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A Systemic and Severe Infection via Cytomegalovirus and Other Herpesviruses in a Young Apparently Immunocompetent Patient: A Case Report

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Abstract

The members of human Herpesviridae family are fully acknowledged as pathogenic agents in immunocompromised individuals, often responsible for a number of severe diseases. On the other hand, in immunocompetent hosts, Herpesviridae-related infections typically display an asymptomatic or paucisymptomatic course, sometimes manifesting with flu-like symptoms. However, such infections can occasionally cause organ damage or multisystemic involvement in healthy subjects. Herein, we describe the first case of a simultaneous co-infection by five different Herpesviridae family members in an apparently immunocompetent young subject. A 30-year-old Caucasian man presented to our medical unit with colitis. During hospitalization, he developed multi-organ damage involving heart, pancreas and liver. Quantitative polymerase chain reaction analysis showed positive results for cytomegalovirus, Epstein-Barr virus, human herpes virus 6, human herpes virus 7, and human herpes virus 8. Remission of clinical manifestations and complete negativization of viral load were achieved by antiviral therapy. To the best of our knowledge, such simultaneous infection by multiple herpesviruses causing a severe multi-organ dysfunction has never been described in patients with preserved immune function. Careful literature review showed that organ damage in immunocompetent subjects was reported in very few cases of co-infection by two herpesviruses, and in only one case of co-infection by three herpesviruses. Multi-organ damage in our patient likely resulted from additional effects induced by Epstein-Barr virus, human herpes virus 6, human herpes virus 7, and human herpes virus 8, through either a superinfection occurring after initial cytomegalovirus disease, or a simultaneous co-infection of the different viral agents. Moreover, the possibility of a transient and partial immune dysfunction, predisposing the patient to develop a severe herpesvirus-associated disease, cannot be completely ruled out. Although a formal indication to antiviral therapy has not been established in herpesvirus-infected immunocompetent individuals, our case supports the usefulness of such therapy in case of severe multi-systemic clinical manifestations. This original case report suggests that the possibility of multiple herpesvirus simultaneous infections should be taken into account in differential diagnosis for severe organ dysfunction, also in apparently immunocompetent subjects.

Keywords: Herpesviruses; Immunocompetent; Colitis; Myocarditis; Hepatitis; Pancreatitis

Introduction

Human herpesviruses are frequently encountered pathogens among immunocompromised individuals. In these subjects, they can cause severe and multiple organ dysfunctions, by either reactivation of latent infections or acquisition of primary infections. On the other hand, in immunocompetent hosts, the herpesvirus infections are usually asymptomatic, or eventually result in subclinical flu-like symptoms. However, severe, multi-visceral organ-damage-involving clinical scenario has been occasionally reported [1]. In particular, colitis, hepatitis [2], pancreatitis [3], pneumonia, myocarditis, mediastinitis, or thrombotic complications [4, 5] have been described in cytomegalovirus (CMV) reactivation or primary infection in apparently immunocompetent individuals, in a few cases occurring in a scenario of multiple organ damage [6]. An association of human herpes virus 6 (HHV-6) infection with hepatitis [7, 8], pneumonia [9], myocarditis or encephalitis [10, 11], as well as of Epstein-Barr virus (EBV) and pneumonia [12], encephalitis [13, 14], hepatitis has been rarely described [15]. The simultaneous infection by multiple herpesviruses is actually extremely rare, usually not associated to any clinical manifestations.

Herein, we describe the first case of a young apparently immunocompetent patient with a simultaneous infection of five different herpesviruses (CMV, EBV, HHV-6, HHV-7, and HHV-8). Furthermore, such multiple infections manifested with a multi-systemic and severe organ involvement.

This case report suggests that multiple infection via CMV and other human herpesviruses should be taken into account in differential diagnosis, when severe organ dysfunction is observed in immunocompetent patients, given that such events may not be exclusive of immunocompromised individuals.

