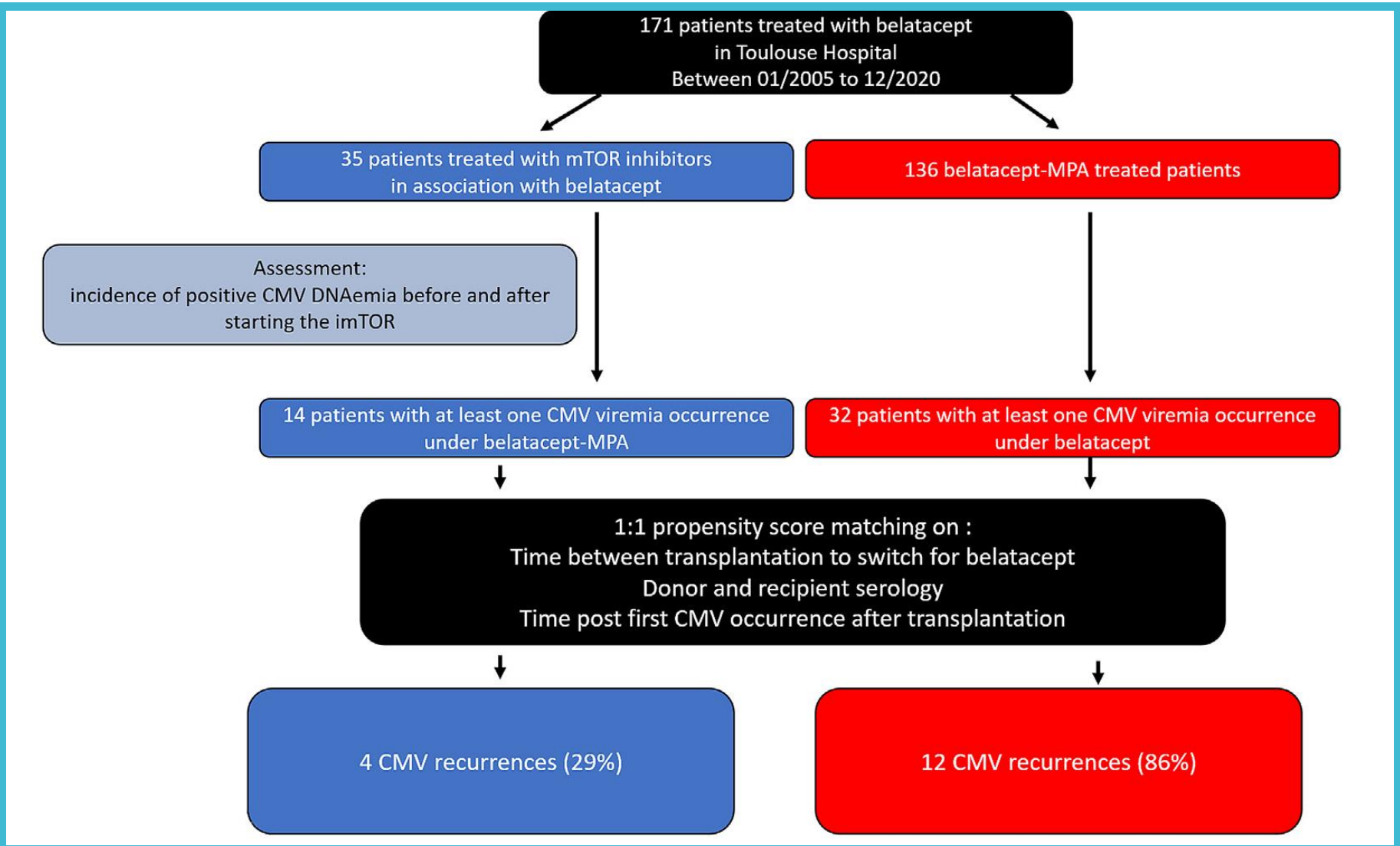
Figure 5. Resected ureter segment. Cells within nephrogenic adenoma with positive immunohistochemic staining for CMV.

