Case Report

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A Rare Case of Rickettsia and Herpes Simplex Virus 1 Co-infection in a Male Patient with Meningoencephalitis

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Abstract

Herpes simplex viruses (HSVs) belong to the *Herpesviridae* family. Close contact is the primary mode of transmission for both HSV-1 and HSV-2, leading to a persistent lifelong infection. HSVs are widely recognized as causative agents of viral infections affecting the central nervous system, capable of presenting as both meningitis and encephalitis. Herpes simplex virus type 1 (HSV-1) is the predominant viral cause of encephalitis, accounting for the majority of cases. Here, a rare co-infection case of meningoencephalitis, associated with HSV-1 and rickettsia is described. A 42-year-old man presenting with non-remitting headache for 6 days, fever, sweating, and muscle aches was admitted to the Emergency Department. His Weil-Felix test was positive for Proteus OX2 indicating rickettsial infection. Therapy started promptly however patient's condition deteriorated. Cerebrospinal fluid (CSF) analysis revealed lymphocytic pleocytosis, and elevated protein concentration. CSF molecular analysis was positive for HSV-1. His cranial MRI indicated cytotoxic edema and gyral enhancement at the right temporal lobe. He was administered acyclovir for 14 days during his hospital stay and was successfully discharged. This case report highlights that HSV-1 meningoencephalitis can co-occur with rickettsia infection in immunocompetent individuals, and co-infection with other agents should always be considered to avoid the progression of the disease.

Keywords: Rickettsia, HSV-1, co-infection, meningoencephalitis, polymerase chain reaction

Introduction

Herpes Simplex Virus (HSV) is a viral agent that causes infections in humans which can result in the formation of painful blisters or ulcers. The infection persists throughout a person's lifetime, and is characterized by periodic re-activation at the initial site of infection [1]. HSV is classified into two distinct types, Herpes simplex virus 1 (HSV-1) and Herpes simplex virus 2 (HSV-2). HSV-1 is mainly spread through oral-to-oral contact and commonly leads to orolabial herpes, also known as cold sores. In addition, HSV-1 can cause less common conditions such as keratitis, ocular complications, and encephalitis. While HSV-1 genital infection resulting from oral-to-genital contact is increasingly observed, re-activation is less frequent compared to HSV-2. HSV-2 is primarily transmitted through sexual contact and causes genital herpes [2]. HSV has the capacity to invade the central nervous system (CNS) during primary infection or through latent state re-activation. Following the primary infection, HSV can become latent in lymphoid tissue or in ganglia. Typically, HSV-1 travels through the trigeminal and/or olfactory ganglia to the CNS, where it duplicates and has the potential to induce encephalitis [3]. Among the herpes viruses currently identified, the neurotropic HSV-1 can invade both CNS and the peripheral nervous system (PNS). HSV encephalitis (HSVE) is a life-threatening medical emergency. The worldwide incidence of HSVE is estimated to be 2-4 cases/1,000,000 [4].

Mediterranean spotted fever (MSF) is a tick-borne rickettsiosis of the spotted fever group (SFG), endemic in the Mediterranean basin. *Rickettsia conorii* is a vector-borne, obligate intracellular bacterium which is the causative agent of MSF, mainly in the Mediterranean area and the surrounding countries [5]. The arthropod vector of this bacterium is known to be the brown dog tick *Rhipicephalus sanguineus*. A recent study in Cyprus has shown that the number of rickettsiae positive patients have gradually increased between 2016 and 2020 [6]. While typical symptoms of MSF are diverse and include fever, maculopapular rash, and a characteristic eschar ("tache noire"), atypical clinical features and severe multi-organ complications may also be present. Meningitis, encephalitis, and acute disseminated encephalomyelitis are the primary neurological conditions frequently observed in cases of rickettsial infections [7].

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In this case report, we present a rare condition of meningoencephalitis due to HSV-1 and rickettsia co-infection in an immunocompetent individual.

Case Report

A previously healthy 42-year-old man, presenting with non-remitting headache for 6 days, fever, sweating, headache and muscle aches was admitted to the Emergency Department at Near East University Hospital, Cyprus. He had used azithromycin previously. He reported not feeling well the night before admission, and had a shoulder fracture after he fell at home. Body temperature was 39°C on admission. On the first physical examination, the patient had decreased level of consciousness, confusion, tendency to sleep, and difficulty in cooperation. In the physical examination of the patient, neck stiffness and Kernig and Brudzinski signs were evaluated as negative. The patient indicated having had tick bites earlier although none were observed upon admission. He also noted living in an area where Phlebotomus flies were abundant. No tissue related to rickettsiosis was found during the examination. The patient was consequently referred to the Infectious Disease Department.

