

Varicella-zoster virus and urologic practice: a case-based review

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Introduction: Each year, varicella-zoster virus (VZV) affects nearly one million people in the United States, often in the form of herpes zoster, or shingles. The urologic system is a rare but often debilitating target. This paper reviews the epidemiology, symptomatology, diagnosis, and management of VZV as it relates to urologic practice.

Materials and methods: We performed a PubMed search using the query “herpes zoster” and “varicella-zoster virus” combined with multiple urological terms.

Results: Infection caused by VZV, specifically the resurgent clinical infection herpes zoster (HZ), is

prevalent and increasing. It often affects older men and women and those in immunocompromised states and usually manifests as a painful cutaneous rash. However, urological conditions such as voiding dysfunction, erectile issues, and flank pain have also been noted in conjunction with an HZ infection. Additionally, urological procedures and treatments may incite an HZ outbreak. Awareness and prompt treatment can ameliorate the intensity and duration of this infection.

Conclusions: An understanding of the atypical manifestations of HZ and disseminated VZV infection may aid urologic practitioners in avoiding misdiagnosis and delay of treatment.

Key Words: varicella-zoster virus, urologic practice

Introduction

Varicella-zoster virus (VZV), causes a highly contagious childhood infection known as chicken pox, which presents clinically with fever, lethargy and pustule skin rash. The childhood infection, however, does not always provide lifelong immunity and adults may be affected due to the ability of the virus to establish latency.¹ Recurrence or reactivation of the latent VZV

in the dorsal root ganglia can cause herpes zoster (HZ), or “shingles”, Figure 1.² Painful vesicular cutaneous lesions are the most common manifestation of HZ though VZV may occur without the dermatome skin eruption in a disease state called “sine herpette”.

While dermatological manifestations are often the main presenting symptom, more complex syndromes and complications may also occur with adult reactivation.³ Complications of HZ often involve multiple organ systems including neurological manifestations (i.e. meningitis, transverse myelitis, Guillain-Barré Syndrome, post-herpetic neuralgia, bladder atony and overactivity).⁴ Increased age and immunosuppressive states enhance the risk and severity of adverse effects and lead to substantially higher hospitalization rates.⁴ Surgeons, including urologists, typically encounter VZV when the virus is reactivated in the form of classical HZ following surgical stress. Rarely, VZV can become disseminated causing

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Figure 1. Herpes zoster cutaneous findings in a 75-year-old male receiving hormonal treatment for prostate cancer.

more systemic urological issues. This paper describes the epidemiology, symptomatology, diagnosis, and management of VZV as it relates to urologic practice.

Materials and methods

After creating an appropriate a priori design, a PubMed search to June 2017 was performed using relevant key terms. An extensive search was conducted using the

terms “herpes zoster” and “varicella-zoster virus” combined with other terms specific to urology, including “bladder”, “cancer”, “calculus”, “erection”, “genital”, “hydronephrosis”, “kidney”, “nephrolithiasis”, “penis”, “prostate”, “radiation”, “renal”, “stones”, “scrotum”, “surgery”, “testis”, “transplant”, “ureter”, “urethra”, “urolithiasis”, “urology”, “urological”, and “voiding”. Two authors working independently performed searches and a joint decision was made for inclusion. Relevant general, pathophysiological, and demographic information was obtained from recent reviews.

Results

Epidemiology

VZV causes a childhood virus, varicella (or chicken pox). Given its highly infectious nature, nearly 99% of individuals older than 50 years are seropositive for VZV globally.⁵ After infection, all strains of VZV have the ability to establish latency in the dorsal-root ganglia allowing for reactivation at a later time, usually presenting as HZ.⁴ Worldwide, the incidence of HZ infection is increasing, Table 1. In North America specifically, the incidence of HZ is approximately 3

TABLE 1. Epidemiological studies of incidence of herpes zoster (HZ)

