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Crystal Nephropathy Induced by Valaciclovir

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Letter

To the editor ;

I am an around－forty－year－old woman, and working as a clinical technician in the department of internal medicine in the university hospital. In summer 2007, attending and getting over tight schedule of the summer school for kidney pathology, I consulted a doctor with a 4－day history of painful and pruritic skin eruption on my left rear－neck (Figure A). The skin eruption began as vesicles on the left rear－neck, the region supplied by the cervical 5th sensory root, and was preceded by burning pain in that area. It remained localized and gradually became encrusted. The results of a full blood count, erythrocyte sedimentation rate, renal and liver function tests were all normal. Immune markers were absent. A standard valaciclovir hydrochloride treatment for herpes zoster (Shingles) had been started (1,000 mg/p.o. three times a day) because of my clinical symptoms and a cytodiagnostic finding that the existence of intranuclear inclusion body in a white blood cell contained in the exudate. Two days after the commencement of the valacyclovir treatment, I felt slight lumbago. Renal function tests showed a raised serum creatinine level of 0.8 mg/dl (reference range, 0.4–0.7 mg/dl). As the examination of urine sediment was my ordinary work, I did my own urine examination. A microscopic examination showed several leukocyte casts and multiple needle－shaped crystals (Figure B), and these findings suggested the development of crystal nephropathy induced by valaciclovir and I promptly stopped taking any medicine. A few days later, the urine sedimentation and the level of serum creatinine had both normalized.

A number of routinely prescribed antiviral drugs can cause crystal nephropathy.[1] The deposition of crystals in the kidney can cause renal failure. Renal injury occurs from crystals that, because of their relative insolubility in human urine, tend to precipitate in distal tubular lumens.[2] Valaciclovir is a prodrug, which is an esterified version of aciclovir that has a greater oral bioavailability (about 55%) than aciclovir (10－20%).[3] Bioavailability is a measurement of the

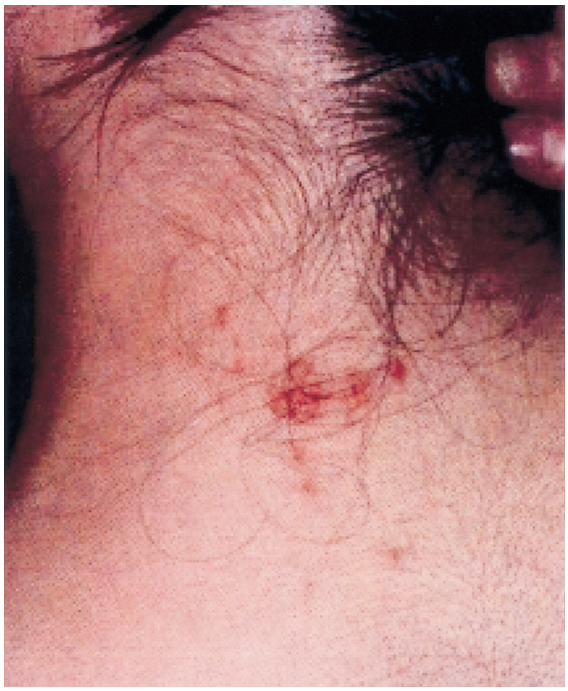

Figure A ; Shingles appeared as a painful rash. It consists several red patches of skin with small vesicles on my left rear－neck. The area of the rash corresponded to the distribution of a single major nerve branch, C5th.