The Conversion From Mycophenolic Acid to Mammalian Target of Rapamycin Inhibitor Reduces the Incidence of Cytomegalovirus Replication in Belatacept-Treated Kidney-Transplant Recipients 2024

Arnaud Del Bello, Joseph Cachoux, Florence Abravanel , Thomas Prudhomme and Nassim Kamar

Abetter long-term graft survival, kidney function, and metabolic profile are observed in de novo kidney-transplant patients given belatacept associated with mycophenolic acid (MPA) than those receiving calcineurin-based immunosuppression.
Similarly, kidney function is better in kidney-transplant patients converted from calcineurins to belatacept than those who were maintained on calcineurins.
In addition, less de novo donor-specific antibodies developed in patients given belatacept.

Conversely, more opportunistic infections, particularly cytomegalovirus (CMV) infection, were observed in patients treated with belatacept. Recurrent CMV infections and unusual presentations of CMV disease were also reported in patients treated by belatacept.. our data suggest that replacing MPA with an mTORi in patients treated with belatacept could significantly decrease the incidence of CMV-viremia. Thus, large prospective studies are required to confirm these data.target of rapamycin inhibitor s (mTORi) prevent CMV replication.


171 patients treated with belatacept
in Toulouse Hospital
Between 01/2005 to 12/2020
35 patients treated with mTOR inhibitors
in association with belatacept
136 belatacept-MPA treated patients
Assessment:
incidence of positive CMV DNAemia before and after
starting the imTOR
14 patients with at least one CMV viremia occurrence
under belatacept-MPA
32 patients with at least one CMV viremia occurrence
under belatacept
1:1 propensity score matching on :
Time between transplantation to switch for belatacept
Donor and recipient serology
Time post first CMV occurrence after transplantation
4 CMV recurrences (29%)
12 CMV recurrences (86%)

Between January, 2005 and December, 2020, 171 kidney-transplant patients were given belatacept-based therapy in our institution

Among them, MPA (given at a fixed dose of 360 mg twice a day) was replaced with an mTORi (24 everolimus and 11 sirolimus) in 35 patients (Figure 1a).

All patients received low-dose steroids, and 4 patients (11.4%) also received low-dose tacrolimus (trough level 2 to 5. Patients were converted to mTORi for intolerance to MPA (n = 16), cancer (n = 5), or viral replication (n = 14, 8 recurrent CMV and 6 polyoma BK virus). Conversion to mTORi was done 28months after transplantation and 18 months after initiation of belatacept. Everolimus trough level was 5.3 +_ 2.7 ng/ml .

SIMULTANEOUS CYTOMEGALOVIRUS COLITIS AND ABDOMINAL TUBERCULOSIS POST KIDNEY TRANSPLANT

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There is recent evidence of simultaneous CMV/tuberculosis infection causing pulmonary disease after solid organ transplant, however gastrointestinal disease caused by co infection of the two pathogens is a rare phenomenon. We describe one such case of enterocolitis caused by co -infection of cytomegalovirus infection and tuberculosis in a renal transplant recipient.

34-year-old male who underwent a renal transplant six years ago presented with complaints of haematochezia for 10 days along with generalised abdominal pain. He denied history of fever, vomiting and diarrhoea. He underwent an ABO incompatible renal transplant for which his desensitisation included 3 sessions of plasmapheresis and 400 mg of rituximab. The native kidney disease was secondary to chronic glomerulonephritis for which he received steroids. His immunosuppressive regimen consisted of an induction phase with basiliximab and 2 mg bortezomib and a maintenance regimen which included tacrolimus, mycophenolate mofetil and prednisone (5 mg/d). His serum creatinine was 1.5 mg/dl on discharge. Both donor and recipient were seropositive for CMV and he was discharged on valganciclovir prophylaxis for 6 months. Three months post-transplant the patient developed allograft dysfunction for which a graft biopsy was done.

Acute cellular rejection
was diagnosed and treated with pulse methylprednisolone and tapering doses of steroids. Graft function stabilised at 1.56 mg/dl. Two months later he had symptoms of fever with cough and was diagnosed as community acquired pneumonia and treated with IV antibiotics. During the current admission he underwent a sigmoidoscopy for his haematochezia which revealed multiple small angiodysplasias in the rectum and sigmoid colon for which he underwent photocoagulation. He was asymptomatic for the next 3 days after which he developed fever, allograft dysfunction and new onset haematochezia. Serum creatinine increased to 3 mg/dl from a baseline value of 1.5 mg/dl with persistent fever spikes. Repeat Ileocolonoscopy was done which showed a deep excavated nodular ulcer in terminal ileum with erythema and ooze. A biopsy was taken from the ulcer and samples were sent for histopathological examination. Serum CMV DNA PCR Quantitative was sent which revealed less than 57 copies/ml. Histopathology showed multiple epithelioid cell granulomas suggestive of mycobacterial aetiology along with occasional large cells with enlarged nuclei suggestive of Owl eye inclusion bodies along with IHC showing positivity for cytomegalovirus.

