Cytomegalovirus causing Haemorrhagic Colitis Requiring Hemicolecotmy in a Kidney Transplant Recipient

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Abstract

71 year old lady with medical history of end stage renal disease due to hypertension received a living related kidney transplant. She received thymoglobulin induction at dose of 6mg/kg and her maintainence immunosuppression consisted of tacrolimus, prednisone and mycophenolic acid. She received valganciclovir for 3 months for CMV prophylaxis as both donor and recipient were positive for serum CMV IgG antibodies. She presented with melena and fevers 4 months post transplant. She developed hematochezia and went into hemorrhagic shock immediately after presentation and required multiple transfusions. Bleeding scintigraphy showed active bleeding in the region of the distal small bowel. Coiled embolization failed to control the bleeding and she underwent emergent right sided hemicolectomy. Her serum CMV virus result was 3,900,000 copies/ml. She was treated with valganciclovir and mycophenolic acid was stopped. Pathology report of the resected segment of colon showed severe ulceration of entire colon with cells containing viral cytopathic effects, confirmed by immunohistochemistry, as CMV.

Keywords: Kidney; Cytomegalovirus

Introduction

Cytomegalovirus (CMV) is one of the most common viral infections in post-transplant immunocompromised patients. It can present in a wide variety of ways including colitis, gastritis, hepatitis and leucopenia. We present a novel case of severe hemorrhagic colitis due to CMV infection.

Discussion

What is CMV

Cytomegalovirus is a common herpes virus [1]. CMV is the most common and single most important viral infection in solid organ transplant recipients. CMV infection usually develops during the first few months after transplantation and is associated with clinical infectious disease (e.g, fever, pneumonia, GI ulcers, hepatitis) and acute and/or chronic graft injury and dysfunction. Many people do not know they have it, because they may have no symptoms. But the virus, which remains dormant in the body, can cause complications during pregnancy and for people with a weakened immune system. Also known as HCMV, CMV, or Human Herpes virus 5 (HHV-5), cytomegalovirus is the virus most commonly transmitted to a developing fetus.

Transmission

The virus can spread in a number of ways [2]:

- **Touching your eyes or the inside of your nose or mouth**
- **Through sexual contact** with an infected person.
- **Through the breast milk** of an infected mother [3].
- **Through organ transplantation** or blood transfusions.
- **Through the placenta**, from an infected mother to her unborn child, or during birth [4].

Pathogenesis

CMV has the potential to spread in the bloodstream to all organs, but only produces overt disease if the viral load increases to high levels. This is normally prevented by a robust immune response, so that the infected individual usually remains asymptomatic. However, this benefit comes at the
cost of committing more and more immunological resources
to controlling CMV with time, so that the overall function of the
immune system is impaired [5].

The CMV genome is composed of lineal, double-stranded
DNA, surrounded by a protein lining, called matrix, which
contains phosphoproteins (pp65, pp150, etc.) that are highly
immunogenic and capable of deregulating the cellular cycle of
the host cell. This lining is surrounded by glycoproteins (gB, gN,
gO, gH, gM, gL) necessary for the virus infectivity; entrance to the
host cell, cell-to-cell dissemination, and maturing.

The fusion of the virus with the cell is mediated by the viral
glycoprotein gB. The fusion is followed by the entrance of the
nucleocapsid and the lining proteins to the host cell cytoplasm;
the nuclei are translocated rapidly and pp65 antigen, a marker
of infection, is detected in the serum in less than an hour. The
main reservoirs of CMV are the fibroblasts, myeloid cells, and
endothelial cells. The infection of endothelial cells and
macrophages plays an important role in the latency, and this
seems to be a critical point in the maintenance of CMV in the
host.

The start of the replication takes about 12-24 hours after the
infection of the cell, and the cytopathic effect in the viral culture
could be seen after 7-14 days. As with other herpes viruses, CMV
invades the host cell, inhibits protein synthesis, and liberates
viral DNA to the nuclei, where the replication starts immediately.
A strategy that it shares with other herpes viruses is the ability
of stopping the immune response of the host by inhibiting RNA
formation, blocking the presentation of antigenic peptides of
the cell surface, and blocking apoptosis. These mechanisms
prompt to a latent infection that may be reactivated in transplant
recipients

**Immunologic mechanism of rejection**

The immune recognition of foreign antigens in the graft is
mediated by MHC class I and II. Class I molecules are expressed
in all nucleated cells and platelets, while class II are expressed
by B lymphocytes, cells of the monocyte-macrophage system and
dendritic cells. The T-cells and non lymphoid cells show class II
proteins only when they are activated by cytokines. Rejection
depends on the coordinated activation of T-cells and antigen-
presenting cells [6].

For example, in kidney rejection, tubulitis is one of the major
diagnostic criteria and consists of the invasion of the tubular
epithelium by lymphoid cells. The CD8 lymphocytes are the
cells mainly involved in tubulitis development. These cells are
attracted by the β-chemokine secretion, especially, MCP-1 and
MCP-1β (monocyte chemotactic peptides). Also participating
are macrophage inflammatory protein MIP-1α and RANTES
(activation regulated peptides expressed in T-cells and possibly
secreted).

