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CASE REPORT

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Disseminated herpes zoster infection in a patient with lymphoma

Abstract: Immunosuppression facilitates varicella zoster virus (VZV) reactivation in immunocompromised patients. Atypical presentation such as disseminated disease of herpes zoster infection has been described in immunosuppressed patients. One of the best choices of therapy in herpes zoster infection is acyclovir, but long-term therapy may cause resistance to it. In this report a disseminated herpes zoster infection is described in a patient with T cell lymphoma after acyclovir/valacyclovir therapy. The infection was irresponsive to acyclovir and valacyclovir and we were unable to control the infection because it was not possible to obtain foscarnet and the patient died due to *Staphylococcus epidermis* sepsis.

Key Words: Acyclovir, disseminated, herpes zoster, resistance, immunosuppression, VZV

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Lenfomalı bir olguda yaygın herpes zoster infeksiyonu

Özet: İmmunsupresif durumlar, bağışıklığı baskılanmış bireylerde Varicella Zoster Virus (VZV) reaktivasyonunu kolaylaştırmaktadırlar. Herpes zoster infeksiyonunun dissemine hastalık gibi atipik prezentasyonları özellikle bu hasta grubunda tanımlanmıştır. Herpes zoster infeksiyonunda en iyi tedavi seçeneklerinden biri asiklovirdir ancak uzun süre tedavi asiklovire direnç gelişimine neden olabilir. Burada T hücreli lenfoması olan bir olguda asiklovir/valasiklovir tedavi sonrası yaygın herpes zoster infeksiyonu bildirilmiştir. Bu olguda infeksiyon asiklovir ve valasiklovire yanıtsız olup, foscarnet bulunmadığı için viral enfeksiyon kontrol altına alınamamış ve hasta *Staphylococcus epidermidis* sepsisinden kaybedilmiştir.

Anahtar Sözcükler: Asiklovir, yaygın, herpes zoster, direnç, immunsupresyon, VZV

Introduction

Varicella zoster virus (VZV) is the pathogen of varicella in childhood. It is the primary cause of latent infection in posterior ganglions and may lead to herpes zoster infection with reactivation in adults (1). Immunosuppression facilitates this reactivation in immunocompromised patients such as AIDS and cancer patients and transplant receivers. Significantly VZV infection has been reported in lymphomas with increased prevalence. Because herpes zoster infection in an older person suggests an underlying malignant disease, VZV infection requires special attention in these cases (1). Herpes zoster infection is generally unilateral; however, bilateral involvement and even disseminated infection may be seen in these special cases. Bilateral infection is seen in 1 in 200 cases. Disseminated infection has also been reported in immunosuppressed patients after vaccination (2). Atypical presentation of VZV infection also has been reported in a patient treated with monoclonal anti-CD52 antibody (3). The best choices of therapy for herpes zoster infection are purine, pyrimidine, nucleotide, and pyrophosphate

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analogs; the best known drug among them is acyclovir. However, long-term therapy may cause resistance to acyclovir. Cross resistance is another problem. Acyclovir-resistant strains are isolated also from treatment-naive subjects and new anti-virals are used for these cases (1,4-5).

Here we report a disseminated herpes zoster infection in a patient with T cell lymphoma after acyclovir and valacyclovir therapy.

Case Report

An 84-year-old man with diabetes mellitus was admitted to hospital with neutropenic fever and he had been diagnosed with T cell NHL (T cell prolymphocytic lymphoma-small cell variant) in September 2006. He was treated with 3 cycles of CVP (cyclophosphamide-vincristine-prednisolone) but did not respond. He had severe neutropenia and infectious episodes. Rituximab was given for probable autoimmune neutropenia but there was no response. Fludarabine plus cyclophosphamide was given and he did not respond again and he was hospitalized 3 times due to febrile neutropenia. He was hospitalized with neutropenic fever again in March 2007 and at that time widespread painful subcapsular vesicular lesions were detected. The Tzanck smear was found to be positive and he was diagnosed with herpes zoster infection and parenteral acyclovir therapy was started. This treatment was given for 4 weeks and a clinical improvement was observed and he was discharged in May 2007. One month later he was admitted to hospital with vesicular and infiltrative skin lesions on the face, trunk, and extremities. Oral valacyclovir was given on an outpatient basis. However, the patient described severe itching of the lesions as well as pain, especially in those located on the face. At this time because of discrimination of disseminated herpes zoster infection and/or lymphomatous skin infiltration, skin biopsies were taken from the face and left femoral lesions. Biopsy showed intra-epidermal bullae formation and there was no evidence of lymphoma infiltration. He was hospitalized with poor general condition and fever (Figures 1 and 2). He had severe anemia and hypoalbuminemia. Supportive therapy was given and the skin lesions were observed to be purulent. Ampicillin-sulbactam and parenteral acyclovir+oral famciclovir were started and foscarnet was prescribed. However, respiratory arrest developed and he died. Blood cultures showed methicillin resistant *Staphylococcus epidermidis*.

