

Dual herpes virus reactivation complicated with encephalitis caused by direct-acting antiviral agents

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Abstract

Direct-acting antiviral agents (DAAs) have been the mainstream treatment of hepatitis C because of tolerability and efficacy. A 67-year-old man presented with acute drowsiness preceded by headache after starting DAAs (sofosbuvir and velpatasvir) for treatment of hepatitis C. Herpes zoster and herpes simplex stomatitis were noted. Later, HSV-1 encephalitis was diagnosed based on positive HSV1-PCR of CSF, while other tests were negative including HSV2-PCR, syphilis, culture of bacteria, tuberculosis and fungus. Further study showed the presence of concomitant Sjögren syndrome. The patient recovered well with the combination of intravenous acyclovir and steroid. Immune reconstitution inflammatory response (IRIS) may be the most important mechanism of this patient's severe illness. In *conclusion*, severe CNS infection instead of just peripheral nervous system involvement may occur due to herpes virus reactivation caused by DAAs. Screening of autoimmune markers may be considered before DAA therapy.

Keywords: Herpes virus, direct-acting antiviral agents, hepatitis C

INTRODUCTION

Direct-acting antiviral agents (DAAs) are nucleotide analogue inhibitors of hepatitis C virus (HCV) NS5B polymerase with potent antiviral activity, has been the mainstream treatment of hepatitis C because of tolerability and efficacy compared with interferon-based regimens. The reactivation of herpes virus in hepatitis C patients during DAA therapy has been reported in different case series of varied ethnicity.^{1,2} We present here the first case with concurrent reactivation of varicella-zoster virus and herpes simplex virus (HSV), causing both mucocutaneous and central nervous system (CNS) involvement, the latter could be lethal if left untreated.

CASE REPORT

A 67-year-old man with a history of chronic hepatitis C, hypertension and end-stage renal disease presented to our emergency department with drowsiness for 2 days. He had just started receiving DAAs (sofosbuvir and velpatasvir) 10 days earlier. On day 6 of the planned 24-week course, painful grouped vesicles over the right T4-T5 dermatomes (Figure 1A) and an

erythematous flat mucosal lesion with a smooth surface and partially ill-defined borders in the oral cavity (Figure 1B) were noted. Two days later, he had severe headache and subsequently drowsiness. Intermittent shouting and purposeless limb movements such as forceful extension and hand grasping were observed. The vital signs were within normal ranges. Neurological examination demonstrated preserved brainstem reflexes, symmetric limb withdrawal response to painful stimulus, and hyperreflexia with negative Babinski sign. DAAs were discontinued due to concerns about the reactivation of herpes virus. Intravenous acyclovir at 250 mg/day was administered empirically. Cerebrospinal fluid (CSF) analysis revealed the absence of pleocytosis with mildly elevated protein (46.7 mg/dl) and normal glucose level. The diagnosis of HSV-1 encephalitis was made based on positive HSV1-PCR of CSF, while other tests were negative including HSV2-PCR, syphilis, culture of bacteria, tuberculosis and fungus. The patient became stuporous with myoclonic seizure during hospitalization. Brain MRI showed absence of enhancing lesions. Electroencephalogram revealed diffuse slow activity with intermittent sharp waves