Laboratory test results showed an increased C-reactive protein level (2,05 mg/dL), high peripheral leukocyte cell count (11,1 x 103/µl), high procalcitonin (0,22 ng/mL), and a high aspartate aminotransferase (serum glutamic-oxaloacetic transaminase, AST-SGOT) level of 49 U/L. The Weil-Felix agglutination test was performed for OX 19, OX 2, OXK strains of Proteus species. The serum Weil-felix (Proteus) test was positive for Proteus OX2 at 1/640. Patient's blood, urine and rectal cultures, brucella agglutination (Rose Bengal) and Grubel-Widal salmonella tube agglutination tests were negative. The patient was immediately treated with 2x1 500 mg ciprofloxacin, however his overall condition deteriorated several hours later.

Patient's serum creatinine levels were high (1,51 mg/dL) therefore brain magnetic resonance imaging (MRI) could not be performed. Patient's creatinine levels were lowered to 0.69 mg/dL with fluid intake and MRI was consequently performed. His cranial MRI indicated signal increase at right temporal lobe on T2W images (Figure 1) and gyral enhancement on T1W C+ images (Figure 2).

Lumbar puncture (LP) was immediately performed and cerebrospinal fluid (CSF) was collected. CSF biochemical analysis revealed high glucose (104 mg/dL) and elevated protein levels (6313 ml/dL) due to the traumatic LP. The cellular CSF analysis indicated pleocytosis, with a leukocyte cell count of 280,000 cells/µL, 90% lymphocytes, suggestive of a possible viral aetiology. RT-qPCR analysis of CSF was performed using QIAstat-Dx Meningitis/Encephalitis Panel and was positive for herpes simplex virus type-1 (HSV-1) (Figure 3).

His HSV-1 IgG was also found to be positive with 27,94 RU/mL (normal range: 0-16 RU/mL), while HSV-1 IgM

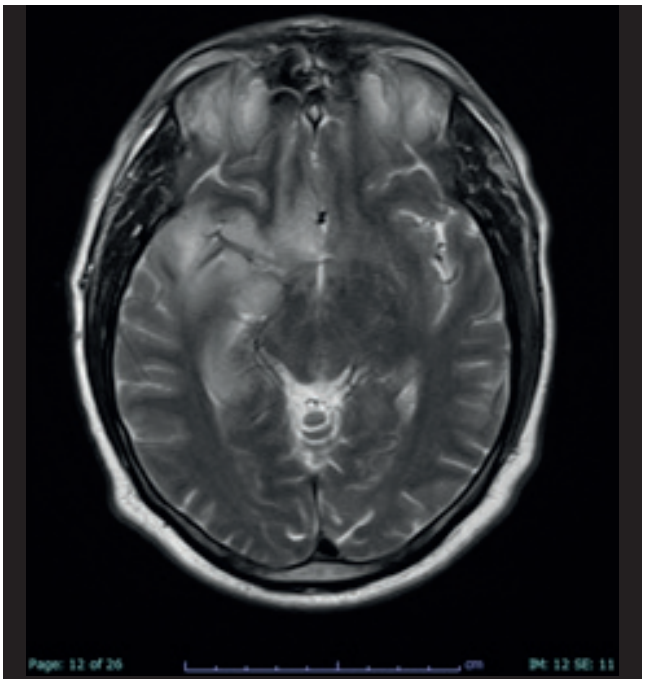

Figure 1. Patient cranial MRI axial T2W image showing hyperintensity at right temporal lobe, due to cytotoxic edema

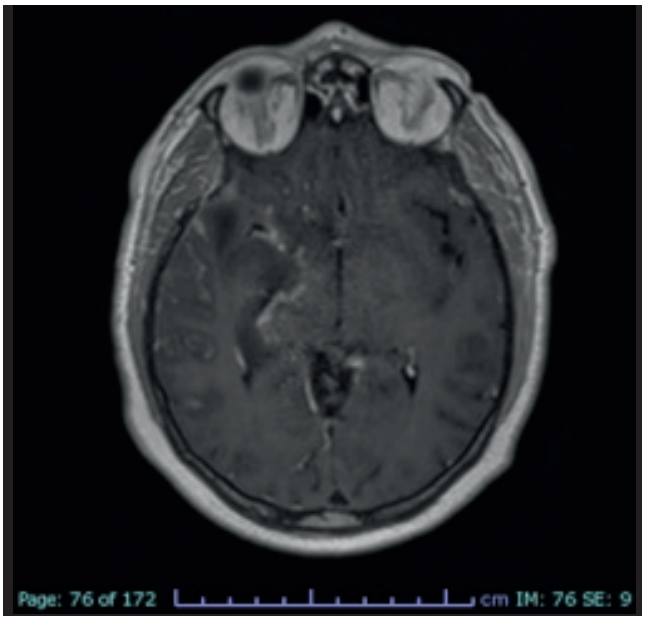

Figure 2. Patient cranial MRIaxial T1W image with IV contrast material indicating gyral enhancement

