



Concurrent Reactivation of VZV and HSV-2 in a Patient with Uncontrolled Diabetes Mellitus

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INTRODUCTION

- Herpes simplex virus 1 and 2 (**HSV-1 and HSV-2**) and varicella zoster virus (**VZV**) are neurotropic alpha herpesviruses that cause self-limited vesicular mucocutaneous eruptions, establish latency in peripheral ganglia and can reactivate to cause episodic outbreaks.¹
- HSV occurs more often in the young and may reactivate in more than half seropositive individuals (90% by age 60) as many as hundreds of times in a lifetime.⁵ Triggers include physical/emotional stress, UV light, trauma or changes in hormone levels. Incidence decreases throughout life, consistent with developing immune response.
- While VZV seropositivity is also >90%, estimated lifetime risk is only 10-20%. VZV usually reactivates only once. Trauma and x-ray are possible triggers. Incidence increases with age due to a decline in the VZV-specific T lymphocyte population.⁵
- Humoral immunity has little effect on reactivation; zoster occurs despite normal antibody levels and with normal frequency in agammaglobulinemic individuals.
- As HSV and VZV both establish latency in sensory ganglia, autopsy studies have predictably shown the presence of both viruses in the same ganglia, even in the same neurons.⁹
- Despite their potential co-localization, HSV and VZV rarely cause simultaneous disease.**
- In most of these cases, the viruses have been isolated at different body sites and in the setting of immunosuppression. Simultaneous dissemination of one or more herpesviruses with or without localized disease has also been reported.
- Clinical disease with concurrent detection of both HSV and VZV from the same anatomic location, even in immunocompetent hosts, is more rarely described in the literature.^{1-3,8}
- This is the first case to our knowledge of diabetes-related concurrent VZV and HSV-2 reactivation involving the penis in an otherwise immunocompetent patient.**

CASE

- A 64-year-old male with a history of type 2 DM, HTN, CKD stage III, CHF, COPD and stage IIIB lung cancer s/p chemoradiation (completed 9 months prior to admission) presented with a **one week history of penile pain, swelling and discharge**.
- Swelling preceded worsening pain and serous discharge by three days. He denied history of STIs and prior episodes of penile discharge/genital ulcers. Sexually active only with his wife.
- Review of systems positive for subjective fever and chills during the past week as well as baseline exertional dyspnea and distal paresthesias.
- Vitals on presentation: Temp 36.7 C, BP 142/82, HR 93, SpO2 95% on room air
- Physical exam revealed an **uncircumcised phallus with multiple small, shallow, clean based ulcers on the foreskin**. There was minimal serous drainage. **Four crusted lesions were also observed in a linear pattern at the inferolateral abdomen (L1 dermatome)**.
- Patient had marked hyperglycemia (577 mg/dL) with associated pseudohyponatremia (Na 125 mmol/L) on admission. Anion gap, lactic acid and CBC were normal. Cr was elevated near baseline at 2.1 mg/dL. HbA1c was elevated at 14.9 from 8.7 two months prior.
- UA was positive for pyuria (10-20 leukocytes/HPF) and glycosuria (>1000 mg/dL) but negative for bacteria. Urine culture, urine GC/Chlamydia NAAT, RPR, and fourth generation HIV test were negative.

HOSPITAL COURSE

- The patient's blood glucose and sodium improved with subcutaneous insulin and fluids. Empiric ceftriaxone and metronidazole that had been started in the ED were stopped.
- Swabs were collected from the base of a penile ulcer. The sample was **positive for both VZV and HSV-2 by PCR**. Cycle threshold (Ct) was 35.3 for VZV and 40 for HSV-2. Culture later grew HSV-2 as well. Serologies indicated prior exposure to HSV-1, HSV-2 and VZV.
- The dose of acyclovir was increased for the treatment of zoster. On discharge, acyclovir was changed to oral valacyclovir at a dose of 1 gm TID. Ulcers had resolved on follow-up with his PCP.
- Glycemic control improved with an increased insulin dose and closer adherence to a diabetic diet. Repeat HbA1c at three months had decreased to 8.8.

DISCUSSION

- The location of herpesvirus latency is key to their reactivation and clinical manifestations.
- HSV localizes exclusively to the neuron**, making it more easily and frequently reactivated. Most genes are silenced during latency, except latency associated transcripts (LATs) which increase the efficiency of latency establishment and reactivation.⁴ They also interfere with superinfection by other herpesviruses, suggesting dual infection of the same neuron is a rare, stochastic event.⁹
- There is minimal if any interneuronal spread of HSV prior to anterograde axonal transport to the periphery, reflective of its characteristic localized mucocutaneous lesions.⁴
- In contrast, **VZV demonstrates extensive intraganglionic spread due to its residence within satellite cells**. The cytopathology associated with this process causes neuralgia.⁵
- VZV is less easily reactivated due to the requirement for intercellular signaling between neuron and satellite cell.¹ The large, dermatomal lesions of zoster reflect peripheral delivery by multiple neurons surrounded by the involved neuroglia.⁴

