Simultaneous cytomegalovirus and herpesvirus meningitis in an adolescent immunocompetent patient: a case report

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Background: Viral meningitis is an inflammatory condition of the meninges that manifests as neurological dysfunction with variable clinical signs, ranging from mild manifestations (such as headache) to seizures and intracranial hypertension. The clinical presentation can vary with the patient's age, immune status, and etiology of the disease, with many symptoms being nonspecific. Coinfections in central nervous system (CNS) infections are rare, more commonly observed in immunocompromised patients. We report the first known case of viral meningitis due to concurrent cytomegalovirus (CMV) and herpes simplex virus type 2 (HSV-2) in an immunocompetent adolescent, highlighting a significant clinical consideration in the management of similar cases.

Case Description: We present a case from March 2021 involving a 16-year-old previously healthy Latin male adolescent with no known immunity-related abnormalities, who presented diarrhea with macroscopic blood, headache, and fever. He was diagnosed with a rare viral coinfection of CMV and HSV-2 meningitis. Investigations to rule out primary or secondary immunodeficiency showed no abnormalities. The patient received antiviral therapy for 21 days with ganciclovir (5 mg/kg/dose), leading to a favorable outcome without subsequent neurological deficit or adverse events.

Conclusions: This case enriches clinical practice by demonstrating effective management in an unlikely host, thereby broadening our understanding of viral meningitis in immunocompetent patients and informing future diagnostic and treatment strategies.

Keywords: Herpes simplex encephalitis; cytomegalovirus (CMV); encephalitis; meningitis; case report

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Introduction

Central nervous system (CNS) infections of viral origin result in inflammation in distinct anatomical areas, including the meninges (meningitis), brain parenchyma and cranial nerves (encephalitis). Nevertheless, some patients may exhibit an inflammatory process that compromises the intricacy of the CNS and can be challenging to differentiate clinically (1). Traditionally, encephalitis is often distinguished by an alteration in the state of consciousness; however, this is not an exclusive finding of this condition (2). Patients with CNS infections may present with headache, neurologic deficit, fever, altered mental status, seizures, cerebrospinal fluid pleocytosis, and/or abnormalities on neuroimaging or electroencephalogram (3). The most common viral etiology varies with geographic location, individual factors (e.g., immunity status), and seasonal changes, particularly in relation to the endemic circulation of enteroviruses arboviruses. Overall, 7 in every 100,000 residents in the United States are hospitalized for encephalitis each year, and it is estimated that 20–50% of cases are attributed to certain types of neurotropic viruses, including herpes simplex virus (HSV) (which accounts for 50–75% of infections), varicella zoster virus, enteroviruses, and arboviruses. Other less commonly identified viruses include cytomegalovirus (CMV), herpes viruses 6 and 7, Epstein Barr virus, and influenza virus (4).

Despite the robust immunological barrier of the CNS, viruses have the capacity to infect nervous tissue through different mechanisms. Some induce endothelial lesions that facilitate their passage through the blood-brain barrier (3). Besides direct infection of the CNS has also been described and can involve the choroid plexus epithelium. Also, hematopoietic cells infected by viruses entering the CNS, direct autoimmune mechanisms, and postinfectious autoimmune responses triggered by specific viruses which may contribute to the development of progressive acute disseminated encephalomyelitis several weeks after an infectious episode (1,2).

To rule out potential infection causes, a comprehensive approach that considers geographic location, travel, and exposure history, contact with animals, health status of close people, contact with sick people, occupation, sexual practices, drug use, and health status [including vaccinations, medical conditions, and medications as well as possible immunosuppression due to human immunodeficiency virus (HIV), medications, or other causes] (2). If viral infection is suspected, the cerebrospinal fluid should be examined for pleocytosis, with predominance of lymphocytes (absence of this finding does not rule out viral encephalitis) and erythrocytes (which may be present with certain viruses, such as herpes or La Crosse virus), a slight increase in protein levels, and low or normal glucose levels (1,2). Currently, there are specific viral panels for CNS infections based on polymerase chain reaction (PCR), which is used as the gold standard for diagnosing this condition (2,5). Nevertheless, in most cases, diagnosis is based on the patient's clinical findings because a specific etiology is difficult to identify despite the use of exhaustive tests (6). However, in rare cases, coinfection has been reported, particularly in patients with compromised immune systems or other risk factors (7).

We present the case of a previously healthy adolescent with no known history of immunosuppression who presented with CMV and HSV-2 meningitis confirmed using PCR test. We present this article in accordance with the CARE reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-23-67/rc).

Highlight box

Key findings

- Immunocompetent patients may have coinfections during central nervous system infections. It should always be suspected in patients with insidious symptoms and neurological impairment.

What is known and what is new?

- Viral coinfection in meningitis is rare, its management will depend on the specific etiology and the prevalence in local epidemiology.
- In coinfection with cytomegalovirus and herpes simplex type 2, management with ganciclovir can be effective and safe in pediatric patients.

What is the implication, and what should change now?