INFECTIONS WITH TUBERCULOSIS AND CYTOMEGALOVIRUS AMONG KIDNEY ALLOGRAFT RECIPIENTS IN A SINGLE CENTRE IN KENYA

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From the 130 kidney allograft recipients who were transplanted between 2010 and 2019 at the Kenyatta National Hospital, twelve (9.2%) recipients developed TB and/or CMV infections posttransplant.

Eight patients got TB infection only, 2 got both TB and CMV infections while 2 got only CMV infection.

Ten (83.3%) were
males. They were aged between 19 and 56 years, with median age of
30.5 years ((interquartile range) .Their HD vintage was
between 7 and 57 months, with a median of 20 months .All the 12 recipients suffered
from hypertension, 7(58.3%) suffered
from glomerulonephritis while 4(33.3%) suffered from diabetes. Donor recipient
HLA –A, -B and –DRB1 matches were a single match in
1(8.3%) recipient, two matches in 3(25.0%), three matches in 6(50.0%),
while four matches were found in 2(16.7%).

All the recipients received induction medication with methylprednisolone and
were on mycophenolic acid analogues. Four (33.3%) recipients received induction with basiliximab. Five (41.7%) were on tacrolimus while 7(58.3%) were on cyclosporine A. Eleven (91.7%) recipients had suffered from at least one episode of allograft dysfunction. Of the 12 recipients, 7(58.3%) were alive with functional allografts, 3(25.0%) were alive with failed allografts and were back to HD, 1(8.3%) was deceased with a functional allograft while 1(8.3%) was deceased after failure of the allograft.

Log_{10}	copies/mL
7	10,000,000
6.9	7,943,282
6.8	6,309,573
6.7	5,011,872
6.6	3,981,072
6.5	3,162,278
6.4	2,511,886
6.3	1,995,262
6.2	1,584,893
6.1	1,258,925

Log_{10}	copies/mL
3	1,000
2.9	794
2.8	631
2.7	501
2.6	398
2.5	316
2.4	251
2.3	200
2.2	158
2.1	126

Log_{10}	copies/mL
4	10,000
3.9	7,943
3.8	6,310
3.7	5,012
3.6	3,981
3.5	3,162
3.4	2,512
3.3	1,995
3.2	1,585
3.1	1,259

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Viral load kinetics and the clinical consequences of cytomegalovirus in kidney transplantation

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We examined the relationship between CMV infection rates and clinical characteristics, CMV viral load kinetics, and graft and patient outcomes in 2510 sequential kidney transplant recipients in the British Columbia Transplant Program.

Duration of the first CMV viremic episode greater than 15 days or a peak viral load ≥4.0 $\log_{10}$ IU/mL offered simple predictors of clinical risk with a 3-fold risk of transplant failure.

Conclusion: Viral load kinetics are closely related to CMV severity and to graft loss following kidney transplantation and provide a simple index of risk which may be valuable in guiding trials and treatment to prevent transplant failure.

QuantiFERON-CMV as a Predictor of CMV Events During Preemptive Therapy in CMV-seropositive Kidney Transplant Recipients

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Background.
Prevention of cytomegalovirus (CMV) infection after kidney transplantation is costly and burdensome.

Methods.
Given its promising utility in risk stratification, we evaluated the use of QuantiFERON-CMV (QFCMV) and additional clinical variables in this prospective cohort study to predict the first clinically significant CMV infection (CS-CMV, ranging from asymptomatic viremia requiring treatment to CMV disease) in the first posttransplant year. A cost-effectiveness analysis for guided prevention was done.