Study	Type	Location	Years	Key findings
Kawai et al ⁶	Retrospective population-based cohort study	United States	1945-1960 1980-2007	HZ incidence rate increased from 0.76 per 1000 PY in 1945-1949 to 3.15 per 1000 PY in 2000-2007.
Li et al ³¹	Retrospective population-based cohort study	China	Not specified	Annual incidence of HZ increased with age. Patients aged 80+ were 3.34 times more likely than 50-year-old to develop HZ. Higher incidence in females than males (26.5/1000 versus 18.7/1000).
Marra et al ³²	Retrospective population-based cohort study	Canada	1997-2012	HZ incidence increased from 1.2 per 1000 to 4.5 per 1000 from 1997 to 2012. Higher rates in females than males (58.3% total HZ cases compared to 41.7%). Higher incidence in older individuals.
Pinchinat et al ³³	Analysis of population-based studies	European Union, Iceland, Norway, Sweden	1960-2010	HZ incidence increases with age, drastically after 50 years of age. Higher incidence in women compared to men.
Schmidt et al ³⁴	Retrospective population-based cohort study	Denmark	1994-2012	HZ incidence increases with age (6 to 9.19 per 100,000 PY between age 50 to > 90).

PY = person years

to 5 new cases per 1000 patient years.⁶ This places the lifetime risk of developing HZ in the general population between 25% and 30%, which increases to nearly 50% in the elderly (80 years and older).⁷

Diagnosis

VZV infections are contagious and spread through direct contact with the skin lesions. Varicella, or chickenpox, has a nearly 61%-100% transmission rate, while HZ is transmitted at a rate of 15%.⁸ Older age, chronic disease, malignancy, and immune therapy enhances vulnerability to HZ and disseminated infection. Awareness of risk factors and potential exposure to infected person (i.e. child with chicken pox) can alert a physician to possibility of VZV infection in a patient.

Development of dermatome skin eruption is the classic presentation of HZ infection and diagnosis can often be made on physical exam alone if classical lesions are observed, but HZ can also present without the cutaneous lesions (*sine herpette*). Prior to visible manifestations, there is often a prodromal, which presents as tingling, itching, or pain lasting 2 to 5 days.⁹ For urologists, the prodromal pain of HZ of the back may mimic renal colic and result in misdiagnosis or delayed diagnosis particularly in the elderly and immunosuppressed.¹⁰ Additionally, unexplained neurologic changes, such as gastrointestinal distention and voiding dysfunction may develop without HZ dermatome manifestation. As such, a high degree of suspicion for HZ should be present in those caring for patients with abrupt onset of unusual symptoms without alternative explanation.

Herpes zoster is often a clinical diagnosis based on history and physical exam. Previously HZ exudate smears known as Tzanck test had been utilized to aid in the confirmatory diagnosis of HZ.⁹ Contemporary practice utilizes molecular methodology and polymerase chain reaction (PCR) of vesicular fluid is the mainstay of diagnosis. PCR results confirm the clinical diagnosis of HZ in 95% of individuals. The sensitivity of virus culture is 20% (specificity 100%), direct immune fluorescent VZV-specific antigen staining in vesicle samples 82% (specificity 76%), and in 48%, there is a serological response to specific IgM and IgA antibodies within 4 days after the onset of rash.¹¹

Treatment

Prevention has become a primary strategy to decrease the incidence of HZ infection particularly in the elderly and immunocompromised patient. In 2006, a VZV vaccine with the tradename Zostavax (Sanofi-Pasteur/MSD) was approved by the US Food and Drug Administration (FDA) as well as by the European Medicines Agency (EMA). Zostavax contains a live attenuated strain of

VZV and is thought to induce primarily T-cell-mediated immunity against the virus. A large double-blind placebo-controlled clinical trial (Shingles Prevention Study) including 38,546 immunocompetent adults > 60 years of age demonstrated that the vaccine reduces the incidence of HZ by 51%, the pain burden by 61%, and the incidence of post-herpetic neuralgia (PHN) by 67%.¹² However, the vaccine-conferred protection declines with age, with an efficacy against HZ of 64% among individuals of 60 to 69 years of age and 38% in individuals aged 70 years and older.¹³

To address this, a new recombinant vaccine, Shingrix (Glaxo Smith Kline) is available in the United States as of 2017. This new HZ subunit vaccine combines a key surface VZV glycoprotein (E) with T cell boosting adjuvant (AS01B). It is highly efficacious in protection against HZ in patients 50 and older subjects (97%), with no decline in advancing age and protection maintained for > 3 years.¹⁴