- The possibility of presenting meningitis due to coinfection with different pathogens in immunocompetent patients should be considered at the diagnostic approach, and if available, molecular diagnostic tests such as polymerase chain reaction are of great importance to guide definitive therapy.

Case presentation

In March 2021, a previously healthy 16-year-old Latino adolescent of Latin American descent, with no known immunity-related abnormalities, presents with 4 days of diarrhea and macroscopic blood associated with fever was transferred to a first-level care center. He was treated with metronidazole and antipyretics, although the specific

Table 1 Patient's cerebrospinal fluid analysis results

Variables	Normal reference	Result
Appearance	Clear colorless	Clear
Protein (mg/dL)	20–45	125
Glucose (nmol/L)	50–65	42
Gram stain	Negative	Negative
White cell count	<5 cells	0
CSF:serum glucose ratio	0.4–0.9	0.41

CSF, cerebrospinal fluid.

dosages are not known. The patient's coproscopy had no evidence of parasitic structures. His gastrointestinal symptoms improved after 4 days of treatment. However, he had new onset high intensity throbbing and holocranial headaches with persistent fever. Additionally, due to respiratory symptoms without respiratory distress, a PCR test for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus was requested, which returned negative. Moreover, he presented with no history of recent travel, medication use, contact with animals, or any other known relevant history. Therefore, after 8 days of persistent symptoms, he consulted our institution.

On admission, the patient presented with good general condition, Glasgow score of 15/15, fever, headache, photophobia, and neck stiffness, with no focal signs and abnormal movements. Therefore, a suspicion of neuroinfection was considered and a lumbar puncture was performed. The cerebrospinal fluid gram stain revealed hypoglycorrhachia, hyperproteinorrachia, and no pleocytosis or the presence of bacteria (*Table 1*). Moreover, the BioFire FilmArray Meningitis/Encephalitis Panel revealed that the cerebrospinal fluid was positive for CMV and HSV-2.

Based on these findings, the patient was examined by the infectious disease and neurology departments and start administration of 5 mg/kg/dose ganciclovir every 12 hours. Cerebrospinal fluid cultures were negative after 5 days. Additionally, given the unusual finding of CNS viral coinfection in this previously healthy patient, further tests were conducted to rule out primary or secondary immunodeficiency. These tests included immunoglobulin level and complement tests as well as flow cytometry of CD3, CD4, and CD8 T lymphocytes; CD19 and CD20 B lymphocytes; CD16 and CD56 natural killer (NK) lymphocytes; and total lymphocytes, all of them normal. Moreover, enzyme-linked immunosorbent assay (ELISA) HIV assay, syphilis, hepatitis B and C serology, Mantoux test, bacilloscopy, acid-fast bacilli smear and culture in sputum were performed with negative result. HIV viral testing was not performed in the cerebrospinal fluid (CSF), and a CMV viral copies of 10,240 copies/mL were detected in the CSF. Furthermore, a standard brain magnetic resonance imaging (MRI) and continuous electroencephalography were performed with normal results.

After 2 days of treatment, the patient's headache and fever resolved. Given the absence of neurological deterioration and favorable clinical progression, it was decided to administer 21 days of intravenous antiviral therapy and a control cerebrospinal fluid study was not performed. Consequently, he was discharged with instructions for a multidisciplinary outpatient follow-up examination and additional immunodeficiency tests. Unfortunately, following discharge, the patient did not pursue further follow-up appointments with our institution. There were no adverse events during patient care.

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee(s) of Instituto Roosevelt and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's mother for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Viral infections of the CNS represent a significant challenge for clinicians because of their diverse and nonspecific clinical manifestations, which may coincide with other etiologies. In a cohort study of patients aged <14 years, of 287 patients who met the criteria for encephalitis, 43% presented with confirmed noninfectious causes, including autoimmune encephalitis and acute disseminated encephalomyelitis (8). Therefore, depending on the individual findings of the patient, other causes must be ruled out. Generally, neurological dysfunction (impaired consciousness, headache, papilledema, and seizures) with an acute presentation (for 24–72 hours) associated with systemic manifestations, such as fever, rash, arthralgia, myalgia, gastrointestinal symptoms, should be suspected in viral encephalitis (1,9).

In the present case, viral meningitis was suspected

because of the acute onset of intense headache associated with an intractable febrile syndrome preceded by gastrointestinal and respiratory symptoms without altered mental status. As a result, tests for suspected neuroinfection were performed, even though other causes had been ruled out.

