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Simultaneous genital ulcer and meningitis: a case of EBV infection

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ABSTRACT

The Epstein-Barr virus (EBV) is associated with a broad spectrum of diseases, mainly because of its genomic characteristics, which result in different latency patterns in immune cells and infective mechanisms. The patient described in this report is a previously healthy young man who presented to the emergency department with clinical features consistent with meningitis and genital ulcers, which raised concern that the herpes simplex virus was the causative agent. However, the polymerase chain reaction of cerebral spinal fluid was positive for EBV. The authors highlight the importance of this infection among the differential diagnosis of central nervous system involvement and genital ulceration.

Keywords
Meningitis, Viral; Epstein-Barr Virus Infections; Ulcer; Genital Diseases.

CASE REPORT

A 27-year-old previously healthy man sought the medical facility complaining of a 4-day history of unmeasured fever, low back pain, nausea, vomiting, pulsatile headache, nuchal stiffness, and pain. He denied any skin rashes. He had unprotected sexual intercourse followed by the emergence of painless genital ulcers a week before the onset of the neurological symptoms. He had no history of chronic oral ulcers and autoimmune family disorders.

The physical examination revealed blood pressure of 140/80 mmHg, pulse rate of 95 beats per minute, respiratory rate of 22 respiratory movements per minute, room air oximetry of 98%, axillary temperature of 37.2°C, and nuchal stiffness. Brudzinski's sign was also present, but a funduscopic examination was not performed. Three clustered, superficial, clean-based, painless ulcers were present on the balanopreputial sulcus (Figure 1). Kernig or Laségue's signs were absent and the remaining physical examination was normal.

Immediately after the initial laboratory work-up had been collected (Table 1), the cerebrospinal fluid (CSF) examination was performed (Table 2) and the patient was hospitalized. The CSF was turbid and xanthochromic after centrifugation. Based on the laboratory data and the CSF mononuclear pleocytosis with negativity of the Gram stain, the hypothesis of aseptic meningitis was highly considered. The presence of genital ulcers following unprotected sexual intercourse raised the concern of meningitis due to the herpes simplex virus type 2; therefore, intravenous acyclovir 10mg/kg/dose every 8 hours

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Table 1. Initial laboratory work-up

Exam	Result	RV	Exam	Result	RV
Hemoglobin	16.1	12.3-15.3 g/dL	ALT	26	9-36 U/L
Hematocrit	47.5	36.0-45.0%	AST	32	10-31 U/L
Leukocytes	15730	4.4-11.3 × 10^3/mm^3	ALP	65	53-128 U/L
Bands	0	1-5%	γGT	39	2-30 U/L
Segmented	82.8	45-70%	TP/Albumin	6.8/4.1	6,4-8,3/3,5-5,2 g/dL
Eosinophils	0	1-4%	Amylase	53	30-118 U/L
Basophils	0.2	0-2.5%	Lipase	51	13-60 U/L
Lymphocytes	11.4	18-40%	ESR	3	0-20mm/h
Monocytes	5.6	2-9%	HIV	Negative	Negative
Platelets	339000	150-400 × 10^3/mm^3	HBs antigen	Negative	Negative
INR	1.09	1.0	Anti-HBc IgM	Negative	Negative
Urea	27	5-25 mg/dL	Anti-HCV	Negative	Negative
Creatinine	0.85	0.4-1.3 mg/dL	VDRL	Negative	Negative
CRP	<5	<10 mg/L			

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; γGT = gamma-glutamyl transpeptidase; HBc IgM = hepatitis B core IgM HBs = hepatitis B surface; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; RV = reference value; TP = total protein; VDRL = venereal disease research laboratory.

Table 2. Cerebrospinal fluid examination

Parameter	Result	RV	Parameter	Result	RV
Cells	1621	<5/mm^3	Gram	Negative	Negative
RBC	64	0/mm^3	Protein	173.8	18-58 mg/dL
Neutrophil	6	Occasional	Glucose	49	*mg/dL
Monocytes	49	30%	Lactate	41.6	<35 mg/dL
Lymphocytes	42	70%	Culture	Negative	Negative

* = two-thirds of the serum glucose. RBC = red blood cell.