DISCUSSION/CONCLUSIONS

- HSV-specific CD8+ cells have been shown to infiltrate murine sensory ganglia and remain apposed during latency, supporting the concept that **viral reactivation is mediated by transient inhibition of T cell function**. VZV-specific T cell infiltrates have not been histologically identified but likely play a similar role.⁴
- Two models for concurrent herpesvirus reactivation have been posited: A) a common triggering event reactivates two viruses at once or B) reactivation of one virus leads to further inhibited cell mediated immunity and subsequent reactivation of another latent virus. **See Figure 1**.
- Two retrospective studies have examined the concurrent detection of HSV and VZV from the same site.^{2,3} In both, just over 1% of specimens suspicious for herpesvirus infection were dually positive.
- In the most recent study, Dhiman et al. consistently observed a lower cycle threshold (Ct) for VZV compared with HSV, indicating a higher burden of VZV at the site of infection. The same was true of our patient. This suggests that **the development of zoster was the primary event that caused secondary reactivation of HSV** (Fig 1B).
- Hyperglycemia is known to cause reversible T cell dysfunction.⁶ Given that waning cellular immunity is implicated in zoster, it is unsurprising that diabetes has been associated with an increased incidence of zoster and post-herpetic neuralgia.⁷
- It is also plausible that hyperglycemia-induced T cell inhibition allows both HSV and VZV to escape immune control, but VZV has a propensity to reactivate first (dashed line Fig 1B).
- The precipitating factor for development of zoster in our patient appears to have been poorly controlled diabetes. Prior chemotherapy and inhaled corticosteroids are not expected to have contributed. There were no other known stressors or traumas.
- Concurrent reactivation of HSV and VZV at the same anatomic site is an uncommon but well described event. The clinical significance of codetection is unknown.**
- The courses of herpes simplex and zoster are not altered when occurring simultaneously.³ However if there is clinical suspicion for both HSV and VZV, testing for both is prudent because higher antiviral doses are recommended for the treatment of zoster.**
- Clinicians should consider the possibility of concurrent infection with these two viruses in patients who present with dermatomal zosteriform lesions, especially those with uncontrolled DM or who are immunocompromised.**

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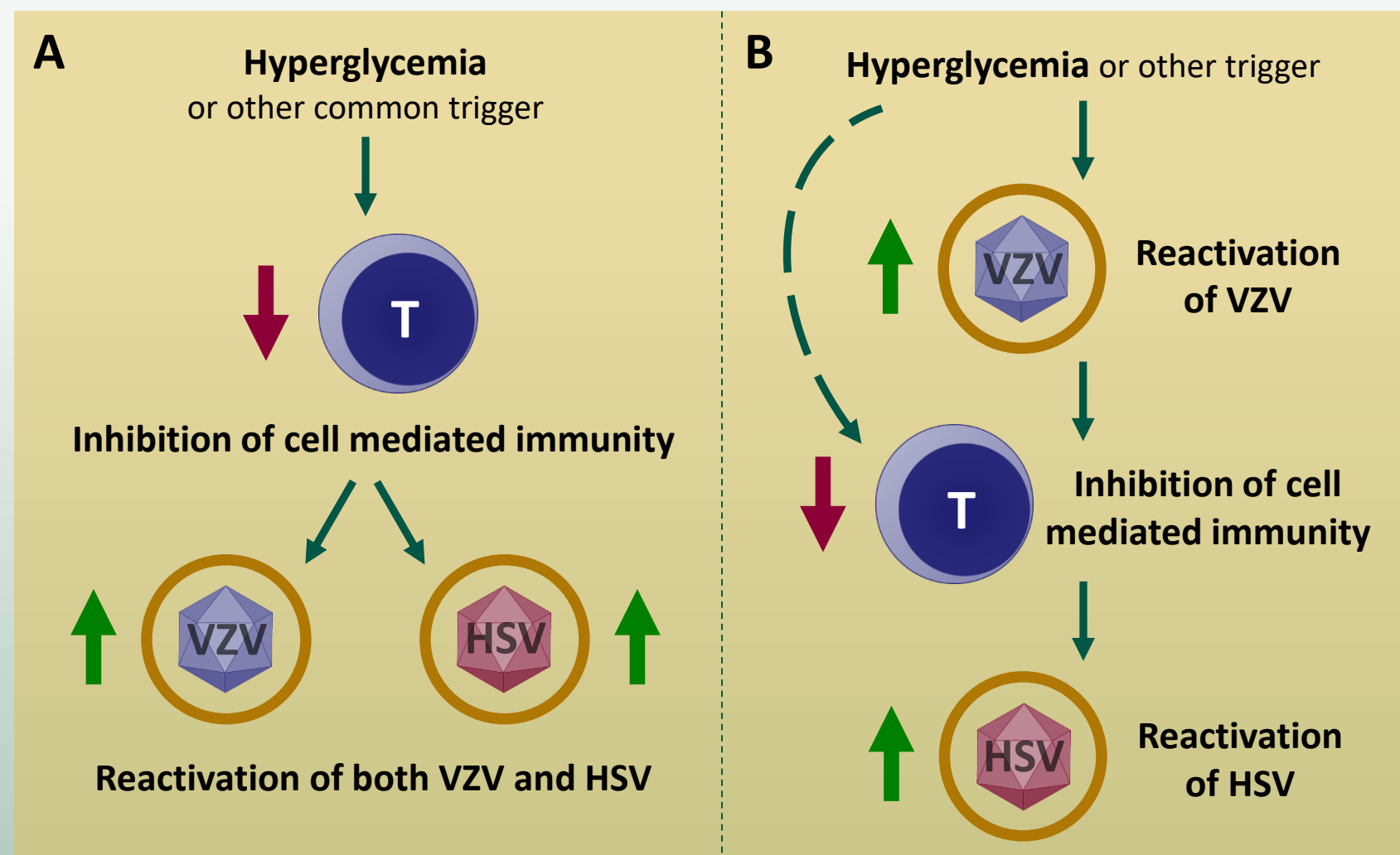


Figure 1: Models for concurrent herpesvirus reactivation