Herpes simplex virus (HSV) causes a wide range of clinical manifestations, varying from minor cold sores to severe necrotizing encephalitis or disseminated systemic infections. The virus has the ability to establish and maintain a latent infection, which can be reactivated. Between 80% and 90% of the European population is infected with HSV type I, and most infections are spread during the initial, subclinical phase. Fulminant HSV infection is very uncommon, and occurs more frequently in patients with impaired immunity. A review of the literature showed that, among 55 patients with fulminant HSV infection, 13 well-documented cases of fulminant primary HSV infection in immunocompetent patients have been reported, but none of these cases involved reactivation of latent infection. If fulminant HSV infection is not diagnosed or considered in time, and antiviral treatment—even empirically—initiated, the condition of both immunocompetent and immunocompromised patients will deteriorate rapidly.

Here we describe an apparently immunocompetent woman with fulminant reactivation of HSV infection.

A 64-year-old woman was admitted to our hospital in March 2000, complaining of sore throat, dysphagia and low-grade temperatures for 4 days. Her family history and previous medical history were unremarkable, and she was taking no medications. Physical examination at admission revealed stomatitis with oropharyngeal ulceration. The white blood cell (WBC) count was 12×10^12/L, with 90% neutrophils and 3% lymphocytes. Biochemical examination showed an elevation of C-reactive protein (CRP) to 150 mg/L. Klebsiella pneumoniae grew in a bacterial throat swab, whereas cultures of urine, sputum and blood all gave negative results. A throat swab for detection of viruses was not taken. A granulating inflammation was found in a biopsy taken from an ulcer on the tongue. Virus serology (α-method without differentiation between HSV I and II antibody, Dade-Behring) revealed a positive HSV IgG titer without IgM positivity. Despite 2 weeks of antibiotic treatment, the patient's clinical condition deteriorated dramatically.

At this time, clinical examination revealed crackles on both lungs, and a chest X-ray exhibited bilateral interstitial pulmonary opacities. Bronchoscopy with bronchoalveolar lavage (BAL) was performed, and HSV type I was found by means of an immunofluorescence assay with fluoroisothiocyanate (FITC)-conjugated monoclonal antibodies and confirmed by tissue culture on MRC-5 cells. Nasal swabs also tested positive for HSV type I in like manner. Because of the patient’s fulminant course, her clinical presentation with tenderness of skeletal muscles and livid erythema around small joints, and the strongly elevated inflammation parameters, we assumed that there was an underlying autoimmune disease, e.g. vasculitis or polymyositis. We performed extensive diagnostic investigations, in-
Fulminant course of herpes simplex virus reactivation in an apparently immunocompetent woman / Tischendorf et al

Fulminant HSV infection is very uncommon in the adult population. Fifty-five well-documented cases have been previously reported in the literature. Disseminated HSV infection occurs more frequently when an underlying condition, resulting in immunosuppression, is present. Of the 55 cases that have been reported, 42 (76%) had an underlying condition that was associated with impaired host defense. Of this group, 11 (26%) were patients who were receiving glucocorticoid therapy for various diseases such as Crohn's disease, systemic lupus erythematosus, or sarcoidosis, and nine (21%) were receiving immunosuppressive therapy following transplantation. In total, eight patients had diseases such as acquired immunodeficiency syndrome, leukemia, or thymus dysfunction. Fourteen cases (33%) were associated with pregnancy.\(^1\) In 13 (24%) of the 55 cases fulminant HSV infection developed in apparently healthy individuals.\(^2\) In some of these patients, a first manifestation of HSV infection was diagnosed; in others, no distinction between primary infection and reactivation was made.

To our knowledge, this is the first report of fulminant HSV reactivation in an immunocompetent person. Repeated serology by ELISA revealed a positive IgG titer against HSV; specific IgM was not detected. This, in combination with HSV detection by immunofluorescence and tissue culture, is strong evidence for reactivated HSV infection. The kinds of opacity in the chest X-ray film being consistent with viral pneumonia, as well as the positive immunofluorescence assay, the positive tissue culture for HSV in the BAL, and the improvement after treatment with acyclovir, are all indicative of a disseminated HSV infection rather than a contamination of the BAL from the pharynx. Because of the fulminant course and our initial assumption of an underlying autoimmune disease, we started acyclovir and corticosteroids in parallel. The extensive diagnostic investigation for an impaired host defense, including cellular immune status, was negative, and the patient's condition improved even after discontinuation of steroids. Considering the negative medical history, and especially the normal findings in the follow up of more than 2 years, we assume that our patient is immunocompetent.

Without antiviral treatment, the mortality rate of disseminated HSV infection is very high, emphasizing the fulminant and lethal nature of this disease. The overall mortality of the 55 cases with fulminant HSV infection was 69%. Ten (77%) of the 13 apparently immunocompetent patients with fulminant HSV infection died. The three surviving patients were all treated with acyclovir.\(^2\) Only three of the 10 patients who died received antiviral treatment, i.e. acyclovir or vidarabine. Independent of the immune status, early antiviral treatment has to be regarded as decisive for patients' outcome. In about half of patients, the 'typical' herpetic mucocutaneous lesions do not occur before HSV dissemination. Therefore, in these patients early diagnosis is difficult to achieve.\(^2\) Fulminant HSV infection should be considered in the differential diagnosis of any patient with a clinical picture of systemic infection. Confirmation of the diagnosis requires the detection of viral antigen in nasal or throat swabs or in BAL by IFA, followed by tissue culture. The detection of IgG specific IgG and/or a significant increase in titer of HSV-specific IgG is certainly not sufficient to detect a reactivation of HSV type I or II, because: (1) in many cases HSV-specific IgM cannot be found; and (2) in most cases, an increase of specific IgG can be observed about 2 weeks after onset of illness. If a disseminated HSV infection is considered, empirical antiviral therapy should be initiated even in cases of pending definitive diagnosis. Early treatment definitely results in an improvement of prognosis, and acyclovir represents the therapy of first choice. As an alternative, foscarnet or cidofovir can be used for systemic infection.\(^8\)
REFERENCES