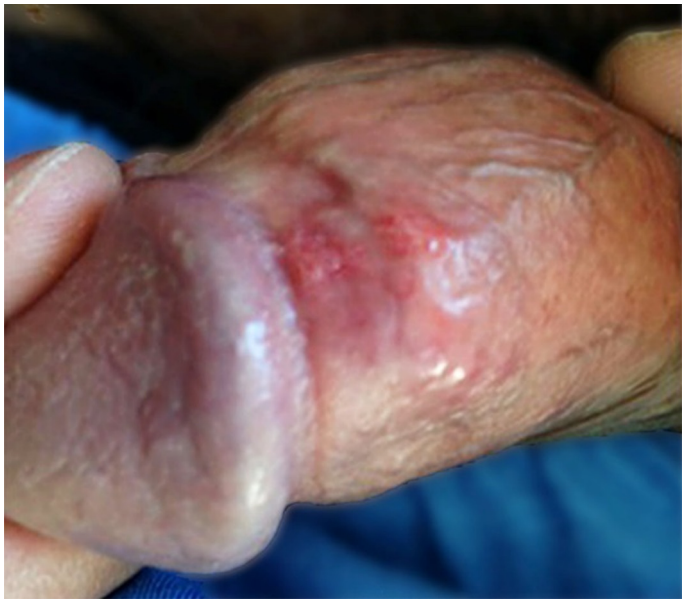

Figure 1. Clustered plain, clean-based ulcers in the balanopreputial sulcus.

was prescribed. Serum antinuclear antibodies and immunologic tests for syphilis in serum and CSF were tested, which were negative.

The patient experienced severe headache during the first 3 days of hospitalization and required dexamethasone and dipyrone for proper analgesia. After a few days, he experienced relief from his head pain, the meningeal irritation signs ceased, and the genital ulcers healed.

Acyclovir was discontinued after 14 days of therapy, and he was discharged after the final dose. Three weeks after hospital admission, the CSF polymerase chain reaction was negative for cytomegalovirus, varicella virus, and herpes virus types 1, 2, 6, 7, and 8. However, it was positive for Epstein-Barr virus (EBV).

DISCUSSION

Acute meningitis is the inflammation of the central nervous system (CNS) meninges that occurs less than a week from the initial diagnosis. The clinical course may be catastrophic, demanding prompt investigation and proper treatment to reduce mortality and sequelae; therefore, in the case of a clinical suspicion, a lumbar puncture should be performed and antibiotics started. In this setting, CSF analysis may reveal patterns of cell count, protein, and glucose that might point towards an etiology, and the Gram stain is 60–90% sensitive and has almost 100% specificity to indicate a bacterial infection.[1] If there is a lymphocytic pleocytosis with normal glucose, and the Gram stain and the CSF culture are negative, the meningitis is called aseptic.[1–3]

Aseptic meningitis has diverse etiologies, including virus, fungi, mycobacteria, neoplasia, autoimmune, and drug-associated.[3] The main etiology is viral, which typically shows a benign course and prognosis.[4] Usually the clinical manifestations reveal an acute or subacute onset and comprise fever, headache, photophobia, and nuchal stiffness.[2] Patients sometimes may present with overlapping syndromes of meningoencephalitis or encephalomyelitis.[4]

As mentioned above, the general characteristics of aseptic meningitis is commonly seen in viral etiologies, which present a mononuclear pleocytosis around 500 cells/mm^3, mild protein elevation, and normal to mildly decreased glucose. However, especially in the first few days of disease, pleocytosis may reveal a polymorphonuclear predominance, mimicking bacterial infections.[3,5] In the context of viral meningitis, the association of xanthochromia may suggest herpes simplex infection, and most commonly, herpes simplex type 2 is the one associated with meningitis as well as with genital ulcers.

Our patient's CSF characteristics could resemble a bacterial infection due to the pleyocytosis (>1,000 cells/mm^3) and the elevated protein concentration. The diagnosis of viral etiology was assumed based on the benign clinical course, the predominance of mononuclear cells, the normal glucose concentration, the negative Gram stain, and the negative bacterial culture.

The enterovirus is the most common virus associated with aseptic meningitis, particularly the coxsackieviruses and the echoviruses.[1,4,6,7] With the improvement of the polymerase chain reactions (PCR) for virus detection, other viral agents have been increasingly reported.

In a recent study conducted by Bastos et al.[6] in the Western Brazilian Amazon, 165 samples were analyzed and one or more agents were detected in 49 CSF samples. The most common agents included enteroviruses (16 cases) and the EBV (11 cases).[6] A previous similar study, by Dupuis et al.[7] in New York, analyzed 2,357 samples of patients who exhibited symptoms of encephalitis or meningitis. Viral etiology was found in 340 of those samples, and, similarly, the most common agents were enteroviruses (129 cases) and EBV (85 cases).

