

# Successful management of 15 years late-onset Cytomegalovirus infection complicated with deep venous thrombosis in a kidney transplant patient: a rare case report and a review of the literature

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## Title page

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## Introduction

Cytomegalovirus (CMV) is one of the herpes viruses known to spread widely; the incidence rate ranges between 60-100% in adulthood (1), CMV is also one of the most prominent viruses that cause infection as a complication of kidney transplantation (1). The donor-recipient (D/R) serostatus is highly responsible for the incidence of CMV infection, with the (R+) constellation bearing the highest risk, followed by (D-/R-), and (D+/R-) (2). CMV infections can be classified into three broad headings: Regarding incidence: autoactivation of latent CMV infection in the recipient, transmitted from the donor by the allograft, or a recent infection acquired from the surrounding environment (1). Clinical presentation includes asymptomatic infection and CMV disease, which is categorized into two main subtypes: CMV viral syndrome and CMV invasive tissue disease.

CMV Viral Syndrome, This subtype presents with various symptoms such as fever, malaise, cervical lymphadenitis, arthralgia, and a reduction in white blood cell count (1, 2, 3). CMV, Invasive Tissue Disease, This subtype manifests as injury and dysfunction in vital organs, commonly involving the liver (hepatitis), gastrointestinal tract (gastroenteritis), and lungs (pneumonitis). In rare instances, it may also affect other organs like the colon (colitis), retina (retinitis), kidneys (nephritis), brain (encephalitis), and pancreas (pancreatitis) (1, 4). The infection usually happens early (within the first 6 months) after transplantation, whereas late cytomegalovirus infection (LCI) is relatively uncommon, with a reported prevalence as low as 4% (5). To diagnose an effective CMV infection, one of two methods can be followed, either the pp65 antigenemia assay or polymerase chain reaction (preferred for early detection and monitoring of viral load after transplantation) (6). Recent studies have shown equal efficacy of intravenous ganciclovir and oral valganciclovir in the treatment of CMV infection, with two ways to apply it: pre-emptive therapy and antiviral prophylaxis (1). It should be noted that antiviral therapy is only licensed for immunocompromised patients (7).

We must take ganciclovir resistance into account when the viral load remains stable or begins to increase with increasing severity of symptoms despite treatment.

Finally, CMV infection showed an increase in the morbidity and mortality of patients, in addition to some indirect complications, including graft dysfunction, coronary atherosclerosis, and opportunistic infections (6). in addition to life-threatening complications associated with hypercoagulability and Deep Vein Thrombosis (DVT), such as pulmonary embolism (7).

## Case presentation

A 65-year-old man with a history of kidney transplant 15 years ago, due to idiopathic chronic renal failure, hypertension, diabetes type 2, and ischemic heart disease and with no past medical or family history of thrombophilic

disorders, the patient presented to the Emergency Department with a complaint of fatigue and hematemesis. The patient has a surgical history of coronary artery bypass grafting and lens implantation two months ago. Drug history was mixed insulin (35 units am and 15 units pm), mycophenolate mofetil, Amlodipine besylate 160mg/10mg, Prednisolone 20mg, and Furosemide (40 mg).

## Methods

Differential diagnoses for the patient include Gastrointestinal Bleeding, Peptic Ulcer Disease, Drug-Induced Nephrotoxicity, and infections.