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Case Report

A 30-year-old Caucasian male patient was admitted to our internal medicine unit with a 2-month history of diarrhea, rectal bleeding and weight loss (8 kg). Medical history was mute for relevant infections as well as for alcohol or drug consumption. At clinical examination, the patient was found afebrile, in general discrete conditions, with normal blood pressure (105/65 mm Hg) and pulse (82 bpm). Abdominal, cardiac, pulmonary and neurological functions were also normal at clinical examination. Laboratory data showed increased values for erythrocyte sedimentation rate (ESR) (35 mm/h, normal value < 20) as well as C-reactive protein (CRP) (20 mg/L, normal value < 2.9), whereas other biohumoral parameters (aspartate aminotransferase, alanine aminotransferase, renal function, electrolytes, glycemia, tumor markers, complete blood count, and blood coagulation tests) were within normal levels. Stool tests for parasites, bacteria and calprotectin were negative. Rectosigmoidoscopy investigation showed numerous hyperemia areas with fingernail shot erosions, appearing as edematous and congested mucosal tissue with lymphocytic, eosinophilic and plasma cellular infiltrates in the lamina propria at histological investigation, suggestive for intestinal bowel disease (IBD).

At the fourth day of hospitalization, the patient developed fever episodes and thoracic pain, exacerbated by breathing acts, and increased values of troponin I (0.62 ng/mL, normal value < 0.04), CRP (329 mg/L), and ESR (76 mm/h) were observed. Chest radiography was normal, while heart ultrasound showed pericardial effusion and a reduction in ventricular ejection fraction (33%), indicating pericarditis. In the following days, despite normalization of troponin values, the patient began to suffer from abdominal pain, associated with progressive deterioration of lipases (5,252 U/L, normal value 73 - 393), amylases (399 U/L, normal value 8 - 53), aspartate aminotransferase (238 U/L, normal value 15 - 37), alanine aminotransferase (278 U/L, normal value 12 - 78), and γ-glutamil-transferase (432 U/L, normal value < 55). Abdomen CT investigation revealed increased liver, spleen and pancreas volume, hyperemia and hyperperfusion of the bowel, and evidence of free fluid in pelvic cavity, suggestive for ongoing hepatitis and pancreatitis. Serological profile was compatible with ongoing CMV infection (CMV IgM: 26.4 U/mL, normal value < 18; CMV IgG: 78 U/mL, normal value < 12). In the scenario of a systemic infection, a broad-range viral screening evaluation was performed by molecular techniques, employing quantitative real-time DNA polymerase chain reaction. Molecular viral load determination was performed on DNA extracted from whole venous blood samples, with subsequent *in vitro* amplification by viral-genome-specific primers and fluorescent- and quencher-dye-labeled probes, and digital results analysis, through a Sample-to-Result protocol, according to manufacturer's instructions amplification (ELITe MGB® kits, run on ELITe InGenius machinery, ELITechGroup, Paris, France). Quantitative polymerase chain reaction disclosed CMV infection (3,220 copies/mL) and was also positive for EBV (796 copies/mL), HHV-6 (766 copies/mL), HHV-7 (889 copies/mL), and HHV-8 (1,092 copies/mL). Alterations of immune function could be excluded, since no variations in lymphocyte subset test and Ig class profile were found, and no evidence of autoantibodies (antinuclear antibodies and anti-dsDNA antibodies) or other common viral agents (HIV, HBV, and HCV) was detected. In light of the diagnosis of multiple viral infections, ganciclovir IV therapy (5 mg/kg every 12 h) was then administered. At 1 month post-treatment, ganciclovir IV treatment permitted complete normalization of CRP, ESR, pancreatic and liver marker values, as well as complete absence of CMV, EBV, HHV-6, HHV-7, and HHV-8 titer at polymerase chain reaction. Partial restoring of normal physiological functions was already evident after 2 weeks post-treatment, with relief to normal systolic left ventricular function (ejection fraction: 60%), regression of pericardial effusion at echocardiogram, and only a mild increase of pancreas volume at CT scan. The patient was then discharged with antiviral oral therapy (valganciclovir 450 mg every 12 h) for 10 days. At follow-up (1 month after discharge), the patient was asymptomatic, in general good clinical condition, with completely negative viral titer, and with no alterations at colonoscopy.