Something similar occurs in heart transplantation. The
expression of self antigens to avoid being recognized and
damaged is a constant mechanism.

**Treatment**

There’s no cure for CMV, and treatment for the virus generally
isn’t necessary or recommended for healthy children and adults.

Newborns and people with compromised immune systems
i.e. Patients after kidney transplantation, however, need
treatment when they’re having symptoms of CMV infection, such
as pneumonia. The kind of treatment depends on the symptoms
and their severity.

Treatment of CMV in solid organ transplant [7] recipients
reduces the risk of allograft injury and death [. The two main drugs
used for treating CMV disease are intravenous (IV) ganciclovir
(5-mg/kg every 12 hours) and oral valganciclovir (900-mg twice
daily). Oral valganciclovir achieves comparable blood levels to
IV ganciclovir and is recommended for the treatment of mild
to moderate CMV disease in solid organ transplant recipients.

In a study of 321 adult solid organ transplant recipients
with CMV disease, the clinical and virologic outcomes were not
significantly different between those patients who received oral
valganciclovir or IV ganciclovir. The rate of viremia eradication for
valganciclovir group and IV ganciclovir group were comparable
- 45.1% versus 48.4% at day 21, and 67.1% versus 70.1% at day
49, respectively. The median time of viremia eradication (21
versus 19 days), side effect profiles, and treatment outcomes
were also comparable between the two groups.

IV ganciclovir is preferred drug for treatment of severe or
life-threatening CMV disease or in those with questionable
gastrointestinal absorption. IV ganciclovir is also recommended
for those with very high viral load. Oral ganciclovir should never
be used in the treatment of CMV disease because of poor oral-
bioavailability leading to sub-therapeutic blood levels.

In addition to the antiviral therapy, it is strongly emphasized
that a cautious reduction in immunosuppression will help
in the clearance of infection. CMV occurs as a result of an
over-immunocompromised state, hence, the reduction in
immunosuppression will allow for the recovery or the generation
of CMV-specific immunity that will allow longer-lasting control
of the virus infection.

The duration of antiviral therapy should be individualized
and be guided by resolution of clinical symptoms and viral load
monitoring. Viral load kinetics that have shown to help predict
clinical response to antiviral therapy include a lower pre-
treatment viral load, a faster rate of viral load decline in response
to therapy, and viral suppression at the end of treatment. In a
recent study which used the WHO international standard for
reporting, patients with a pretreatment CMV DNA < 18,200 IU/
Ml were more likely to have CMV disease resolution. Moreover,
CMV suppression < 137 IU/mL was predictive of clinical response to therapy (Table 1).

**Table 1: Preferred and alternative drugs active against CMV.**

| Preferred Drugs | Antiviral prophylaxis | Treatment | Side effects/Remarks |
|-----------------|-----------------------|-----------|----------------------|
| Valganciclovir  | 900mg PO once daily    | 900 mg PO twice daily | Bone marrow suppression - Leucopenia |
| Ganciclovir IV  | 5 mg/kg once daily    | 5 mg/kg twice daily | Bone marrow suppression - Leucopenia |
| Alternative drugs | Antiviral prophylaxis | Treatment | Side effects/Remarks |
| Oral ganciclovir | 1 g PO thrice daily | Not recommended | Leucopenia, high pill burden Induction of resistance |
| Valaciclovir    | 2 g PO four times daily | Not recommended | Only in kidney recipients Second line even in kidney SOT High pill burden |
| Foscarnet       | Not recommended       | 60 mg/kg IV every 8h or 90mg/kg every 12h | Used in high level UL97 mutant ganciclovir resistance Nephrotoxic |
| Cidofovir       | Not recommended       | 5 mg/kg once weekly x 2, followed by q 2 weeks thereafter. | Used in alternative drug in UL97 mutant ganciclovir resistance Nephrotoxic |

**Prevention**

Careful hygiene is the best prevention against CMV. Health care workers have the greatest chances of exposure, but because of precautions used in the health care setting, their risk of acquiring the disease is low.

**CMV in solid organ transplantation (SOT)**

While most infections in immunocompetent individuals are benign and self-limited, CMV is an important cause of morbidity and mortality in individuals with underdeveloped or compromised immune function, including transplant recipients. Despite significant advances in its diagnosis and therapy, CMV continues to have a major impact on patient and allograft survival among solid organ transplant (SOT) recipients through a variety of direct and indirect effects.

Advances in the field of CMV and solid organ transplantation will be facilitated by the development of [8] optimized threshold for viral diagnosis, [9] effective vaccines for prevention, [10] diagnostic assays to stratify risk of late onset CMV disease by immunological monitoring, and newer antiviral agents with unique mechanisms of action and ideally with much less toxicity.

**Conclusion**

Gastrointestinal CMV disease is an increasingly recognized clinical problem in immunocompromised patients [11]. Its presentation can be very mild diarrhea, nausea and vomiting which is common, to very severe colitis which is rare. Our patient developed hemorrhagic shock due to severe colitis and ultimately required hemicolectomy [11a-d]. If kidney transplant recipient presents with a gastrointestinal bleed, CMV disease should be considered immediately. Timely diagnosis and treatment is extremely important as it can have fatal consequences.

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