

Meningoradiculoneuritis Due to Acyclovir-Resistant Varicella-Zoster Virus in a Patient with AIDS

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Colleagues—Varicella-zoster virus (VZV) has been recognized as one of the most frequent viral opportunistic infections in patients infected with the human immunodeficiency virus (HIV). The classic presentation of VZV infection in patients with AIDS is a multidermatomal zoster with or without dissemination. Persistent VZV infections with atypical cutaneous lesions have been recognized with increased frequency [1, 2]. Here we describe the case of an AIDS patient who developed meningoradiculoneuritis while on oral acyclovir given prophylactically at 400 mg twice daily for 8 months after several episodes of multidermatomal zoster. The virus isolated from skin lesions before the start of acyclovir prophylaxis was fully sensitive to acyclovir (isolate 1).

The patient then had a series of symptoms including low back pain, associated with bilateral sciatalgia, and weakness in both legs. Physical examination at admission confirmed the neurologic syndrome characterized by neck stiffness and symmetric distal weakness of both legs with a diminution of both Achilles tendon and knee-jerk reflexes. There also was perianal hyperesthesia and vesical atonia. The CD4 cell count was 24/mm³.

Lumbar puncture on the day of admission showed high protein levels (7.8 g/L) suggestive of Guillain-Barre syndrome. Culture of cerebrospinal fluid (CSF) on human fibroblast cells was positive for VZV (isolate 2). Intravenous treatment with foscarnet at 60 mg/kg three times daily was started immediately.

While no clear neurologic improvement was seen with foscarnet treatment, a second lumbar puncture showed a normal protein level and no virus could be isolated. When the patient was clinically stable after 35 days of treatment, the foscarnet dosage was reduced from 180 to 90 mg/kg/day. Within 1 week, necrotic retinitis developed, and the foscarnet dosage was increased back to 180 mg/kg/day. CSF collected 1 week later showed a normal protein level but was again positive in cell culture for VZV (isolate 3). On foscarnet therapy, the patient had slow clinical deterioration in both neurologic status and general condition and died ~ 12 weeks after beginning foscarnet therapy.

Drug susceptibility of the 3 VZV isolates obtained during the clinical course of infection was assessed by both virus plaque reduction (table 1) and flow cytometry [3]. Isolate 1 was fully sensitive to the seven compounds tested, while isolates 2 and 3 were clearly resistant to all the drugs requiring the virus-encoded thymidine kinase (TK) for phosphorylation (acyclovir, ganciclovir, bromovinyl-deoxyuridine, and bromovinyl-uridine arabinoside) but remained sensitive to foscarnet, vidarabine, and the acyclic nucleoside phosphonates HPMPA and HPMPA (hy-droxyphosphonylmethoxypropyl-cytosine and -adenosine).

Significant TK activity was observed in cells infected with VZV isolate 1, whereas this activity was decreased by at least 10-fold in cells infected with VZV isolate 2 or 3 (data not shown). In restriction endonuclease cleavage of genomic viral DNA with *Bam*HI, the pattern described for isolate 1 was comparable to that of the reference strain Ellen; the pattern of isolates 2 and 3 was clearly different. The fragment corresponding to the TK gene of isolates 2 and 3 had a lower molecular weight than that of isolate 1 (data not shown).

Direct sequencing of the polymerase chain reaction product showed that the coding sequence of isolate 1 corresponded exactly to that of the reference sequence, whereas the deletion observed in isolates 2 and 3 was 873 bp long and in the middle of the coding region of the *tk* gene.

Table 1. Sensitivity of different VZV strains to selected antiviral drugs as evaluated by plaque reduction assay.

Compound	Isolate 1	Isolate 2	Isolate 3	Oka (TK ⁺ reference strain)	YS-R (TK ⁻ reference strain)
BVDU	0.002	10	0.25	0.002	>50
Acyclovir	0.17	10	5.5	0.13	15
Ganciclovir	0.11	1.2	0.6	0.02	2.6
Foscarnet	17	20	14	15	10
Vidarabine	0.5	1.1	1.1	0.45	ND
HPMPA	0.013	0.04	0.05	0.069	0.011
HPMPC	0.2	0.12	0.12	0.25	0.033

NOTE. Data are EC₅₀ in µg/mL: drug concentration required to reduce viral cytopathic effect by 50%. Inoculum was 20 pfu/well. ND, not determined; TK, thymidine kinase; BVDU, bromovinyl-deoxyuridine; HPMPA and HPMPC, hydroxyphosphonylmethoxypropyl-adenosine and -cytosine.

This is the first description of an acyclovir-resistant VZV strain, proved to be TK-deficient, that was isolated from the CSF of an immunocompromised patient. Recently, several case reports have described the emergence of acyclovir-resistant VZV strains in AIDS patients following long-term acyclovir therapy [4-6], Talarico et al. [7], in an analysis of the *tk* gene of acyclovir-resistant VZV strains isolated from AIDS patients, could detect only limited mutations (substitutions or deletions). The deletions introduced premature termination codons resulting in the expression of a truncated TK protein. In the case of the virus strain(s) isolated from our patient, most of the ATP-binding site and the entire nucleoside binding site were missing, thus rendering the protein totally inactive.

Finally, the phosphonate derivatives HPMPC and HPMPA, which do not need the virus-encoded TK to be phosphorylated, were as active against the 2 TK-deficient VZV isolates as against isolate 1. These molecules have a long-lasting antiviral effect, thus allowing infrequent administration. HPMPC seems to be an excellent drug candidate for the treatment of acyclovir-resistant herpesvirus infections in immunocompromised patients [8].

References

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