Discussion

To the best of our knowledge, concomitant infections by multiple herpesviruses, associated to severe multi-organ derangement, have never been reported before in immunocompetent patients. In fact, the human Herpesviridae family members rarely cause symptomatic infections and organ dysfunctions in healthy and immunocompetent patients, despite their acknowledged role as determining severe diseases in immunocompromised individuals [1]. Only a few reports can be found in literature, describing cases of multi-organ-involving herpesviruses infection in immunocompetent adults, CMV being the most frequent etiological agent [6]. Despite most cases in literature mainly showed single organ or system dysfunction, some case reports documented a scenario of multi-systemic involvement with two or, rarely, more organ damages [6, 16]. The gastrointestinal tract is generally the primary site to be involved by CMV, with typical symptoms consisting in diarrhea and rectal bleeding [17]. However, infections in other organs have also been described, such as hepatitis and pancreatitis, generally characterized by asymptomatic specific marker alterations, meningitis, encephalitis, hemolytic anemia, thrombocytopenia, thrombosis, uveitis, and pneumonitis [5, 6]. A cardiac system involvement with myocarditis or pericarditis presentation has also been reported, ranging from silent electro-/echocardiography anomalies to symptoms of overt cardiac dysfunction, including heart failure, cardiogenic shock, arrhythmias, and death [18].

In the case herewith reported, the patient initially presented with symptoms of colitis, thus giving rise to the suspicion of IBD. Even though a possible relationship between IBD and CMV infection is documented, as IBD and CMV infection were reported to trigger and exacerbate each other [19, 20], colitis in our case regressed after anti-viral treatment, suggesting that it was a manifestation of multiple herpesvirus infection. Furthermore, our patient also developed severe myocarditis

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and pancreatitis associated with liver involvement, thus giving to an unusual clinical scenario of multi- organ dysfunction.

Due to the severe and multi-systemic infection, we hypothesized a possible co-infection/superinfection via other viruses, and decided to perform a quantitative molecular viral panel search, including both CMV, that is more frequently observed in immunocompetent subjects, and other Herpesviridae family members, mainly detected in immunocompromised subjects. Noteworthy, the polymerase chain reaction analysis, which is a highly sensitive investigation for viral infection diagnosis and viral load monitoring, was positive for CMV and for four other herpesviruses, namely EBV, HHV-6, HHV-7 and HHV-8. Literature data report very few cases of herpesvirus co-infections in healthy immunocompetent individuals, mainly consisting in simultaneous EBV/CMV infection [21], while CMV/HHV-7 co-infection has been found to occur only in one case, manifesting as encephaloradiculomyelitis [22]. Moreover, a triple and asymptomatic infection of EBV/CMV/HHV-6, albeit uncommon, was reported in apparently healthy individuals aged ≥ 17 years [23].

Either a superinfection of EBV, HHV-6, HHV-7, and HHV-8, occurring after initial CMV disease, or a simultaneous co-infection of the different viral agents, may account for multi-organ involvement and enhanced clinical manifestations observed in our patient. As already hypothesized, clinical consequences associated to these other herpesviruses can be explained by indirect effects, consisting in interactions with CMV and promoting replication/persistence of other viruses, or by direct effects of viral co-infection within single cells [24]. Moreover, the possibility of a partial and transient immune dysfunction, likely due to psychophysical stress or another unknown asymptomatic disorder, cannot be excluded, resulting in increased herpesvirus disease risk in our otherwise healthy patient.

Although no established formal indications to antiviral therapy currently exist for immunocompetent subjects, the use of ganciclovir in case of severe clinical manifestations has been reported [5]. Moreover, previous observations reported an increased mortality in CMV-infected immunocompetent patients with extra-CNS vs. only-CNS involvement [6], thus placing our patient in a higher-risk class and making him a suitable candidate for antiviral therapy. Actually, our patient did benefit from ganciclovir and valganciclovir treatment, with complete relief of symptoms and normalization of altered biohumoral and viremia values after 1-month-long therapy.

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Declarations

The study was performed in accordance with the ethical standards on human experimentation and the Helsinki Declaration of 1975, as revised in 1983. Written informed consent for publication of this case report was obtained from the patient.

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

All authors certify that he or she has participated sufficiently in the intellectual content, the analysis of data. Each author has reviewed the final version of the manuscript and approves it for publication.

Abbreviations

CMV: cytomegalovirus; HHV: human herpes virus; EBV: Epstein-Barr virus; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IBD: intestinal bowel disease

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