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CASE REPORT

## **Anemia as very late-onset cytomegalovirus disease after kidney transplantation**

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**Abstract:** Very late-onset cytomegalovirus (CMV) disease after solid organ transplantation is not associated with classic risk factors; therefore, it does not follow a pattern of predictable appearance. A high index of suspicion is necessary to make an accurate diagnosis. Anemia has multiple etiologies among kidney transplanted recipients, and CMV could be one of them. We report the case of a kidney recipient with anemia refractory to treatment which proved to be secondary to extremely-late CMV digestive disease.

**Keywords:**

anemia, cytomegalovirus, kidney transplantation, tissue invasive disease, very late-onset cytomegalovirus disease

**1 INTRODUCTION**

Cytomegalovirus (CMV) persists as the most dangerous viral pathogen post-kidney transplantation.<sup>1</sup> CMV disease usually occurs within the first 6–12 months post transplantation after the interruption of antiviral prophylaxis; however, beyond 1 year, it is rarely seen.<sup>2</sup> Anemia is an important complication in kidney transplants, and it occurs in roughly 40%–50% of recipients in the first 6 months post transplantation.<sup>3</sup> Although anemia has traditionally been connected to loss of endogenous erythropoietin (EPO) production, it is now known that multiple factors contribute to its genesis.<sup>4</sup>

## 2 CASE REPORT

A 65-year-old man presented to the Transplantation Unit of our hospital with uncontrolled and symptomatic anemia (hemoglobin 8.6 g/dL), despite receipt of erythropoiesis stimulating agents (ESAs) and large boluses of iron, with an elevated C-reactive protein (CRP). He received no blood transfusion before his hospitalization. He had undergone deceased-donor kidney transplantation 24 years earlier and had received prednisone and cyclosporine as induction therapy. He had developed an acute cellular rejection during the post-transplant period, which properly responded to steroid treatment. The donor's CMV serostatus was unknown, but the recipient's response was nevertheless positive.

Thirteen years later, the patient was moved to our hospital to continue follow-up with prednisone, cyclosporine, and mycophenolate for immunosuppression maintenance; importantly, he had completely stable graft function (serum creatinine 1.9–2.1 mg/dL). From that time to the present, he has suffered several urinary tract infections and four pneumonias. Two years ago, he started ESAs and oral iron for graft dysfunction associated anemia and remained stable until five months ago, when his darbepoetin required increases that progressively reached resistance parameters without external bleeding signs. Due to a lack of control of hemoglobin levels, he was admitted for study (Table 1). His peripheral blood smear and immunofixation were normal and negative, respectively. His fecal occult blood was negative times three, and endoscopic study results showed a normal colonoscopy and Forrest III pyloric ulcer when gastroscopy was carried out based on high index of suspicion for gastrointestinal (GI) disease. Except for asthenia, the patient had no other symptoms.

Additional laboratory tests were pursued: lactic acid dehydrogenase (LDH) = 620 (reference range: 203-480 IU/L), haptoglobin = 351 mg/dL (reference range: 50-320 mg/dL), and a negative Coombs test. A CMV real-time polymerase chain reaction (PCR) was then requested, with a positive result of 604643 UI/mL (CMV Real-time PCR Focus Simplexa®, Focus Diagnostics, Cypress, CA USA), and endoscopic tissue sample revisions were completed, in which the CMV immunohistochemistry was positive in the duodenum and pylorus (Figure 1 A and B). Other viruses were negative (hepatitis B and C, human immunodeficiency virus, parvovirus B19, and BK polyomavirus). Therefore, extremely late-onset GI CMV disease and secondary anemia diagnoses were made.

The patient began treatment with endovenous ganciclovir (5 mg/kg/12 h) without toxic effects, showing good evolution of the viral load, hemoglobin levels (Figure 2), and platelets after 50 days ( $175410/\text{mm}^3$ ); 10 days later, he was switched to oral valganciclovir, which was adjusted by estimated glomerular filtration rate. He did not receive intravenous immunoglobulins during hospitalization. At the time of discharge, his serum CRP was 19.7 mg/L and LDH = 278 IU/L, remaining asymptomatic.

