Widespread herpes simplex virus type 1 infection on the back of a 79-year-old male patient with respiratory failure and ICU admission

Dominique C. Burgers – Bonthuis¹, Jan C. Pompe², Iringo E. Kovacs³, Willeke A.M. Blokx⁴, Patrick Sturm⁵
¹ Department of Intensive Care Medicine, Gelderse Vallei Hospital, Ede, the Netherlands, ² Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, the Netherlands, ³ Department of Pathology, Radboud University Medical Center, Nijmegen, the Netherlands, ⁴ Department of Pathology, Radboud University Medical Center, Nijmegen, the Netherlands, ⁵ Department of Medical Microbiology, Laboratory for Pathology and Medical Microbiology (PAMM), Veldhoven, the Netherlands

Correspondence
D.C. Burgers-Bonthuis – burgersd@zgv.nl

Keywords - ICU, herpes simplex virus type 1, atypical presentation, pustules, reactivation, immunosuppression

Abstract
We present a rare cutaneous presentation of herpes simplex virus type 1 (HSV-1). A 79-year-old patient was admitted to the ICU with respiratory failure due to bilateral pneumonia complicated by development of a non-dermatomal pruritic rash on his back. The rash was characterised by partly confluent pustules with a raised erythematous base. A skin biopsy was taken and serological tests were performed. Skin biopsy showed typical cytopathic effects of herpetic infection: ground-glass nuclei, multinucleation, moulding, intranuclear inclusion bodies and acantholysis. Immunohistochemical stain on skin biopsy showed HSV positivity. Polymerase chain reaction with skin biopsy confirmed HSV-1 infection. No antiviral medication was started since the erythematous stage of the illness had pasted. After five weeks the patient was discharged from the hospital.

Conclusion: Besides orolabial lesions, reactivation of HSV-1 infection can present anywhere on the body. HSV-1 reactivation is common in response to various local or systemic triggering factors such as physical or emotional stress, fatigue, fever, exposure to ultraviolet light, tissue damage, (critical) illness and immunosuppression. Direct cutaneous triggers that have been reported to be associated with HSV infection are tattooing, burns, autologous skin grafting or cosmetic procedures such as deep chemical peeling and dermabrasion.

Introduction
Primary HSV-1 infection is typically transmitted during childhood via close personal contact and causes orolabial vesicles. However, most primary HSV-1 infections are asymptomatic. Retrospective studies demonstrated that only about 25% of patients with HSV-1 antibodies have a history of oral or labial infections. Once epithelial cells are infected there is a replication of the virus around the lesion and entry into peripheral nerves to innervating neuron and nuclei of sensory ganglia. HSV-1 infection reactivation is common in response to various local or systemic triggering factors such as physical or emotional stress, fatigue, fever, exposure to ultraviolet light, tissue damage, (critical) illness and immunosuppression. Direct cutaneous triggers that have been reported to be associated with HSV infection are tattooing, burns, autologous skin grafting or cosmetic procedures such as deep chemical peeling and dermabrasion.

Examples of unusual presentation of HSV-1 infection are herpetic whitlow, eczema herpeticum and herpes gladiatorum. Herpetic whitlow, HSV-1 infection of the finger, can occur as a complication of primary oral or genital herpes by inoculation of the virus through the axon to the free nerve endings in the epidermis where it can infect epithelial cells. Extension and possible dissemination of the epithelial infection can be enhanced by other local factors such as skin disease and close skin-to-skin contact.

References
More severe HSV infection may develop in immunocompetent or immunocompromised patients involving the central nervous system, respiratory tract, oesophagus and gastrointestinal tract. HSV encephalitis is one of the most devastating of all HSV infections and it has been estimated that it accounts for almost 20% of all cases of encephalitis worldwide.

No signs are pathognomonic for HSV encephalitis but symptoms include headache, fever, altered level of consciousness, seizures and localised neurological findings. The aetiology is not known; hypothesis about pathways for entry of HSV to the brain include both the olfactory and the trigeminal nerves and haematogenous spread and may be caused either by a primary infection, viraemia or by reactivation of latent virus. Variation in HSV genome affects neurotoxicity and neuroinvasiveness and may play a role in aetiology. Early diagnosis is important since a treatment delay of more than two days can have devastating clinical consequences. A pitfall is that cerebral spinal fluid polymerase chain reaction (PCR) may be negative for HSV-1 during the first three days of illness.