Discussion

It is known that the frequent involvement of nervous tissue by pressure of infiltration appears to predispose one to contracting herpes zoster. The use of cytotoxic immunosuppressive therapy affecting immune response causes the activation of the disease (1). Our patient was in the high risk group for VZV infection due to his advanced age,

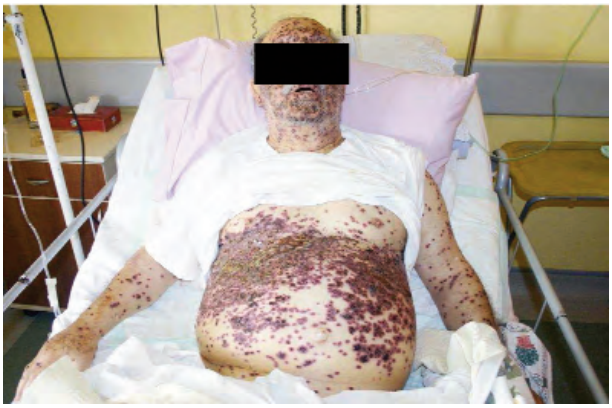

Figure 1. VZV skin lesions on the face, trunk, and extremities.

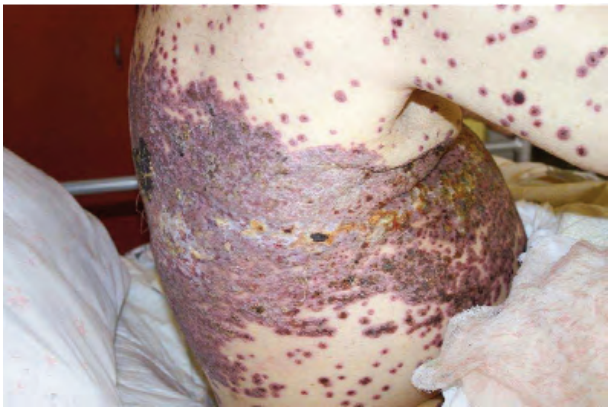

Figure 2. Necrotic and infiltrative lesions on the trunk.

underlying lymphoproliferative disease, and diabetes mellitus, and also due to the use of cytotoxic chemotherapy and immunotherapy including rituximab and anti-CD52 therapies. These factors caused the dissemination of the disease and long-term use of acyclovir was the cause of resistant disease in this patient. Hepatitis B virus, CMV, and VZV reactivations have been reported related to the use of cytotoxic chemotherapy and immunotherapy (6,7).

Acyclovir is the standard treatment for herpes virus infections. Acyclovir resistance is the consequence of a mutation in the viral thymidine kinase that abolishes enzymatic activity (TKD mutations) in 95% of cases. Less frequently, mutations in the viral thymidine kinase lead to the inability to recognize acyclovir as a substrate, or mutations in the viral DNA polymerase lead to the inability to recognize acyclovir triphosphate. This lastly defined mechanism also leads to cross resistance to foscarnet. Acquired resistance to acyclovir occurs in severely immunocompromised patients (8).

Host immune response has a critical effect on the severity of infection and resistance to therapy. Primary infection or recurrences of herpetic infection in the immunocompetent host typically last for only a few days with rapid clearance of the virus. Selection for resistant virus may occur only when there is sufficient viral replication despite the presence of anti-virals. The risk factors for resistance are poor absorption of the drug, noncompliance, and the occurrence of suboptimal antiviral concentrations (9).

The first reported case of acyclovir resistant VZV infection occurred in a patient with lymphoma and he was treated successfully with foscarnet (10). VZV strains with VZV DNA polymerase gene mutations are sensitive to bicyclic pyrimidine nucleoside analogs while they are not sensitive to VZV strains with viral thymidine kinase gene. Transmission of acyclovir-resistant isolates has not been documented, but due to the increased use of acyclovir and newer drugs, such as famciclovir, this transmission might occur in the future. Continued surveillance in both immunocompetent and immunocompromised hosts for the development of clinical acyclovir-resistant disease is necessary (11).

In summary, acyclovir resistant strains show cross resistance to all anti-virals dependent to thymidine kinase. Effective drugs for viruses having thymidine kinase gene mutation are cidofovir and foscarnet (1). Foscarnet and cidofovir are not available in Turkey, and therefore we were unable to use these drugs in the early stage.

Our patient died due *S. epidermidis* bacteremia secondary to disseminated VZV infection. However, dissemination and no clinical response (probably resistance) to acyclovir are the important points of our case. Early recognition of resistance and the use of effective anti-virals without cross resistance are critically important in these immunosuppressed patients.

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