On the other hand, a prospective study conducted by Nesher et al.[1] at the University of Texas analyzed 323 patients with aseptic meningitis, with 89 etiological confirmations, but only three cases were caused by EBV.[1] Similarly, a study by Ory et al.[8] in Madrid (Spain) evaluated 340 patients with meningitis, which had 194 evidenced etiologies; among them, three were positive for EBV.

These different results may be due to varied PCR methodologies and panels of viral agents. Another possibility is the distinct incidence of each virus in these diverse regions. Development of new methodologies and reduced costs of PCR will make the test more available and provide more numbers to be analyzed in the future.

EBV is one of the most common isolated viruses in the adult population.[9] Typically, the primary infection occurs in the nasopharyngeal epithelial cells, and after a lytic cycle with viral replication, it remains inactive mainly within the memory B cells, but may also be present in T cells, natural killer cells, macrophages, monocytes, smooth muscle cells, and endothelial cells.[7,9] The EBV genome may express different combinations of nuclear antigens and latent membrane proteins, which may correlate with different patterns of latency.[9] The patient described in this case study could have had a latent infection and the reactivation of the virus could have caused both genital ulcers and meningitis, but the presence of genital ulcers associated with the patient's sexual history raised the possibility of a primary infection by sexual transmission.

EBV can be found in immune system cells in a chronic phase, and is the most frequent herpesvirus

found in association with other microorganisms in the CNS, which may raise doubts of its causative association with CNS disease.[7]

Despite this uncertainty, EBV has been associated with different manifestations in the CNS, including meningitis, encephalitis, acute cerebellar ataxia, myelitis, acute disseminated encephalomyelitis, and vasculopathy.[10,11]

Dermatologic manifestations of EBV infection are also diverse and include infectious mononucleosis, papular acrodermatitis of childhood (Gianotti–Crosti syndrome), hypersensitivity to mosquito bites, oral hair leukoplakia, histiocytic necrotizing lymphadenitis (Kikuchi–Fujimoto syndrome), hydroa vacciniforme, and genital ulcers.[9,12,13]

The reactive non-sexually related acute genital ulcers (NSRAGU), also known as Lipschütz ulcers, are typically acute, painful ulcers, with a clean or fibrinous base, and are commonly found in young women and adolescents. It was first described in 1913 by Lipschütz, and since then diverse agents have been related to these ulcers, with EBV predominance.[9,12,13]

EBV genital ulceration and its association with sexual activity is theme of speculation by some authors, but there is evidence in the literature to suggest that it may occur even without direct genital exposition to the virus.[13-16]

Genital ulceration may occur by a cytotoxic immune response to the virus, immune complex deposition (type III hypersensitivity), or direct cytolysis by EBV replication in the keratinocytes.[9,13] NSRAGU is a self-limited condition that resolves in 2–6 weeks without scarring, and requires only symptomatic treatment.

The patient described herein had recent unprotected sexual intercourse, and presented genital ulcers in the week prior to the presenting neurological symptoms, which raised the concern of herpes simplex virus type 2 as the causative agent, as well as syphilis. The absence of pain—a typical finding in NSRAGU—makes the ulcer presentation atypical. In spite of this, we concluded that the genital lesions were NSRAGU-like.

Simultaneous genital lesions and meningitis raised the concern of herpes simplex type 2 infection and Behçet's disease. The herpes simplex type 2 infection causes painful vesicular or ulcerative genital lesions that aggregate and have clean-based, erythematous borders.[17] Patients may describe previous or concurrent lesions with the symptoms of meningitis.[17] The herpes simplex type 2 CNS infection may have a distinct course of a benign recurrent meningitis, called Mollaret's meningitis.[18] Behçet's disease is a systemic autoinflammatory vasculitis that causes frequent oral and/or genital ulcers, cutaneous lesions, ocular manifestations (typically, uveitis), and aseptic meningitis.[19] As a systemic vasculitis, it may also affect other organs.

Since the clinical history and physical examination did not suggest any specific cause, and the laboratory findings ruled out other etiological agents, we concluded, after the positive PCR in the CSF, that our patient had an EBV infection resulting in meningitis. Also, we dare consider the painless genital ulceration as the initial infection, although we cannot consistently affirm that the genital ulcer was associated with EBV since the presence of this agent was not demonstrated from the genital ulcer. Once the CSF EBV-PCR result was available, the genital lesions had already vanished, which hampered the research.

Currently, more epidemiological studies are needed to understand the role of each viral agent in the clinical setting of aseptic meningitis. In addition, it was not fully understood how to investigate those patients in the scenario of advanced PCR techniques.[1]

This case report illustrates the role of EBV infection in cases of CNS infections and genital ulcers.

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