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Case report

First description of herpes simplex virus type 1 epididymo-orchitis: A new clinical form of herpes simplex virus infection during septic shock?

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ABSTRACT

Genital herpes is increasingly caused by herpes simplex virus type 1 (HSV-1), but recurrences are less frequent than with HSV-2. Distinguishing between primary genital infection and reactivation can be difficult, but HSV-1 more often causes severe primary infections and fewer recurrences. However, as virus reactivation is common during septic shock, a severe form of HSV-1 reactivation can occur in locations other than the lungs, which remain the most common site. The case of a 79-year-old Caucasian man who presented with HSV-1 epididymo-orchitis after three episodes of severe sepsis or septic shock in the context of acute biliary necrotizing pancreatitis is described. This is the first reported case of HSV-1 epididymo-orchitis due to virus reactivation during sepsis.

Introduction

Genital herpes is the most prevalent sexually transmitted disease in the United States [1]. The prevalence of sexually acquired herpes simplex virus type 1 (HSV-1) is underestimated, with an increased incidence of HSV-1 genital infection in the past two decades [2]. Genital HSV-1 almost always causes a true primary severe infection, but with fewer recurrences and less asymptomatic carriage [3]. However, HSV-1 reactivation is common during septic shock, and HSV is a common pathogen in immunocompetent individuals that persists in the host after primary infection. We present herein the first reported case of HSV-1 epididymo-orchitis due to virus reactivation during severe sepsis. This case highlights the fact that HSV reactivation does not solely occur in the lungs during severe sepsis. The importance of early diagnosis and treatment of severe viral infection is discussed.

Case report

Herein, we report a case of epididymo-orchitis as a severe form of HSV type 1 genital recurrence. A 79-year-old patient was admitted to the ICU with severe biliary acute necrotizing pancreatitis that developed in the month prior to admission. He presented with many septic and abdominal complications. First, endoscopic transluminal drainage was performed because of a retrogastric abscess. One week later, he developed a new episode of severe sepsis with spontaneous bacterial peritonitis and late-onset ventilator-associated pneumonia, with *Escherichia coli* and *Proteus* spp. isolated from bacterial cultures of both sites. The patient received appropriate antibiotic therapy with amoxicillin/clavulanic acid, with a good therapeutic response. After three weeks, he again developed a new episode of severe sepsis. CT-guided drainage was performed twice for two new peripancreatic collections. Despite antibiotic therapy with cefepime and ofloxacin, septic shock developed again, and was rapidly complicated by multiple organ failure with an abdominal compartment syndrome and acute respiratory distress syndrome. Septic shock was caused by ampicillin-susceptible *Enterococcus faecalis*, secondary to ileus with bacterial translocation. The patient's condition improved rapidly after initiation of empirical broad-spectrum antimicrobial therapy. He underwent percutaneous CT-guided drainage of a new subcapsular left liver abscess on day 5. Moreover, because a large

Abbreviations: ICU, intensive care unit; CT, computed tomography; WOPN, walled-off pancreatic necrosis; PCR, polymerase chain reaction; ELISA, enzyme linked immunosorbent assay; SOFA, sepsis-related organ failure assessment score.

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retrogastric abscess persisted, a cystogastrostomy was performed for internal drainage with concomitant debridement of WOPN on day 7. Independent of the abdominal complications, the clinical course was marked by an episode of HSV-1 epididymo-orchitis on day 10. Clinically, the patient first presented with an enlarged scrotum. Two days later, groups of painful vesicles appeared (Fig. 1).

Sonography identified a hydrocele, cutaneous swelling, and diffuse hypoechoic heterogeneous enlargement of the right epididymis without any abscess. Color Doppler imaging revealed hyperemia, which suggested inflammation (Fig. 2).