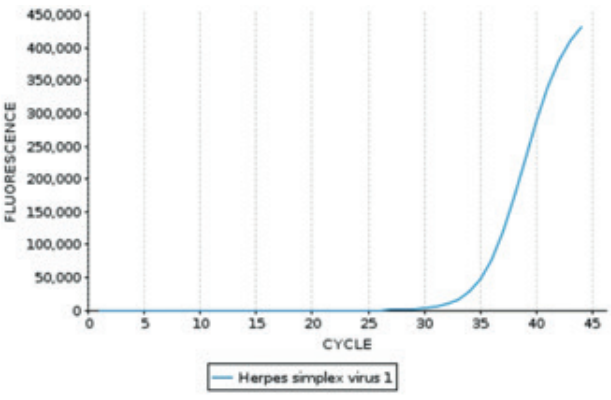

Figure 3. RT-qPCR amplification of Herpes Simplex Virus-1 DNA in the patient CSF sample

was negative. He was immediately administered with 750 mg of acyclovir intravenously three times daily (2250 mg total) and 2x1 1 g ceftriaxone intravenously for 14 days. The patient recovered successfully within two weeks and was followed up to ensure no neurological sequelae.

Discussion

The current study represents a rare case of co-infection of HSV-1 and rickettsia in a patient presenting non-remitting headache, fever, sweating, headache, and muscle aches. Analysis of CSF revealed a positive HSV-1 PCR test, lymphocytic pleocytosis, and elevated protein concentration. The patient had positive HSV-1 IgG levels which indicated HSV-1 re-activation, resulting in HSV-1 encephalitis. Furthermore, his serology tests also showed a rickettsia co-infection.

Despite the Enteroviruses being the most common agents, HSVs are also among the main agents responsible for viral meningitis and may cause neurological morbidity [8]. HSV can lead to diverse neurological symptoms such as meningitis, myelitis, polyradiculopathy, and encephalitis. While these syndromes may indicate primary HSV infection, they typically arise from the re-activation of the latent virus in the sensory ganglia. Apart from viral encephalitis, HSV-1 is infrequently responsible for meningoencephalitis and may lead to permanent neurologic sequelae. In the diagnosis of viral meningitis, detection of HSV DNA in CSF via polymerase chain reaction (PCR) is considered as the gold standard with high sensitivity [9]. In the case of HSV encephalitis, as symptoms are not specific to the HSV-1, prompt diagnosis and therapy are essential for reducing mortality and morbidity.

Rickettsia is an obligate bacterium that causes flea, tick, or mite-borne diseases. In addition, they can cause neurological illnesses including encephalitis, meningitis, and acute disseminated encephalomyelitis. In cases of neurological involvement, convulsion, altered sensorium, fever, behavioural changes, confusion, headache, rash, and semi-comatose conditions have been reported in the literature. Serological evaluation of different rickettsial species is usually performed by the Weil-Felix test which is an easy and rapidly performed test that can be implemented to confirm the diagnosis of rickettsial infections. Although the test has low sensitivity and specificity, it is simple and cost effective, hence can guide the clinicians for the appropriate treatment.

This report presents a rare case of rickettsia and HSV-1 co-infection without blisters or ulcers. The patient presented with diverse symptoms not only specific to HSV-1 encephalitis. He did not have any travel history or rash to suggest rickettsial infection but he indicated living in a rural area where *Phlebotom*us flies were frequently observed. Following the LP procedure, laboratory investigations revealed CSF pleocytosis with mononuclear predominance, suggesting a viral infection. A positive RT-PCR test for HSV-1 confirmed the viral aetiology assumption and the resulting diagnosis was HSV-1-associated encephalitis. The elevated protein levels observed in the CSF analysis have been reported to be commonly detected in HSV-1-associated encephalitis cases [8].

As the patient was immunocompetent and had no history of recent symptoms, the serological analysis was suggestive of HSV re-activation. It can be hypothesized that HSV-1 re-activation occurred due to the rickettsial co-infection. However, the opposite is also conceivable, in which infections due to both agents occurred simultaneously. In the literature, a similar viral co-infection with *Rickettsia helvetica* and HSV-2 has been documented in a meningoencephalitis case [10].

In conclusion, the early diagnosis of encephalitis is essential for the rapid implementation of appropriate therapy. This study highlights the significance of investigating the presence of rickettsial infections in endemic areas for meningitis cases of uncertain aetiology. During diagnosis, co-infections should also be always considered by the clinicians.

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