The patient's initial tests showed an increase in creatine numbers. An upper gastrointestinal endoscopy was performed, which revealed inflammation at the end of the esophagus, a thickened fundus, a 3 cm deep atrophic ulcer on the superior side of the pylorus, and an edematous pylorus. A biopsy was taken, and the patient was placed on appropriate treatment and discharged pending the results of the biopsy. Furthermore, creatinine numbers began to decrease. Five days later, the patient was admitted to the hospital due to watery diarrhea, weakness, asthenia, anorexia, oliguria, dysphagia, and back pain, with no fever. On clinical examination, blood pressure was 130/70 mm Hg, heart rate 85 bpm, saturation 98%, axillary temperature 36.2°C, paleness, soft purrs in the left lung more than the right lung with no wheezing, generalized reluctance, and pain in the abdomen, which was mostly located in the left and right iliac fossa, with no signs of deep venous thrombosis (DVT). Electrocardiography (ECG) and digital rectal examinations (DRE) were normal. The laboratory exam was analyzed as shown in Table {1}. The biopsy revealed signs of chronic gastritis, erosive ulcers, negative for HP, eosinophilic intranuclear inclusions, variable granular purple cytoplasmic inclusions, and no malignancy. A CMV-polymerase chain reaction (PCR) was requested, which came back positive. The diagnosis was acute renal failure and chronic CMV gastritis. Other laboratory tests, including urine culture, diagnosed a Klebsiella urinary tract infection, which was found unrelated. The patient was treated with intravenous ganciclovir 200 mg, metronidazole 200 mg, levofloxacin 250 mg, Ceftriaxone 1g, mycophenolate 500 mg, cyclosporine 100 mg, Prednisolone 20 mg, Angiotensin Receptor Blocker 160 mg, Amlodipine besylate 10 mg, Furosemide 40 mg, Omeprazole 40 mg, spasmo (Dicyclomine + Paracetamol + Tramadol), nystatin, and insulin. The general condition improved, and the patient was discharged two weeks later with no signs of DVT. Five days later (22 days after the initial CMV infection), the patient presented to the hospital complaining of fatigue, weakness, fever, chills, drowsiness, back pain, and hypotension. The clinical exam showed pitting edema (+4), redness, pain, calf rigidity, and increased skin temperature in the lower right limb. The abdominal examination showed a generalized reluctance, mostly located in the right hypochondria. ECG revealed normal sinus rhythm, left axis deviation, left ventricular hypertrophy, and T wave inversion in v1 to v6, I, and aVL. A transthoracic echocardiogram (TTE) showed severe hypertrophy in the septal wall of about 27 mm and severe apical and septal hypokinesis. Echo Doppler of the right leg showed acute thrombosis in the right femoropopliteal vein. Head computed tomography (CT) was normal. A laboratory examination is shown in Table {2}. Regrettably, in the context of the medical infrastructure in Syria, comprehensive testing, particularly for specialized conditions such as cryoglobulinemia, faces significant challenges. The economic hardships experienced by the patient and his family further compounded the situation, rendering them unable to afford the necessary diagnostic tests, which are not locally available. Additionally, the precarious situation in the country and the unfortunate financial constraints deterred any possibility of seeking these tests in neighboring countries.

Given these circumstances, despite the clinical relevance of a cryoglobulinemia test in confirming the diagnosis of CMV-related DVT, it was practically unfeasible to pursue this diagnostic avenue. Consequently, the clinical diagnosis of CMV-related DVT was established based on the patient's unilateral symptoms, the timing of DVT onset in correlation with the initial CMV infection, and concomitant urinary tract infection. DVT was treated with Memantine 20mg twice daily, leg elevation, and absolute rest in addition to his drugs and continuous therapy of ganciclovir 200mg. **Conclusion and results** On follow-up one week later, the patient developed superficial vein thrombosis in his right arm and was treated and left to rest. On further follow-up the patient remains well with a well-functioning graft and is free of evidence of CMV.

## Discussion

CMV is a viral infection that infects up to 60–100% of people in childhood, and it is one of the most common agents to cause infectious complications after transplantation (1, 6). There is a remarkable relationship between kidney transplantation and infection with CMV, with statistics showing that between US kidney transplants, 18% of the transfers are from a seropositive donor to a seronegative recipient (D+/R-) (2, 8-21), 61% are to the seropositive recipient (R+) (2, 11, 22-26), and 21% are both donor and recipient seronegative (D-/R-) (2, 27), which made kidney transfer stand out as a risk factor for CMV infections, especially with the use of immunosuppressants after transplantation to reduce allograft rejection(2), other statistics showed that before the effective CMV prevention post-transplantation, the probability of developing an active infection

is 69% in (D+/R-) (2, 20, 21), and 67% in (R+) (2), on the other hand, the probability of developing a CMV disease is 56% in (D+/R-) (2, 9-19) and 20% in (R+) (2, 11, 22-26).

In our case, the patient's serostatus is D+/R+ with a CMV disease, which is the less common type of CMV presentation.

CMV infection in transplant patients can occur in three ways: The most common way of transmission is endogenous reactivation of CMV in the transplant patient. The second most common way is a donor-derived infection transmitted by allograft. The third is a de novo infection acquired from the surrounding population (1). The widespread usage of CMV prevention strategies after kidney transplantation has changed the epidemiology of CMV infection. There are different CMV prevention strategies, including prophylaxis therapy with antiviral medications such as acyclovir (2, 19, 28), ganciclovir (2, 13), and valganciclovir (2, 8-10, 12, 14-17, 20, 23), while some patients didn't get prophylactic therapy (11, 18, 22, 26, 27, 29). Another prevention method is preemptive treatment once an asymptomatic viral replication is detected in the blood (2).