HSV-1 polymerase chain reaction (PCR) of scrotal swabs was positive on day 10, in association with a viral blood load of 1100 copies/ml. Bacterial and fungal cultures of scrotal cutaneous swabs, urethral smears, and a single catheter urine specimen were negative. Cytological diagnosis was positive with detection of typical cytopathic effects of HSV-1 (syncytial multinucleated giant cells) in scrapings from genital vesicles using Papanicolaou staining. No specific serologic tests were performed. As soon as the diagnosis was confirmed by the urologist, intravenous acyclovir treatment was initiated because of the clinical severity, and was continued for ten days. Complete healing took two weeks, but HSV-1 viral load was negative after only three days, and the vesicles were transformed into ulcerations. After four more transgastric necrosectomies of walled-off pancreatic necrosis and CT-guided percutaneous transhepatic gallbladder drainage for acute cholecystitis on day 23, the patient was finally discharged from the ICU on day 43.

Other similar cases and comparative cases in the literature

Most genital HSV-1 infections are primary infections rather than recurrences. Even though most primary infections are severe, no case of epididymo-orchitis has been described. In men, HSV presents most often as multiple grouped vesicles, painful erosions, and ulcers that occur mainly on the prepuce and subpreputial areas [4]. Our patient presented with a typical form of epididymo-orchitis, confirmed by sonography and typical HSV-1 cutaneous vesicles and erosions. HSV reactivation – especially HSV-1 – is common during septic shock, but our patient presented no risk factor for a primary genital infection after one month in the ICU. Many possible confounders exist during sepsis but the hypothesis of a bacterial pathogen was excluded. Data from the literature are lacking about HSV-1 reactivation, but a few cases of true infections other than pneumonia due to HSV reactivation, such as hepatitis [5,6] or extensive perinephric abscess [7], have been described. Therefore, we conclude that this is the first reported case of epididymo-orchitis due to HSV-1 reactivation in a relatively immunocompromised ICU patient in septic shock.

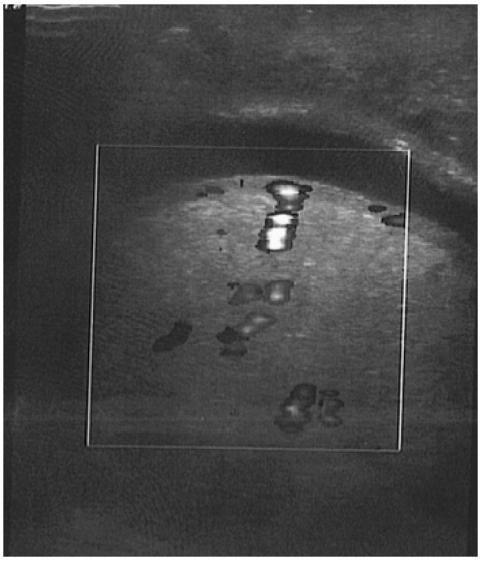

Fig. 2. Hydrocele of the right epididymis and increase in vascularization on color doppler imaging.

Discussion

This patient developed HSV-1 epididymo-orchitis as a severe form of genital HSV infection. Even though genital HSV-1 infection is often severe, we found no case report of epididymo-orchitis linked to HSV. In this patient, the diagnosis was not based solely on clinical elements. Sonography, a polymerase chain reaction (PCR), and a viral culture of scrotal swabs were positive for HSV-1. Epididymo-orchitis is most often a sexually transmitted disease in young men caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae,* and can also be caused by Enterobacteriaceae after a complicated urinary tract infection. A few cases of tuberculous epididymo-orchitis after BCG therapy for bladder cancer have also been described, but no cases have yet been linked to a virus [8]. Sonography is currently the best imaging technique for the study of scrotal contents, and confirmed the diagnosis of epididymo-orchitis [9]. Various echographic patterns have been described for epididymitis including diffuse hypoechoic, nodular hypoechoic, heterogeneous enlargement, or other typical findings including hydrocele, cutaneous swelling, or abscess in the most severe case. This patient presented four of these findings, making the diagnosis certain (Fig. 2).

During both genital HSV-1 and HSV-2 infections, groups of vesicles or ulcers develop in a single anatomical site and disappear within 10 days.