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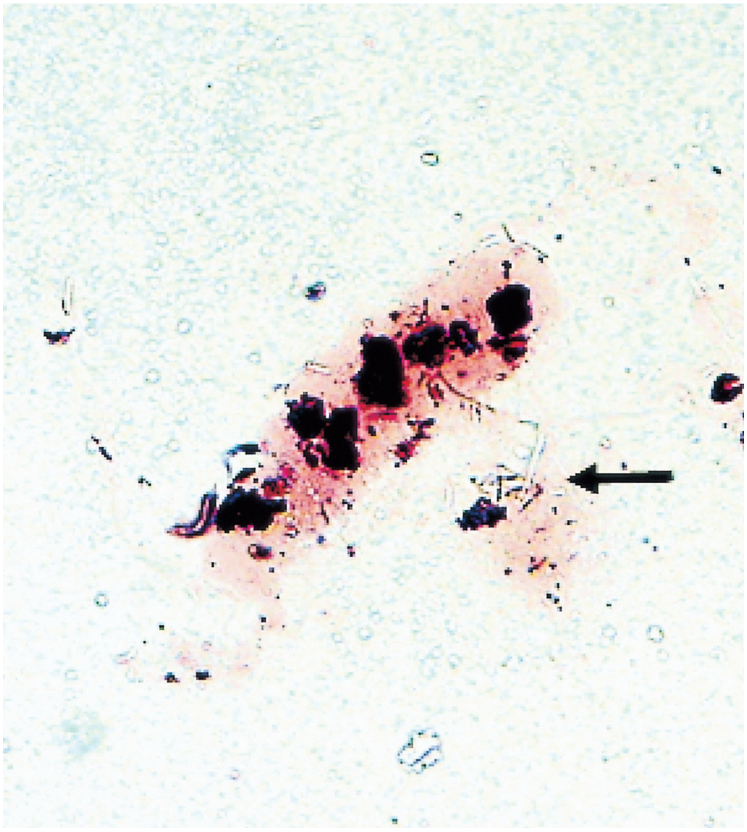

Figure B ; A variety of casts were seen in the urine sediment. Needle－shaped acyclovir crystals beside leukocytes cast were indicated by arrow.

extent of a therapeutically active drug that reaches the systemic circulation and it is available at the site of action.[4] By definition, when a medication is administered intravenously, its bioavailability is 100%. It is converted by esterases to the active drug aciclovir via hepatic first－pass metabolism. Aciclovir is relatively insoluble in urine, with a maximum solubility of 2.5 mg/ml at physiological pH.[5] This low urine solubility and low urine output occurring with volume contraction may therefore induce drug crystallization in kidney tubules. Among the factors that increase the likelihood of renal crystal deposition, severe volume depletion, underlying renal impairment, excessive drug dosing, and metabolic perturbations are the most important known risk factors.[5)6)] Urinalysis usually shows both hematuria and pyuria, whereas needle－shaped acyclovir crystals also can be seen in urine sediment, and such crystals are easy to recognize by polarizing microscopy.[5)] Although asymptomatic renal insufficiency is most common, renal failure associated with neurotoxicity following valaciclovir has generally been reported among patients with preexisting impaired renal function.[7)–9)]

References

1) Perazella MA：Drug－induced renal failure：update on new medications and unique mechanisms of nephrotoxicity. Am J Med Sci 325：349－62, 2003.
2) Fogazzi GB：Crystalluria：a neglected aspect of urinary sediment analysis. Nephrol Dial Transplant 11：379－87, 1996.
3) Glaxo Smith Kline：Valtrex Prescribing Information. 2007.
4) Shargel L, Yu, A. B.：Applied biopharmaceutics & pharmacokinetics (4th ed.). New York：McGraw－Hill. 1999.
5) Perazella MA and Brown E：Electrolyte and acid–base disorders associated with AIDS：an etiologic review. J Gen Intern Med 9：232－6, 1994.
6) Berns JS, Cohen RM, Stumacher RJ and Rudnick MR：Renal aspects of therapy for human immunodefi-

ciency virus and associated opportunistic infections. J Am Soc Nephrol 1 : 1061－80, 1991.
7) Peyriere H, Branger B, Bengler C, Vecina F, Pinzani V, Hillaire－Buys D and Blayac JP : Neurologic toxicity caused by zelitrex (valaciclovir) in 3 patients with renal failure. Is overdose associated with improvement of product bioavailability improvement ?. Rev Med Interne 22 : 297－303, 2001.
8) Saurina A, Ramirez de Arellano M and de las Cuevas X : [Neurotoxicity after the first dose of oral administration of valaciclovir in a female hemodialyzed patient]. Nefrologia 22 : 83－4, 2002.
9) Linssen-Schuurmans CD, van Kan EJ, Feith GW and Uges DR : Neurotoxicity caused by valacyclovir in a patient on hemodialysis. Ther Drug Monit 20 : 385－6, 1998.

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