In our case, the patients didn't receive any prevention therapy after the transplant. Time of infection development: early-onset CMV infection (appears within the first 6 months after transplantation, five times as common) (5, 9, 10, 12, 13, 15-17, 19-21, 24, 26, 28, 29), late-onset CMV infection (takes more than 1 year to appear, associated with CMV sero-mismatch and impaired allograft function) (5, 8, 14, 17, 18, 22, 25, 31), very late-onset CMV infection (develops 10 years after transplantation) (8, 11, 27, 32).

In our case, our patient had developed a very late onset CMV infection after 15 years of kidney transplant, which is a rare onset of CMV infection. CMV infection in kidney transplant recipients is classified as either asymptomatic CMV infection (2, 20, 21) or active CMV disease. Active CMV disease is divided into CMV syndrome and tissue-invasive CMV disease (2). CMV syndrome is considered to be the presence of detectable viral replication in the blood associated with fever, leukopenia, arthralgia, and thrombocytopenia in the absence of tissue-invasive CMV disease (2, 9, 29, 31). The definition of tissue-invasive CMV disease is the presence of clinical symptoms and indicators of tissue invasion in addition to microbiologic evidence of active CMV infection. It can also be demonstrated in tissue biopsy specimens by histopathology or viral culture (2, 8, 10-20, 22-28, 32). Due to the wide tropism of CMV, tissue-invasive CMV disease has a variety of clinical presentations, such as enteritis (abdominal pain, nausea, vomiting, or diarrhea in the absence of any other cause) (2, 8, 10, 11, 17, 18, 21, 26, 27, 32), hepatitis (an increase in aspartate aminotransferase and alanine aminotransferase in the absence of any other cause) (2, 12), pneumonitis (cough, shortness of breath, or pulmonary infiltrates on radiologic imaging plus CMV in bronchoalveolar lavage fluid) (2, 16), meningoencephalitis (headache, nuchal rigidity, changes in mental state, or paralysis, together with CMV in cerebral spinal fluid) (2), retinitis (ophthalmologist-reported retinal edema or hemorrhage) (2, 12, 22), uveitis (10), sinusitis (23), and a scrotal ulcer (28). The cytopathic effects of CMV infection on kidney transplant cells, which can cause nephropathy (2, 13, 15, 16, 21, 24) and allograft loss (2, 9-11, 16, 21), as well as morbidity and death from severe CMV illness (2, 9, 11, 19), are its direct impacts. In our case, the patient had an invasive-tissue CMV disease confirmed by biopsy that showed eosinophilic intranuclear inclusions and variable granular purple cytoplasmic inclusions. The patient presented with a complaint of watery diarrhea with bloody threads, weakness, asthenia, anorexia, oliguria, and dysphagia and was diagnosed with CMV enteritis. The patient didn't develop any nephropathy or graft loss and remained alive. Upregulation of human leukocyte antigens (HLAs) and adhesion molecules, which might encourage acute allograft rejection, allograft loss, and death, are indirect effects of CMV infection. While R+ individuals are at moderate risk and D-/R- patients are at low risk, D+/R- patients are at the highest risk of having an active CMV infection or illness through primary infection with the virus. The administration of lymphocyte-depleting therapy or high-dose steroids to treat acute cellular rejection, as well as the use of lymphocyte-depleting agents for induction immunosuppression and mycophenolate for maintenance immunosuppression, are additional risk factors for CMV disease (2). As mentioned earlier, the clinical features of CVM are non-specific and are similar to many diseases, both infectious and non-infectious. The primary method for making the diagnosis is laboratory confirmation. However, CMV infection should be at the top of the differential diagnosis for