HSV isolation from the respiratory tract in critically ill patients has been related to poor outcome in several studies. However, it is unclear whether increased HSV load in bronchoalveolar lavage from ICU patients represents a true HSV pulmonary infection or reflects viral reactivation without lung parenchymal involvement. Tuxen et al. reported that 30% of biopsied acute respiratory distress syndrome (ARDS) patients had histology-confirmed HSV lung involvement. True HSV bronchopneumonitis has mostly been described in case reports about immunocompromised patients.

Gastrointestinal complications of HSV infection include oesophagitis and hepatitis. Herpes oesophagitis often presents with retrosternal pain and odynophagia and is frequently diagnosed in immunocompromised patients but can also occur in immunocompetent patients. The disease is self-limiting in immunocompetent patients. HSV hepatitis is an uncommon cause of liver failure, seems to mainly affect neonates, pregnant females and immunocompromised patients including solid organ recipients and is associated with a poor prognosis.

We report the case of an unusual presentation of HSV-1 infection localised on the back of the patient without a known history of primary HSV-1 infection.

Case report

A 79-year-old man was admitted to our intensive care unit (ICU) with respiratory failure due to bilateral pneumonia. His medical history revealed chronic obstructive pulmonary disease (COPD), recurrent pneumonia and herpes zoster with an unknown localisation. There was no history of skin disease or herpes labialis. He used inhaled corticosteroids and anticholinergic bronchodilators for COPD. Therapy consisted of cefotaxime, ciprofloxacin and corticosteroids. Culture of blood and sputum yielded *E. coli*.

He improved clinically, did not need any cardiovascular support and was weaned off the ventilator when he developed a fever and a pruritic rash on his back on day 11 after admission to our ICU. He was still on antimicrobial treatment with cefotaxime and ciprofloxacin. No other drugs prone to elicit an allergic skin eruption were administered. However, the clinical presentation was not compatible with a drug-induced rash or with herpes zoster. The rash was only located on the back of the patient, with a non-dermatomal distribution, and was characterised by partly confluent pustules with a raised erythematous base (figures 1 and 2).

Figure 1 and 2. Non-dermatomal, partially confluent pustules with a raised erythematous base on the back of the index patient. The picture in figure 1 is taken two days after the appearance of the eruption and the picture in figure 2 is taken one week after the appearance of the eruption. The picture in figure 1 also has a different contrast setting.

Two days after the appearance of the rash a biopsy specimen was taken and showed typical cytopathic effects of herpetic infection: epidermal erosion, areas with extensive acantholysis, ground-glass nuclei and nuclear moulding. There were no signs of intracorneal or subcorneal pustules. The upper dermis showed...
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an infiltrate composed of neutrophilic granulocytes, partly with abscess formation. Lower dermis showed no neutrophilic infiltration, nor collagen degeneration (figures 3A-3B).

Figure 3. Skin biopsy, HE, x20, Olympus slide scanner. Typical cytopathic effects of herpetic infection are seen, with ground-glass nuclei, multinucleation, moulding and intranuclear inclusion bodies. Further, ballooning degeneration, acantholysis, necrotic keratinocytes and a neutrophilic infiltrate in the epidermis and dermis are noted. Red and blue arrows: both arrows show ground-glass nuclei, multinucleation and moulding. The red arrow also shows intranuclear inclusion bodies.

Figure 4. Skin biopsy, immunohistochemical staining for HSV, x20, Olympus slide scanner. Note the positive nuclear staining of the infected keratinocytes.

Serology was performed on a blood specimen obtained on admission which was positive for IgG anti-HSV (257 U/ml) and negative for IgM anti-HSV indicating HSV seropositivity without reactivation at the time of testing. Repeated serological testing to confirm active infection was not performed. Immunohistochemical stain on skin biopsy revealed HSV positivity. Subsequently PCR with skin biopsy was performed and confirmed HSV-1, four days after development of the rash. PCR for varicella zoster virus (VZV) and HSV-2 was negative. His blood cultures were negative for bacterial, viral or fungal organisms.

