



## BRIEF REPORT

# Acute Human Cytomegalovirus Infection with Bleeding in Iran

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### Abstract

In December 2011, a 42-year-old male farmer was admitted to a hospital in Sanandaj (Western Iran) with fever and anemia in order to check whether he suffered from some infectious diseases. During the first 3 days after admission, the patient gradually developed progressive oliguria, fever, abdominal pain in the right upper quadrant, leukocytosis with toxic granulation, petechiae and ecchymosis, oral bleeding, and vomiting. The sonographic findings revealed splenomegaly and an increase in the thickness of the gall bladder wall. In order to manage the patient and taking into consideration the most probable differential diagnoses, diagnostic tests were performed on two blood samples collected from him, and real-time polymerase chain reaction for human cytomegalovirus was positive.

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## 1. Introduction

Human cytomegalovirus (HCMV) is a member of the *Betaherpesvirinae* subfamily of *Herpesviridae*, with double-stranded linear DNA genomes. There are many ways of detecting this family in the blood or sera [1]. This virus has a worldwide distribution. Between 40% and 100% of adults from different populations become infected by the 4<sup>th</sup> decade of life [2]. This virus can cause acute infection and serious complications in immunocompromised people, especially in transplanted patients or in pregnant women (which can cause fetal anomalies). Most HCMV infections in immunocompetent people are asymptomatic, and some produce a mononucleosis-like syndrome [3]. There have been reports of severe hemolytic anemia, severe thrombocytopenia, and various types of hemorrhage in some HCMV patients [4].

In the present study, an uncommon case of acute infection, which was caused by HCMV and involved multiple organs, is outlined. Reactivation of CMV occurs frequently in critically ill, immunocompetent patients and is associated with prolonged hospitalization or death.

## 2. Case report

On December 26, 2011, a man was admitted to Tohid hospital in Sanandaj (Western Iran), for the removal of kidney stones, with the following profile: farmer, 42 years old, diabetic, and resident of a village near Sanandaj, Iran. The patient had a fever of 38.9°C (102°F) and appeared anemic on early examination.

The patient had no history of hepatic, renal, vascular, or digestive system disorders. He consumed rabbit meat 2–3 weeks prior to admission. There were no significant findings on clinical examination of the cardiovascular system, pulmonary system, or abdomen, but he was restless and suffering from dizziness on admission. Over the first 3 days post admission, the patient gradually developed progressive oliguria, fever, abdominal pain in the right upper quadrant, leukocytosis with toxic granulation (in peripheral blood smear), petechiae and ecchymosis (Figure 1), oral bleeding, and vomiting. On an initial sonographic examination to evaluate the patient for the possibility of cholangitis, the spleen was found to be larger than usual (150 mm) and the thickness of the gall bladder wall was increased. The right kidney was larger than normal, and its corticomedullary echo was increased. On the 3<sup>rd</sup> day post admission, there were severe thrombocytopenia and increases in creatinine, alkaline phosphatase, bilirubin, and hepatic enzymes (alanine aminotransferase and aspartate aminotransferase; Table 1). Over the next few days, the patient's consciousness decreased, and he became disoriented with respect to time and place. Gradually, by the 7<sup>th</sup> day, the patient developed myalgia and hematuria, and became



**Figure 1.** Petechiae and ecchymosis in the upper limbs of the patient. Petechiae were seen on the 2<sup>nd</sup> day until the 16<sup>th</sup> day post admission.

icteric. On the following day, icterus decreased. On the 9<sup>th</sup> day, consciousness levels improved and his general condition gradually improved over the next few days.

Blood and urine cultures were negative during hospitalization. After admission, the patient was treated with supportive therapies, including blood transfusion, antibiotic therapy (ciprofloxacin, ampicillin/sulbactam, and metronidazole; from the 2<sup>nd</sup> day), receipt of fresh frozen plasma (from the 6<sup>th</sup> day), dialysis (from the 7<sup>th</sup> day), and administration of dexamethasone 8 mg Q, which was gradually tapered to 4 mg Q 12 hours (from the 12<sup>th</sup> day until discharge). The fever gradually diminished from the 13<sup>th</sup> day; dexamethasone dose was tapered and intravenous antibiotic therapy changed to cefixime and metronidazole.

The patient was transferred from an intensive care unit isolation ward to an infectious disease ward, on January 11, 2012. Meanwhile, the patient's platelet count was >85,000 and bleeding had stopped. On January 18, 2012, he was discharged with complete recovery after 23 days. The patients did not receive any antiviral treatment during his stay in the hospital.

The patient returned to the hospital for renal stone removal after 1 month and was operated upon. He was discharged with complete recovery after 48 hours. After 1 year, the patient was monitored, and he had no major medical problems.

The blood and serum samples were referred to the Department of Epidemiology of the Pasteur Institute of Iran on December 31, 2011 (the 5<sup>th</sup> day of admission) and January 18, 2012 (discharge day). The samples were sent to the relevant laboratories of the Pasteur Institute of Iran, to test for Crimean–Congo hemorrhagic fever (CCHF), hantavirus (Seoul, Khabarovsk, and Puumala), dengue fever, plague, tularemia, and leptospirosis. A survey of antihepatitis A virus antibody had already been carried out in the Tohid hospital (on the 2<sup>nd</sup> day post admission).