any kidney transplant patient who presents with signs of CMV syndrome, end-organ damage, and other CMV symptoms previously mentioned. The diagnostic techniques include microbiology, ophthalmology, and histopathology. The most common microbiological methods of diagnosis are viral culture, PCR amplification, and CMV pp65 antigen detection in peripheral blood leukocytes. The results of histopathology can also be used in the diagnosis and supported by in situ hybridization CMV tests or any immunohistochemistry tests. The PCR nucleic acid amplification test, which detects viral DNA or RNA, is currently the golden standard test for diagnosis, and it is the test that was used to establish the diagnosis in our case (2). In our case, the clinical presentation and the medical history of the kidney transplant of our patient led us to consider CMV infection, and after the findings on the upper gastrointestinal endoscopy and PCR test, we managed to confirm the diagnosis. Treatment for CMV infection is always indicated in viral syndrome and CMV disease, and when histological and immunohistochemical changes present tissue and organ damage, the antiviral treatment should be started as soon as the presence of the replicating virus is found by either antigenemia or reverse transcription polymerase chain reaction (RT-PCR) testing (6). The essential treatments for CMV infection in kidney transplant patients are ganciclovir (1, 8-11, 13-17, 19-23, 25-29, 31, 32) and valganciclovir (1, 8-14, 17-19, 21-23, 26, 27, 31, ), whereas intravenous ganciclovir is lately considered to be the gold standard treatment for severe CMV infections. On the other hand, there is not enough evidence of the efficiency of oral valganciclovir. As for mild to moderate cases of infection, we can use valganciclovir. The use of valacyclovir and acyclovir is no longer indicated (6). Ganciclovir resistance is an increasingly common problem in kidney transplantation patients. There is not enough information or clinical experience to determine the most appropriate treatment in the case of a resistant CMV infection (21). In cases of resistant CMV infection, the alternative choice is foscarnet, but it has limited use due to its frequent side effects and mainly nephrotoxicity (1, 9-12, 20, 21). Our patient was treated with intravenous ganciclovir; then, the patient remained well with a well-functioning graft and was free of evidence of CMV. CMV infection has a variant of a life-threatening complication such as DVT (which can lead to pulmonary embolism) (7), graft rejection, coronary atherosclerosis, and opportunistic infections (6). CMV viral infection can cause cryoglobulinemia which can induce hyperviscosity syndrome that can be responsible for the DVT(33).

In our case, our patient was admitted for the first time in the hospital for signs of CMV infection, which was treated for and discharged with no signs of DVT. Then, 5 days after the discharge (22 days after the initial CMV infection), he presented to the emergency room with signs of DVT, which were pitting edema, redness, pain, calf rigidity, and increased skin temperature in the lower right limb. He developed superficial vein inflammation, both of which were ipsilateral to the transplanted kidney and as mentioned earlier, in the context of the medical infrastructure in Syria, comprehensive testing, particularly for specialized conditions such as cryoglobulinemia, faces significant challenges. The economic hardships experienced by the patient and his family further compounded the situation, rendering them unable to afford the necessary diagnostic tests, which are not locally available. Additionally, the precarious situation in the country and the unfortunate financial constraints deterred any possibility of seeking these tests in neighboring countries.

Given these circumstances, despite the clinical relevance of a cryoglobulinemia test in confirming the diagnosis of CMV-related DVT, it was practically unfeasible to pursue this diagnostic avenue. Consequently, the clinical diagnosis of CMV-related DVT was established based on the patient's unilateral symptoms, the timing of DVT onset in correlation with the initial CMV infection, and was treated for both and discharged. Table {3}

In conclusion, cytomegaloviruses can cause deep venous thrombosis through a mechanism that needs to be better studied and analyzed. It is important to note that there is only one case report in the medical literature that is similar to ours (33) to the best of our knowledge, which makes our case considered to be a very rare case. In addition, CMV infection is a predisposing factor for thrombosis that needs to be considered in kidney transplant patients. Therefore, physicians should be aware of this serious complication and consider using prophylactic anticoagulants for high-risk patients.

### Author's contributions

R.H.A: design of the study, data collection, data interpretation and analysis, drafting, and the approval of

the final manuscript.

R.A: design of the table, data collection, data interpretation and analysis, drafting, and the approval of the final manuscript.

H.K: data collection, data interpretation and analysis, drafting, critical revision, and the approval of the final manuscript.

M.M: data interpretation and analysis, drafting, critical revision, and the approval of the final manuscript.

Z.A: data interpretation and analysis, drafting, critical revision, and the approval of the final manuscript.

A.A: The supervisor, patient care, drafting, critical revision, and the approval of the final manuscript.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

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**Consent** Written informed consent was obtained from the patient for publishing this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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