### 3 DISCUSSION

Human CMV is a DNA virus of the  $\beta$ -herpesviridae family of herpesviruses, with seroprevalence varying from 30% to 97% and showing increases with age.<sup>5</sup> The first CMV infections in renal transplant patients were described between 1964 and 1966.<sup>6</sup>

CMV establishes a latency inside the host and shows periodic reactivations in both immunocompetent and immunocompromised individuals<sup>7</sup>; notably inflammation, stress, and

other infections can induce viral reactivation through tumor necrosis factor- $\alpha$ , and the clinical significance will depend on the patient's immune status.<sup>8</sup> Patients may have asymptomatic CMV infection (often diagnosed in recipients undergoing surveillance for CMV), viral syndrome, and tissue-invasive disease. CMV infection has both direct and indirect effects.

Depending on the moment of appearance after solid organ transplantation, infection or disease can be referred to as early, late, or very late. Traditionally, CMV has been seen in the immediate post-transplant period. Systematic use of anti-CMV prophylaxis has changed its epidemiology, resulting in markedly delayed occurrence of CMV infection and disease.<sup>9,10</sup> When CMV infection occurs late, it becomes a risk factor for graft loss and mortality.<sup>11</sup> Currently, cases of late and very-late onset are rarely reported, and when they are, they are documented as an atypical presentation pattern (frequently tissue-invasive disease and, above all, GI) unrelated to classical risk factors (donor and recipient serostatus, type and dosage of immunosuppressive drugs, donor age >60 years, simultaneous pancreas-kidney transplant, acute graft rejection, and impaired graft function).<sup>12</sup> So far, other risk factors of delayed-onset have been identified, such as the female gender, previous use of ganciclovir, and CMV mutation. Several studies have documented CMV in patients with moderate or severe hypogammaglobulinemia, which is defined as IgG levels < 400 mg/dL<sup>9</sup> and is a circumstance that occurred in the reported case.

Razonable and Blumberg<sup>12</sup> intended to differentiate the time of disease onset with the terms 'post-prophylaxis' (up to 6 months after completion of an antiviral prophylaxis), 'late-onset' (>4 months after transplantation in patients who did not receive antiviral prophylaxis or >6 months after its completion), and 'very late' CMV disease (incorporated in the previous

concept and referred to in cases of primary infection or reactivation because of late immune dysregulation).

Butler et al<sup>13</sup> reported that human CMV (hCMV) infection inhibited cellular EPO production and proposed that, in cases of renal transplant where a recipient presents with either low blood EPO levels or anemia of unknown cause, it should be determined whether active hCMV infection is present. In addition, treatment against persistent viral infection in an attempt to correct the anemia through the elimination of possible hCMV-induced inhibition in EPO production should be considered.<sup>13</sup>

The diagnostic challenge in this case was based on a lack of symptoms, late and unusual presentation of severe CMV digestive involvement, and the remoteness of the previous transplant.

We would like to emphasize the need for awareness of proper presentation that is distinct from traditional methods regarding CMV disease to avoid greater morbidity and mortality in these patients. This case of CMV disease after kidney transplant is the latest occurrence, to our knowledge, among those published until now.

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**FIGURE LEGENDS:**

**FIGURE 1** (A) Positive immunohistochemistry against cytomegalovirus. (B) Hematoxylin and eosin, x10. Pyloric mucosa with marked inflammatory infiltrate and presence of cells with morphological signs concordant with viral cytopathy (cytoplasmic and nuclear inclusions)

**FIGURE 2** Cytomegalovirus (CMV) and hemoglobin (Hb) evolution after ganciclovir onset



**TABLE 1** Baseline parameters on admission

Parameter	On Admission	Reference in adults, hospital
Hemoglobin (g/dL)	8.6	13-17.5
Mean cell volume (fl)	87.5	80 – 100
Platelets (/mm <sup>3</sup> )	103 000	150 000-450 000
Leukocytes (/mm <sup>3</sup> )	4200	4000-11 000
Reticulocytes (/mm <sup>3</sup> )	73 800	20 000-80 000
B12 vitamin (pg/mL)	980	211-911
Folic acid (ng/mL)	18.09	(> 5.4) normal
Serum iron (ug/dL)	24	59-158
Ferritin (ng/mL)	1540	20-250
Transferrin saturation index (%)	15	20-50
Transferrin (mg/dL)	128	215-365
Proteinogram	Alpha 1 & 2 fractions elevation	
IgG/IgA/IgM (ml/dL)	284/169/63.5	600-1700/90-410/55-350
IgE (UI/mL)	2	0-100
CRP (mg/L)	115	0-5
ESR (mm/1 <sup>st</sup> hour)	29	
CMV PCR (UI/mL)	60 4643	Lower limit of detection: 713

Ig, immunoglobulin; CMV, cytomegalovirus; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCR, real-time polymerase chain reaction.





