Chronic Recurrent Acyclovir-Resistant Genital Herpes in an Immunocompetent Patient

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Herpes simplex virus (HSV) can develop resistance to acyclovir (ACV) through mutations in the viral genome encoding thymidine kinase (or DNA polymerase less frequently) [1]. Drug resistance was considered a rare condition until the emergence of the acquired immunodeficiency syndrome (AIDS). Most of the ACV-resistant strains of HSV have been isolated and characterized in immuno-compromised patients [2, 3]. In immunocompetent patients, ACV-resistant strains have been identified, but clinical response to ACV does not seem to be modified. Recently, Kost et al. [4] reported a case of recurrent ACV-resistant HSV-2 infection in an immunocompetent patient having sexual intercourse with HIV-seropositive homosexual men. We report the case of a 64-year-old immunocompetent Caucasian woman chronically infected with an ACV-resistant strain of HSV-2 in whom neither immunodeficiency nor risk for HIV infection were found. In 1983, she experienced painful, ulcerative vulvar lesions. Viral isolation demonstrated the presence of HSV-2, and intravenous ACV was prescribed (15 mg/kg body weight daily for 10 days). The lesions resolved, but viral isolation was still positive for HSV-2 at the end of this treatment and clinical relapse occurred within 2 days. Between 1984 and 1993, she had chronic pseudotumoral and erosive vulvar lesions which motivated long-term therapy with ACV (200 mg 2-5 times a day) with short periods of withdrawal. During these years, no clinical sample was taken for HSV isolation. In 1993, physical examination revealed a large erythematous pseudotumoral vulvar lesion with superficial ulcerations. The remainder of the clinical examination

was without any abnormality. HSV-2 was isolated by culture on human embryonic lung cells (MRC 5) and characterized by polymerase chain reaction on a vulvar biopsy. Intravenous ACV (30 mg/kg body weight daily for 10 days) failed to provide clinical healing. Viral culture was still positive for HSV-2 at the term of this regimen. Isolates obtained from the patient before, during and after treatment were tested for susceptibility to antiviral drugs with a late antigen synthesis reduction assay. They were all resistant to ACV (median inhibitory dose (ID₅₀) ranging from 14 to 21 µg/ml). They were also resistant to ganci-clovir but sensitive to foscavir (ID₅₀: 20 µg/ml). Our patient had a single sexual partner (her husband who was not available for evaluation). She reported no history of infectious diseases or systemic illness. Her complete

blood cell count was normal; she had 2,333 lymphocytes/mm³ with 1,171 CD4/mm³ and 659 CD8/mm³. Serum protein electrophoresis and immunoelectrophoresis were normal. No antibodies to HIV1 and 2 or HTLV1 (ELISA) were found. Blast transformation of lymphocytes to various antigens (tuberculin, candidin, varidase, tetanus anatoxin, cyto-megalovirus and *Toxoplasma gondii*) was normal. Chest roentgenogram and abdomino-pelvic computed tomography (CT) scan were normal.

Resistance to ACV can arise in HSV-infected mice undergoing suboptimal therapy and it has been demonstrated that isolates exhibit intraindividual heterogeneity and contain mixtures of strains with different levels of thymidine kinase and susceptibility to ACV [5]. Her clinical history suggests that the initial sensitivity of our patient's HSV

was poor but we believe that the long-term regimen of low-dose ACV may have contributed to select ACV-resistant strains. No underlying immunodeficiency or sexual contact with an immunocompromised individual can otherwise explain the ACV-resistance in our patient. It is, to our knowledge, the first case of clinical herpes infection with an ACV-resistant strain in an immunocompetent patient without increased sexually transmitted disease risk.

References

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