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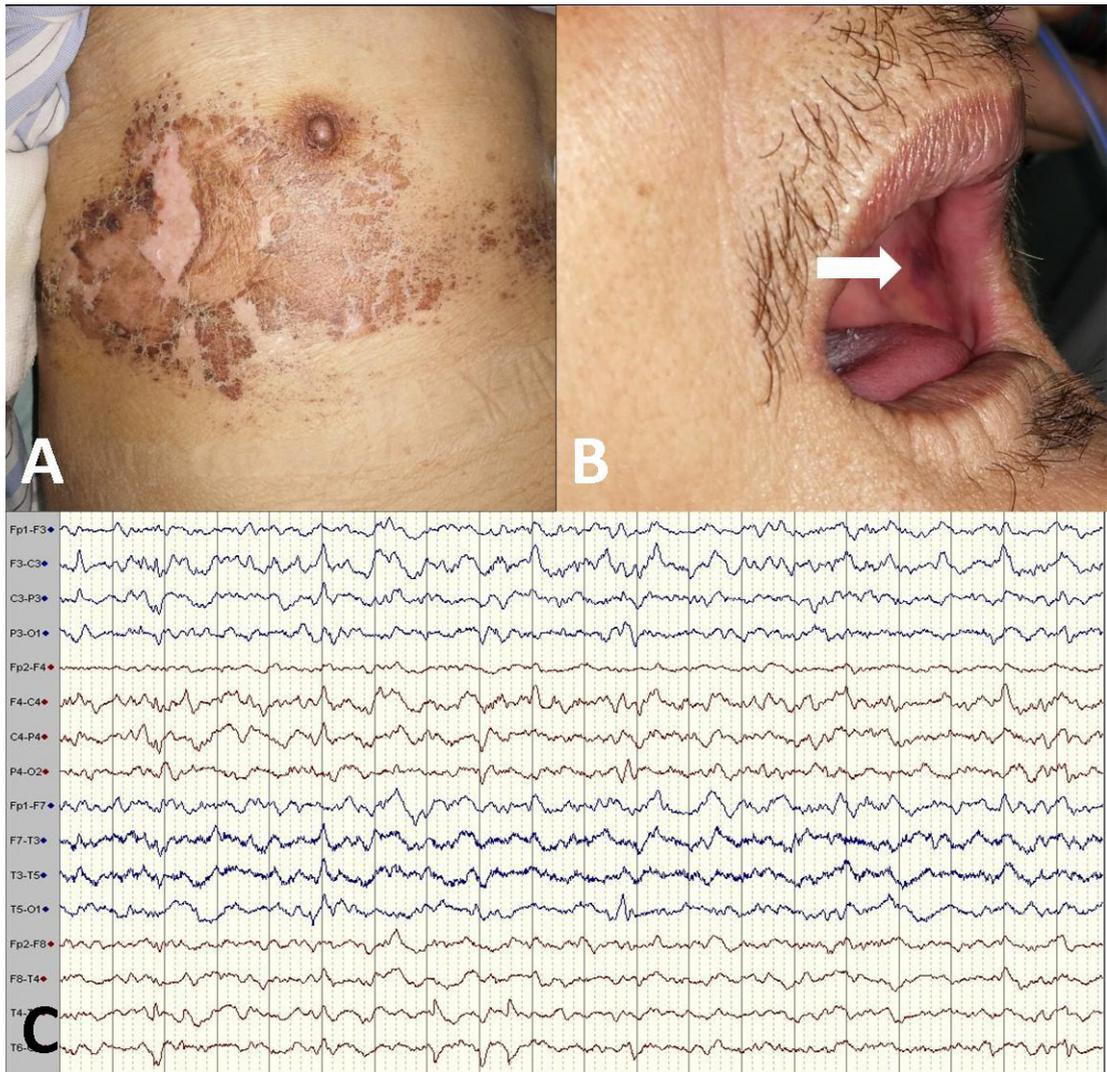


Figure 1. A: Herpes zoster (crusted) over right T4-T5 dermatomes. B: Herpes stomatitis (arrow). C: Electroencephalogram showed diffuse delta and theta activities with intermittent multifocal sharp waves predominantly over the frontal region.

predominantly over the frontal region (Figure 1C). Further study disclosed positive serum antinuclear and anti-SSA/Ro antibody. With a positive Schirmer test and chronic dryness in the mouth and skin, Sjögren syndrome was diagnosed. His consciousness improved significantly after intravenous methylprednisolone 40 mg/day was added to acyclovir. Mucocutaneous lesions compatible with herpes zoster and herpes simplex stomatitis healed gradually. Upon the completion of a total 3-week course of treatment, the patient recovered well with a mildly impaired mental status and postherpetic neuralgia as sequelae.

DISCUSSION

The reactivation of the herpes virus is a complication of DAA therapy in HCV patients according to a previous study.¹ The possible mechanisms include (1) HCV-induced interference on herpes virus replication might be disrupted by rapid virus clearance due to IFN-free regimens³; (2) immune reconstitution inflammatory response (IRIS), which implies a pathologic inflammatory response to previously acquired latent herpes virus in the setting of an improved immune function after DAA therapy. IRIS can be also seen in human immunodeficiency virus-infected patients after active antiretroviral therapy⁴; and (3), the down-regulation of interferon-stimulated genes,

which are key elements of antiviral defense, occurs after HCV clearance.⁵ In our patient, IRIS may be the most likely mechanism as we presume that stronger pathological immune response, which is associated with pre-existing autoimmune disorders would affect the CNS. The shorter duration of herpes reactivation after DAAs and the effectiveness of steroid could support this hypothesis. The information about steroid or underlying autoimmune disorders in this situation is lacking in our literature review. Hypotheses of simultaneous reactivation of two different herpes viruses includes the possible reduced suppression of those latent infections due to the aforementioned down-regulation of antiviral defense in association with HCV clearance.

In conclusion, DAAs therapy may cause reactivation of severe CNS viral infection and not solely peripheral nervous system involvement. Screening for autoimmune markers may be considered before DAA therapy. Moreover, steroid may be beneficial for DAA-related herpes reactivation. Although sofosbuvir based regimens and genotype 1 HCV seem more common in cases encountering herpes virus reactivation, larger studies are necessary to confirm this correlation.

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DISCLOSURE

Conflict of interest: None

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