Two of the main causes of viral CNS infection in pediatric patients are enterovirus and HSV. The latter, HSV, belongs to the *Herpesviridae* family, have a single linear double-stranded DNA molecule, an icosahedral capsid surrounded by a tightly adherent integument, and a lipid bilayer envelope (10). Furthermore, like the other members of the *Herpesviridae* family, these viruses have latency and reactivation properties that cause recurrent infections, mainly in immunocompromised patients. Neurological conditions linked to HSV can arise from either the initial infection or the reactivation of latent virus (10-12). Clinical manifestations of HSV CNS infection vary, but these typically include fever, behavioral changes, aphasia, seizures with focal electroencephalographic alterations, focal signs, or altered mental status. In a 12-year prospective study of pediatric patients, fever was observed as the primary symptom, followed by seizures (69%) (11). Additionally, changes in neuroimaging have been documented, such as the areas of hyperintensity or decreased attenuation of the temporal lobes, cingulate gyrus, orbitofrontal cortex, and insular region. These patients may present with hemorrhagic foci as a late finding. Elevated erythrocytes and pleocytosis are documented in the cerebrospinal fluid as characteristic findings in approximately 50% of patients, although many patients may not present with this finding without exclusion of an infection. Subacute and mild cases have also been documented, although the typical presentation of this infection is severe (2,10). Our patient had elevated protein and decreased glucose levels in the cerebrospinal fluid, but without pleocytosis, and MRI scan revealed no abnormalities in the brain parenchyma (10,13).

Another rare virus, mainly observed in immunocompromised patients, is the CMV, which also belongs to the *Herpesviridae* family. It has a double-stranded DNA, a capsid, an amorphous integument or matrix, and a phospholipid-rich envelope. Due to its clear tropism for the central and peripheral nervous system, CMV can cause encephalitis, aseptic meningitis, transverse myelitis, radiculopathies, Guillain-Barr syndrome, Horner syndrome, brachial plexus neuropathy, and polyneuropathies, among others (14-16). It should be considered in infants with the onset of seizures and in elderly patients with fever, altered mental status, signs of neurological focalization, and cranial nerve abnormalities. Hyperproteinorrachia is documented as a characteristic finding on cerebrospinal fluid examination in these patients. Brain MRI scans may also reveal nonspecific diffuse white matter hyperintensities. A retrospective study of immunocompetent pediatric patients with CMV encephalitis found that infants were the most affected group of patients, seizures were the most frequently occurring symptom, and elevated cerebrospinal fluid protein was the most characteristic finding (15). Our patient's age is a striking feature as it represents a rare age group for infection with this virus and was immunocompetent. The treatment of choice for such cases is ganciclovir, which is a competitive inhibitor of CMV DNA, and inhibits its synthesis by acting on viral DNA polymerase. Treatment over 4 weeks has demonstrated reasonable efficacy and complete recovery rates (2,13-15).

As previously mentioned, coinfection is rarely found and is generally associated with immunocompromised patients. VanderVeen *et al.* reported the case of a 15-year-old patient who developed encephalitis due to varicella zoster virus and Jamestown Canyon virus after a short course of oral corticosteroids for the treatment of radicular pain, with subsequent adverse outcome (17). However, among immunocompetent patients, cases of coinfection have been described. El-Duah *et al.* reported the case of an 11-year-old patient with an acute episode of fever, malaise, and deterioration of general condition with subsequent diagnosis of coinfection with varicella zoster virus and HIV (18). Another study evaluating the viral etiology of patients suspected of having encephalitis, three cases of viral coinfection were documented; of these, two were caused by HSV-1 + herpes virus 6 and the other by HSV-1 + parvovirus B19 (19). The question of whether neurological symptoms related to CMV arise from a primary infection or a reactivation of the disease is often debated. However, when CMV is documented alongside 'more common' neuroinfectious viruses like HSV, the hypothesis of reactivation is generally favored (12).

Patients who do not receive early treatment have high risk of complications and mortality. However, even with the use of an optimal therapy, mortality rates in the case of HSV-1 encephalitis are found to be approximately 25% (9). Therefore, this infection must be treated as a true emergency with prompt diagnosis and treatment. The treatment of choice for our patient was ganciclovir because of its efficacy against both pathogens, although studies supporting its use as a first-line treatment are limited. The

use of ganciclovir along with foscarnet is also described in the literature for patients with viral infections caused by CMV (13,15).

To the best of our knowledge, this is the first documented case of viral meningitis caused by coinfection of CMV and HSV-2 in an adolescent immunocompetent patient. This underscores the significance of a comprehensive clinical approach, enabling the suspicion of this pathology even amidst a non-specific clinical presentation and in a patient lacking recognized risk factors. Regrettably, we were unable to assess the patients' HSV and CMV serological status, making it impossible to distinguish between primary infection and reactivation. Additionally, we acknowledge limitations in our understanding, notably the absence of information regarding the patient's follow-up and clinical progression.

Conclusions

In conclusion, it is important to consider viral encephalitis when treating patients with some degree of neurological changes. Some patients exhibit an insidious onset with mild clinical symptoms, although the clinical course is often severe. Therefore, diagnostic suspicion is important for the appropriate treatment of such patients. In addition, the possibility of presenting encephalitis due to coinfection with different pathogens in immunocompetent patients should be considered at the diagnostic approach, and if available, molecular diagnostic tests such as PCR are of great importance to guide definitive therapy. Finally, we insist in the relevance of this case being an immunocompetent adolescent, encouraging us to bring light to the diagnosis of encephalitis in different types of patients.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://pm.amegroups.com/article/view/10.21037/pm-23-67/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-23-67/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee(s) of Instituto Roosevelt and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's mother for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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