Despite the widespread use of these vaccines, HZ still affects many globally. The optimal treatment of herpes zoster requires early antiviral therapy (within 72 hours of the rash) and careful pain management. Multiple randomized controlled clinical trials have determined that efficacy of antiviral therapy in patients with HZ has been demonstrated with acyclovir (800 mg 5 times daily for 7-10 days), famciclovir (500 mg 3 times daily for 7 days or valacyclovir (1000 mg 3 times daily for 7 days). These antiviral agents are phosphorylated by viral thymidine kinase and cellular kinases to form a triphosphate form that inhibits viral replication.¹⁵

In patients that are unvaccinated, fail vaccination or have delayed treatment, virus-mediated neuronal destruction and inflammation may lead to significant discomfort caused by the acute and chronic pain of post-herpetic neuralgia (PHN).² The resultant pain interferes with activities of daily living and subsequently reduces quality of life in older adults. For patients who have PHN, evidence-based pharmacotherapy using topical lidocaine patch, gabapentin, pregabalin, tricyclic antidepressants, or opiates can reduce pain burden. The attenuated zoster vaccine is effective in reducing pain burden and preventing herpes zoster and PHN in older adults.¹

VZV infection in urology practice

Voiding dysfunction

Voiding dysfunction is the most common urological issue associated with VZV and may occur in nearly 4% of patients with VZV.¹⁶ The mechanism by which this occurs is likely by way of one of three inflammatory processes: cystitis, myelitis, neuritis.¹⁶ The increased

incidence of bladder dysfunction in those with lumbosacral dermatome involvement (29%) supports the inflammatory nature of the virus. Cystitis involves direct invasion of HZ into the bladder wall, leading to voiding dysfunction. It may manifest as bullae and inflammatory changes visible on cystoscopy. Neuritis-associated dysfunction results from the spread of the virus from dorsal root ganglia to the sacral motor neurons often leading to atonicity. Lastly, dysfunction as a result of myelitis, or direct inflammation of the spinal cord, may manifest as spastic bladder. A literature review from 1955 to 2017 for HZ and urinary retention returned 72 publications. The earliest study, published in 1959, detailed the cases of two 70-year old females exhibiting erythematous sacral and genital rashes associated with voiding dysfunction requiring cauterization. Urodynamic studies showed bladder hypertonicity and cystoscopy was positive for bullous lesions in the bladder of one patient.¹⁷ Since then, several larger studies have been published demonstrating similar findings of bladder dysfunction associated with HZ.¹⁶⁻¹⁹ The most recent study from 2002, involved 423 patients with HZ.¹⁷ Of those 17 (10 men and 7 women) presented with cutaneous rash in addition to urological manifestations including urinary retention, dysuria, frequency, and overflow incontinence requiring catheter drainage. All patients with sacral or lumbar disease in this series (n = 16) also had positive urinary analysis (UA) with greater than 5 red or white blood cells and more than half also had constipation. While all 17 patients required catheter drainage, three underwent urodynamic studies which confirmed bladder atony. Normal voiding returned to all patients within 6 weeks without additional intervention. Taken together, these studies demonstrate a significant incidence of voiding dysfunction in patients presenting with HZ. While many patients have dermatological manifestations confirming HZ infection, urologists must be aware of other presenting symptoms including positive UA in the absence of an infection and constipation. Voiding dysfunction should be managed symptomatically and is likely self-resolving. .

Sexual dysfunction

Erectile dysfunction has been reported in patients with HZ involvement of the sacral dermatomes (S2-S5). Several studies found urine retention and concomitant erectile dysfunction.^{20,21} Often, urinary function returns within several weeks but erectile dysfunction may persist for 6 months. Additional physical findings include perineal and testicular rashes compatible with distributions of sacral dermatomes, decreased cremasteric and anal reflexes, abdominal distention,

and difficulty with defecation. Treatment with acyclovir for HZ and sildenafil for erectile dysfunction have been shown to be efficacious.