Results

One hundred adult kidney transplant recipients, CMV IgG+, were given basiliximab induction and maintained on steroid/mycophenolate/tacrolimus with weekly CMV monitoring. Thirty-nine patients developed CS-CMV infection (viral syndrome, n = 1; end-organ disease, n = 9; and asymptomatic viremia, n = 29). A nonreactive or indeterminate QFCMV result using the standard threshold around day 30 (but not before transplant) was associated with CS-CMV rates of 50% and 75%, respectively. A higher QFCMV threshold for reactivity (>1.0 IU interferon-γ/mL) outperformed the manufacturer's standard (>0.2 IU interferon-γ/mL) in predicting protection but still allowed a 16% incidence of CS-CMV. The combination of recipient age and type of donor, along with posttransplant QFCMV resulted in a prediction model that increased the negative predictive value from 84% (QFCMV alone) to 93%. QFCMV-guided preemptive therapy was of lower cost than preemptive therapy alone ($P < 0.001$, probabilistic sensitivity analysis) and was cost-effective (incremental net monetary benefit of 210 USD) assuming willingness-to-pay of 2000 USD to avoid 1CMV disease.

Conclusions.

Guided CMV prevention by the prediction model with QFCMV is cost-effective and would spare from CMV surveillance in 42% of patients with low risk for CS-CMV.

Pre-Transplant Frequencies of $FoxP3^{+}CD25^{+}$ in $CD3^{+}CD8^{+}$ T Cells as Potential Predictors for CMV in CMV-Intermediate Risk Kidney Transplant Recipients

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recipient $CD8^+$ T cells play a crucial role in CMV control. The optimal preventive strategy (prophylaxis vs. pre-emptive treatment), particularly for seropositive (intermediate risk) recipients, remains uncertain. We investigated $CD8^+$ T cell subpopulation dynamics and CMV occurrence (DNAemia ≥ 100 IU/mL) in 65 kidney transplant recipients, collecting peripheral blood mononuclear cells before (T1) and 1 year after transplantation (T2). Comparing the two timepoints , we found an increase in granulocyte, monocyte and $CD3^+CD8^+$ T cells numbers, while $FoxP3^+CD25^+$, LAG-3^+ and PD-1^+ frequencies were reduced at T2. Intermediate risk recipients developing CMV after transplantation exhibited lower leukocyte, monocyte, and granulocyte counts and higher $FoxP3^+CD25^+$ frequencies in $CD3^+CD8^+$ T cells pre-transplantation compared to patients staying CMV negative. Pre-transplant $FoxP3^+CD25^+$ in $CD3^+CD8^+$ T cells had the best discriminatory potential for CMV infection prediction within the first year after transplantation .The $FoxP3^+CD25^+$ $CD3^+CD8^+$ T cell subset may aid in selecting intermediate risk kidney transplant recipients for CMV prophylaxis.

Results

The total patients included in the study were 81.All were D+/R+. Among them 28 developed CMV infection (34.5%).

Males were 8 and females were 20.

78% of the patients underwent deceased donor renal transplant. 80% of the patients developed CMV infection within 3 months of completion of prophylaxis with valganciclovir. Among the CMV disease, most common involved organ is gastrointestinal tract and most common symptom is abdominal pain.

Conclusions

In our study,the incidence of post prophylaxis CMV is 34.5% and most of them were asymptomatic. Almost 3/4th of the patients had leukopenia. The CMV infection has negatively affected the graft survival and has no impact on the patient survival.

RISK OF NEW-ONSET DIABETES AFTER TRANSPLANTATION AMONG KIDNEY TRANSPLANT RECIPIENTS WITH CYTOMEGALOVIRUS INFECTION

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In the present study, 45 (76.3%) patients were found to have no NODAT (controls), while 14 (23.7%) patients were diagnosed with NODAT. The CMV load and CMV viremia was elevated in NODAT cohort in comparison with their control counterparts (4000 versus 3600 and 51.1 versus 47.6, respectively); however, no statistical relationship was observed ($P = 0.79$ and $P = 0.84$, respectively). We witnessed that there was significantly high CMV DNA replication in first (1-6 months) half of the post-transplant period in both controls and NODAT patients; however, statistical significant CMV DNA replication was only observed for NODAT cohort ($P<0.001$). Interestingly, our findings indicated that majority of the NODAT diagnosis; 9 out of 14 (64.3%), in our cohort was made during the first six months of kidney transplantation ($P<0.001$). Overall, 7 (11.9%) of the kidney transplant recipients recruited in our study progressed to symptomatic CMV infection. We also witnessed that a greater CMV viremia load was worsening the kidney allograft function at 12 months post transplantation.

Conclusions: the present study demonstrated that CMV infection is not a risk factor for NODAT development among kidney transplant recipinets. The early diagnosis and rigorous treatment and control of both CMV infection and NODAT could potentially improve the allograft and patient survival.