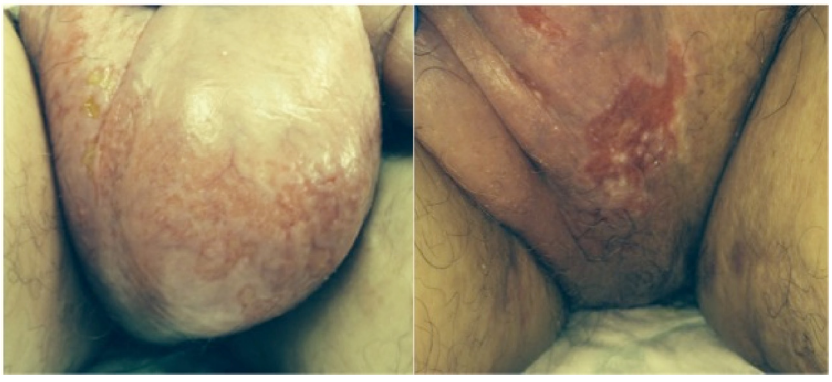

Fig. 1. Enlarged scrotum associated with groups of vesicles on both testicles.

Usually, HSV-1 infection is defined as the isolation of HSV-1 from cultures of the genital tract [10], and the laboratory confirmation of infection and typing of HSV is essential for the prognosis [4].

The diagnosis of HSV-1 epididymo-orchitis was certain but it was difficult to determine whether this patient had a primary infection or reactivation.

No risk factors for primary HSV-1 infection, especially no recent oral sex, were identified. Our patient developed symptoms after one month in the ICU, and we presumed he had a recurrence. Usually, HSV-1 primary infection is defined as the isolation of HSV-1 from cultures of the genital tract or seroconversion to HSV-1 in an originally seronegative patient [10]. Accuracy of serological assays was limited in the past by the extensive cross-reactivity between antibodies to HSV-1 and HSV-2, but sensitive serological tests such as ELISA can be helpful to diagnose seroconversion and to differentiate an initial from a recurrent infection [11]. No specific serologic tests were performed on this patient because there was no likely impact on his treatment. We assume that this unusually severe recurrence is explained by relative immunosuppression induced by multiple preceding episodes of severe bacterial sepsis. A recent study revealed that patients with prolonged sepsis had reactivation of two or more latent viruses, especially cytomegalovirus (CMV), Epstein-Barr virus (EBV), and HSV. In this study nearly half the blood samples for HSV converted from negative to positive on day 7 after sepsis onset, and HSV viremia was associated with higher SOFA scores [12]. Here, conditions were compatible with HSV-1 reactivation in the genital tract.

This reactivation could have been from viremia or from travel down a sensory nerve. During primary infection, HSV infects genital epithelial cells, and then travels via sensory nerves to the sacral root ganglion, where lifelong latency is established. Intermittent reactivation of HSV from the sacral ganglia and lytic replication of virus in the epithelium is thought to result in viral shedding at the genital mucosa, and recurrences are thought to occur predominantly at the site of primary acquisition. The scrotum, testicle, and epididymis are innervated anteriorly by the ilioinguinal, iliohypogastric, and genitofemoral nerves, which originate from the lumbar plexus. Only the posterior portion of the scrotum is innervated by the perineal branches of the pudendal sensory and motor nerve, which originates from the S2, S3, and S4 ganglia of the sacral plexus. Moreover, reactivation from travel down a sensory nerve did not seem to be the most likely hypothesis. However, a recent study reported that HSV-2 genital reactivation in women is often multifocal and occurs in a wide anatomic distribution in the genital tract. This reveals that reactivation from the ganglia that form the pudendal nerve could result in the potential appearance of HSV throughout the branches of the nerve [13]. However, the outbreak was limited to one nerve and the sacral plexus, and in our case did not explain reactivation from the ganglia that form the lumbar plexus.

In addition, the reactivation was probably related to viremia, as most cases of viral orchitis are caused by hematogenous spread. The most typical example is orchitis developing in association with mumps [14].

For the treatment of recurrent HSV infection, European guidelines for the management of genital herpes recommended episodic antiviral therapy with acyclovir 400 mg three times a day for five days, starting early in an outbreak [15]. We decided to treat our patient for ten days because we assumed he was severely immunocompromised, but the clinical course was favorable, with HSV-1 sampling negative for viremia within only three days.