Pseudo-renal colic

Prodromal HZ manifestation in the lumbar or flank area may simulate acute renal colic. There is sparse documentation of these clinical observations but flank pain and neuronal deficits associated with HZ may precede the cutaneous manifestations by a few days.¹⁰

Urological cancers

Several studies found a positive association between kidney, bladder and prostate cancer and the risk of HZ.^{22,23} Specifically, in one recent case-matched series of a national UK database, Hansson et al determined the association between 21 of the most common cancers and HZ incidence. The analysis found that patients with prostate, kidney and bladder cancers had an increased risk of subsequent HZ diagnosis compared to those without cancer (adjusted odds ratios (ORs) 1.14 to 1.28). For kidney cancer, HZ diagnosis peaked 1-3 years after diagnosis. Additionally, malignancy was more strongly associated with HZ in younger patients, those less than 50 years old (OR = 1.70 (1.54-1.86)) compared to those older than 80 years old (OR 1.11 (1.06-1.16)). This study suggests that patients with cancer experience cell-mediated immunosuppression from the disease or treatment (chemotherapy, surgery or radiotherapy) which may place them at higher risk for HZ. Knowledge of recent diagnosis should prompt early treatment of HZ-related symptoms.

Syndrome of inappropriate ADH (SIADH)

Inappropriate secretion of antidiuretic hormone can be a consequence of numerous clinical situations, most commonly malignancy. VZV infections and SIADH have occurred in association with immunotherapy for treatment of malignancies of the hematopoietic system.²⁴ While the association is not frequent, 12 case reports discuss localized HZ infection presenting with SIADH.²⁵ The basis of this mechanism is unclear, but it has been suggested that the Varicella-zoster virus may interact with peripheral osmoreceptors that route through the dorsal-root ganglia and influence the regulatory pathway of ADH secretion.²⁶

VZV activation associated with urologic procedures

Shock wave lithotripsy

One case report details shock wave lithotripsy (SWL) reactivating HZ following treatment of renal

stones in a 63-year-old male with a prior history of HZ infection in the same area.²⁷ Multiple vesicular eruptions distributed along the dermatome of the 11th subcostal nerve on the right side with pruritus and severe burning pain following SWL. Reactivation was confirmed by biopsy of vesicular lesion and Tzanck smear (multinucleated giant cells found in exudate of skin lesions) and treated appropriately to resolution. These findings are unsurprising given the mechanical stress applied to the area with the SWL technology. Providers should probe about previous dermatological issues to the area if localized pain is prolonged after this treatment.

Renal transplantation

HZ is common and results in significant morbidity for solid organ transplant recipients.²⁸ In a Canadian study, all solid organ transplants performed between 1994 and 1999 (n = 869) were analyzed to determine the incidence, complications and risk factors for developing HZ. The overall incidence of HZ was 8.6% (liver 5.7%, renal 7.4%, lung 15.1%, and heart 16.8%). The median time of onset was 9.0 months. There were high rates of cutaneous scarring (18.7%) and post-herpetic neuralgia (42.7%). Independent organ-specific risk factors included: female gender and mycophenolate mofetil therapy (liver), and antiviral treatment for suspect cytomegalovirus (CMV).

Radiation

Radiotherapy generates an area of immune depletion, increasing susceptibility for reactivation of HZ often in the form of a skin eruption at or near the radiation treatment field.²⁹ It often occurs early following radiation treatment as previously demonstrated in breast cancer patients though it has not been noted to alter cancer prognosis.³⁰

Conclusion

Infection caused by VZV is prevalent and increasing in incidence largely due to the aging population. Whereas immunization of the pediatric cohort will decrease infection in children, this will not preclude resurgent dermatomal infection commonly known as HZ in adult life. HZ may sometimes manifest in atypical ways including genitourinary abnormalities. Given the aging and immunosuppressed population seen by urologists, a high degree of suspicion must be warranted when evaluating patients for pain, acute onset voiding dysfunction, or suspicious skin lesions. Furthermore, conditions that modulate the immune system, such as surgery and anti-rejection therapy,

may also incite an outbreak of herpes in the urological population. VZV can disseminate into systemic and spinal cord infection that can have adverse effect on lower urinary tract function and erectile capabilities. The complications of poorly treated disease, post-herpetic neuralgia, is often debilitating. Awareness and prompt treatment can ameliorate the intensity and duration of this infection. □

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