## 3. Results

The results of the tests on the first blood samples were negative for CCHF [enzyme-linked immunosorbent

**Table 1.** Hematological and biochemical test results from the 3<sup>rd</sup> day of admission until the recovery day.

| Tested variable | Day of admission |                 |                 |                 |                  |                  |
|-----------------|------------------|-----------------|-----------------|-----------------|------------------|------------------|
|                 | 3 <sup>rd</sup>  | 4 <sup>th</sup> | 5 <sup>th</sup> | 8 <sup>th</sup> | 13 <sup>th</sup> | 23 <sup>th</sup> |
| PTT             | —                | 30              | —               | 30              | 39               | —                |
| PT              | —                | 12              | —               | 12              | 13               | —                |
| INR             | —                | 1.2             | —               | —               | 1.5              | —                |
| WBC             | 23.7             | 29.41           | 20              | 19.5            | 13.8             | 23.9             |
| Hb              | 8                | 10.5            | 13              | 8.2             | 10.8             | 9.5              |
| Plt (×1000)     | 17               | 12              | 13              | 88              | 131              | 145              |
| Neutrophil (%)  | 95               | 88              | —               | —               | 94               | —                |
| Cr              | 10.2             | 9.4             | 9.9             | 7.4             | 4.5              | 3.3              |
| Bili T          | —                | 29.9            | 19              | 7.1             | 5.3              | 4                |
| Bili D          | 16.5             | 12.7            | 10.5            | 3.8             | 2.9              | —                |
| ALP             | 127              | 274             | 278             | 310             | 296              | 345              |
| Na              | —                | —               | 140             | 120             | 130              | —                |
| K               | —                | —               | —               | —               | 4.9              | —                |
| AST             | —                | 52.5            | 57              | 130             | —                | —                |
| ALT             | —                | 40              | 35.5            | 129             | —                | —                |

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bili D = bilirubin, direct; Bili T = bilirubin, total; Cr = serum creatinine; Hb = hemoglobin; INR = international normalized ratio; Plt = platelets; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cell.

assay (ELISA) and real-time polymerase chain reaction (RT-PCR), leptospirosis (ELISA and IFA), plague (ELISA, RT-PCR, and rapid test), and tularemia (RT-PCR). The patient's second blood sample was rechecked for leptospirosis, plague, tularemia, CCHF, hantavirus (Seoul, Khabarovsk, and Puumala; RT-PCR), dengue fever (ELISA and RT-PCR), HIV (ELISA rapid test), and Epstein–Barr virus (RT-PCR), and all were negative.

Tests for antihepatitis A antibodies was also carried out for the patient and his family, the results of which were positive for the patient, his wife, and one of his children, but immunoglobulin M was negative. Both test results were negative for his two other children.

After receiving the negative results for all the above infectious agents and according to the decision of the infectious disease specialist, an HCMV test was carried out on two blood samples (on the 5<sup>th</sup> day of admission to the hospital and on the day of discharge from the hospital), and the result of RT-PCR Primerdesign Ltd, Southampton, United Kingdom according to the manufacture's protocol, was positive for HCMV.

#### 4. Discussion

As the patient had fever, hemorrhage, icterus, and myalgia, along with abnormalities in the hepatic enzyme level and severe thrombocytopenia, which are indicative of hemorrhagic fever diseases, the necessary laboratory tests (for hantavirus, CCHF, dengue fever, and leptospirosis) were performed on received sera samples. Because the patient had been living in an area where cases of tularemia and plague infection had been reported many years ago, and as the patient reported rabbit

meat consumption 2–3 weeks prior to admission, the samples were also tested for plague and tularemia.

Suspicion of hepatitis A was based on an elevation of hepatic enzymes levels and its continuation over the following few days. According to the patient's condition and based on the laboratory results, a microorganism that was capable of causing acute multiple organ dysfunction was searched for. While manifestations of CMV infection in immunocompromised patients have been reported extensively in the literature, little attention has been paid to this infection in immunocompetent patients. Several reasons must be considered for the under-reporting of severe CMV infections in immunocompetent hosts. One reason may be the rather moderate accuracy of some routinely available diagnostic methods, such as serological tests. By contrast, molecular diagnostic methods, such as PCR, which are more commonly used in immunocompromised patients appear to be more sensitive and specific than serological or virus isolation tests [5]. There are relatively few studies evaluating the incidence of severe CMV disease in immunocompetent patients; in a study among 116 immunocompetent adults with acute CMV infection, 1.7% developed severe complications [6]. In another cohort study on 115 patients with acute CMV infection, 5.2% developed severe disease (including hematologic manifestation) [7]. CMV infection or reactivation occurs in 0–36% of the critically ill, but otherwise immunocompetent, hosts in the intensive care unit. Sepsis is one of the most frequently studied inciting events for CMV infection in these patients [8]. HCMV was considered by the infectious disease specialist, and the molecular test of the patient's serum later showed a positive result, indicating an acute self-limiting infection caused by this

virus. It should be mentioned that acute CMV infection only rarely causes these symptoms in patients [4,9]. Thrombocytopenia was reported in acute forms of CMV infection in immunocompetent persons in several studies, which parallels the findings of this case [4]. The acute clinical signs that were seen in this patient are usually seen in immunocompromised persons or transplanted patients, yet this patient was immunocompetent.

Because there were no documented findings of renal damage caused by HCMV in an immunocompetent patient, the renal disorders in this case are probably due to nephrolithiasis.

In general, the clinical process of the patient can be divided into three phases. The 1<sup>st</sup> week consisted of mild clinical signs and body temperature elevation. In the 2<sup>nd</sup> week, organ dysfunctions (such as hepatic, neurologic, hematologic, vascular, and renal dysfunctions) occurred, and finally over the last 9 days there was improvement in the patient's condition with supportive therapies, and he was discharged from the hospital. Severe life-threatening complications of CMV infection in immunocompetent patients may not be as rare as previously thought. As multiple organ involvement is rarely seen in acute CMV infection, consideration of this clinical probability may assist physicians in accurate diagnosis and appropriate treatment.

### Conflicts of interest

The authors declare that they have no conflict of interest.

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