Conclusion

This is the first reported case of epididymo-orchitis linked to HSV-1 recurrence after several severe episodes of sepsis. Reactivation of latent viruses is common in prolonged sepsis, with frequencies similar to those occurring in patients in an immunosuppressed state. However, this unusual presentation of HSV-1 reactivation is evidence of clinically-relevant immunosuppression due to severe sepsis. This case highlights the importance of diagnosing viral infection, because we do not know whether reactivated latent viruses may contribute to morbidity and mortality in sepsis.

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None.

Competing interests

None declared.

Ethical approval

Not required.

References

[1] Fleming DT, McQuillan GM, Johnson RE, Nahmias AJ, Aral SO, Lee FK, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. N Engl J Med 1997;337:1105–11.
[2] Lafferty WE, Downey L, Celum C, Wald A. Herpes simplex virus type 1 as a cause of genital herpes: impact on surveillance and prevention. J Infect Dis 2000;181:1454–7.
[3] Engelberg R, Carrell D, Krantz E, Lawrence C, Wald A. Natural history of genital herpes simplex virus type 1 infection. Sex Transm Dis 2003;30:174–7.
[4] Sen P, Barton SE. Genital herpes and its management. BMJ 2007;334:1048–52.
[5] Ichai P, Roque Afonso AM, Sebagh M, Gonzalez ME, Codes L, Azoulay D, et al. Herpes simplex virus-associated acute liver failure: a difficult diagnosis with a poor prognosis. Liver Transplant 2005;11:1550–5, doi:http://dx.doi.org/10.1002/lt.20545.
[6] Miyazaki Y, Akizuki S, Sakaoka H, Yamamoto S, Terao H. Disseminated infection of herpes simplex virus with fulminant hepatitis in a healthy adult. A case report. APMIS 1991;99:1001–7.
[7] Alleyne SA, Bukhari SS, Fraser M, Spiers P. Extensive perinephric abscess complicated by herpes simplex virus 1 reactivation. J Clin Pathol 2010;63:365–6, doi:http://dx.doi.org/10.1136/jcp.2009.071787.
[8] Briceño-García EM, Gómez-Pardal A, Alvarez-Bustos G, Artero-Muñoz I, Mar Molinero M, Seara-Valero R, et al. Tuberculous orchiepididymitis after BCG therapy for bladder cancer. J Ultrasound Med 2007;26:977–9.
[9] Dogra VS, Gottlieb RH, Oka M, Rubens DJ. Sonography of the scrotum. Radiology 2003;227:18–36.
[10] Langenberg AG, Corey L, Ashley RL, Leong Wai Ping, Straus Stephen E, Chiron HSV Vaccine Study Group. A prospective study of new infections with herpes simplex virus type 1 and type 2. Chiron HSV vaccine study group. N Engl J Med 1999;341:1432–8.
[11] Wald A. Genital HSV-1 infections. Sexual Transm Infect 2006;82:189–90.
[12] Walton AH, Muenzer JT, Rasche D, Boomer JS, Sato B, Brownstein BH, et al. Reactivation of multiple viruses in patients with sepsis. PLoS One 2014;9:e98819 10.1371/journal.pone.0098819. eCollection 2014.
[13] Tata S, Johnston C, Huang ML, Selke S, Magaret A, Corey L, et al. Overlapping reactivations oh herpes simplex virus type 2 in the genital and perianal mucosa. J Infect Dis 2010;201(February (4)):499–504, doi:http://dx.doi.org/10.1086/650302.
[14] Chandrashekar P, Sathiasekar AC, Namaratha K, Singarayan JL, Gnanam AP. A rare case of mumps orchitis. J Pharm Bioallied Sci 2015;7(August (Suppl. 2)):773–5, doi:http://dx.doi.org/10.4103/0975-7406.163555.
[15] Patel R, Barton SE, Brown D, Cowan FM, Kinghorn GR, Munday PE, et al. European guideline for the management of genital herpes. Int J STD AIDS 2001;12(Suppl. (3)):34–9.