The patient did not receive antiviral medication since the diagnosis was confirmed after the erythematous stage of the infection. He stayed on the ICU for 4 weeks and on the general ward for 1 week before he could be discharged from the hospital. The lesions were fully healed at discharge.

Discussion

The differential diagnosis of a pustular rash includes bacterial folliculitis, furunculosis, acute generalised exanthematous pustulosis (AGEP), acute febrile neutrophilic dermatosis (Sweet's syndrome), pustular psoriasis, subcorneal pustular dermatosis (Sneddon-Wilkinson), herpes zoster and herpes simplex. However, the clinical picture was not typical for any of these entities.

In our patient, the lesions were located on his back with no history of skin disease besides herpes zoster and no history of contact sports. Anamnesis, appearance, localisation, and distribution of the lesions excluded folliculitis, furunculosis and herpes zoster. Histologically, the absence of subcorneal pustules and the presence of nuclear changes in the biopsy excluded AGEP and Sweet's syndrome respectively.

The histological findings of HSV, when present, are pathognomonic for a herpes infection. The key histological feature is a vesicle or ulceration with keratinocytes, acantholysis, ballooning and necrosis. Keratinocytes will show the nuclear changes of HSV infection. These include nuclear moulding, peripheral margination of ground-glass chromatin, multinucleation and Cowdry type A intranuclear inclusion bodies. Histology does not differentiate between an infection with VZV infection and HSV-1 and HSV-2. Further subtyping of the virus needs additional diagnostic methods.

Although virus isolation in culture remains the definitive diagnostic method, real-time HSV PCR assay is a more sensitive method to confirm HSV infection in clinical specimens obtained from the infected site. Serological diagnosis of HSV infection is of limited clinical value. Therapeutic decisions cannot be postponed until the results of serological studies are obtained. Our patient had no history of labial or genital HSV infection but tested positive for IgG anti-HSV. However, the use of ELISA for detecting antibodies allows only definition of past infection or seroconversion but cannot distinguish infection due to HSV-1 from that due to HSV-2. The widespread distribution of the HSV-1 infection in our patient is more likely caused by reactivation rather than primary infection. A primary infection would indicate asymptomatic
past infection with HSV-2 since anti-HSV IgG was positive and primary HSV-1 infection through a healthcare worker via close skin-to-skin contact on the back of our patient. We think this is highly unlikely since we work with a barrier nursing protocol.

Type-specific identification of the VZV and the two main types of herpes simplex virus can also be made in paraffin sections using immunoperoxidase techniques. Several triggering factors probably played an important role in the aetiology of this atypical presentation of HSV-1. First, prolonged sepsis can cause immunosuppression. Walton et al. showed that reactivation of latent viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV) and HSV is common in septic ICU patients with frequencies similar to those occurring in transplant patients on immunosuppressive therapy and consistent with the development of an immunosuppressive state. The investigators examined urine and plasma for viral DNA and found that reactivation of HSV-1 infection occurred in 14.1% of septic ICU patients. HSV detection occurred in 75% of the patients ten days after sepsis criteria were fulfilled. It was also shown that septic patients with detectable CMV and EBV in plasma had an increased risk of fungal and ‘opportunistic’ bacterial infections such as Acinetobacter, Stenotrophomonas and Enterococcus. Reactivation of HSV was not correlated with increased fungal infection. Furthermore, viraemia was associated with increased ICU length of stay and higher Sequential Organ Failure Assessment (SOFA) scores. They state that monitoring viral load might be useful as an indicator of immunosuppression.

Second, the unusual distribution of his skin lesions could have been triggered by the abrasive properties of a bed causing disruption of skin integrity and enabled cutaneous extension of the infection. In geriatric bedridden patients it has been previously described in the perineal region. The treatment of choice for herpes labialis / HSV-1 infection is acyclovir, valacyclovir or famciclovir. It modestly reduces viral shedding, the duration of pain and time to complete healing and only when treatment is started during the prodromal or erythematous stage of infection. Topical therapy provides little benefit.

In conclusion, this uncommon case describes a patient with a rare presentation of HSV-1, localised on his back, without a known history of primary HSV-1 infection or history of skin disease, other than herpes zoster.

References