HERPES ZOSTER AND SYSTEMIC COMPLICATIONS

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ABSTRACT

Herpes zoster or shingles is a common disease that is widely known to affect the skin. If usually manifests as unilateral grouped herpetiform vesicles developing erythematous base, known as herpes rash. This typical rash is usually preceded by fever, dermatomal pain and regional lymphadenopathy. Treatment for shingles consists antiviral therapy and pain management. Even though considered self-limiting, herpes zoster can cause a series of complication like post herpetic neuralgia, ophthalmic herpes zoster and secondary infections. Recent studies have shown more systemic complications of herpes zoster, involving various organs such as the gastrointestinal tract, the genitourinary tract, the ENT and even the central nervous system. This paper aims to elaborate more regarding herpes zoster and its systemic involvements.

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INTRODUCTION

Herpes Zoster, also known as Shingles, is a disease caused by the reactivation of varicella zoster virus (VZV), a virus that also causes varicella. The incidence of shingles increases with age, presumably due to a reduction in the population of VZV specific T lymphocytes (immunosenescence), increased comorbidity with age, and environmental influences. *Herpes zoster* has been better known as a viral infection involving the skin and nervous system. However, many recent reports have shown systemic involvement of VZV infection outside the typical clinical manifestations that we are familiar with, such as neurological, ophthalmological and visceral involvement. This paper aims to review herpes zoster and systemic complications from VZV infection.

Epidemiology

The incidence of herpes zoster is around 3-5 cases per 1000 population each year and can occur throughout the year.[1,2] The incidence of herpes zoster is influenced by factors that influence the host's immune response to latent VZV. The incidence increases with age. Research conducted in America, Canada, Europe and Asia shows a drastic increase in the incidence of herpes zoster, especially after a person passes 50 years of age.In older age groups, the incidence of shingles increases to 8-12 cases per 1000 population each year. This is presumably because the response of cell mediated immunity is inversely proportional to age. An in vitro study stated that patients from a younger age group had about five times the CD4 population that produced interferon-g, interleukin-4 and interleukin-5, as well as more effector CD4 and CD8 effector memory cells when compared with patients over 60 years old. [1,3]

The incidence of herpes zoster is also many times higher in groups of individuals with impaired immune status (organ transplant recipients, patients undergoing cytotoxic or radiation therapy, and HIV / AIDS patients) to around 29.4 to 51.5 per 1000 population each year. In addition to the above, the following are also risk factors for herpes zoster infection: diabetes, female sex, certain genetic vulnerabilities, mechanical trauma, psychological stress, and Caucasian race. [1,2]

Etiology and Pathogenesis

Herpes Zoster is caused by VZV, a DNA virus that belongs to the herpesvirus family. Varicella zoster virus has morphological similarities to other herpesviruses. Varicella zoster virus and herpes simplex virus are membersof the a-herpesvirus because they are latent in sensory nerves after their primary infection.[3,4]VZV primary infections are transmitted through aerosols (airborne). During varicella, the VZV from the skin and mucosal lesions will enter the sensory nerve endings and will be carried along these nerve pathways to the sensory ganglion be it the cranial nerve ganglion, posterior horn or autonomic ganglion.[2,4]

Latent VZV can reactivate at any time and produce infectious viruses. Reactivation of VZV does not always show clear clinical manifestations, this is due to the formation of VZV-specific immunity from first exposure. When the

patient recovers from varicella, VZV-specific T-cell mediated immunity consisting of CD4, effector CD8 and memory T cells will form, and is detectable within about 1-2 weeks after the rash disappears. It is this VZV-specific T cell mediated immunity that maintains VZV in the latent phase of the neural ganglion.[2,5]

However, if VZV-specific T cell-mediated immunity is low the reactivation of the virus can no longer be controlled hence the multiplication and spread of the virus in the nerve ganglion that causes neuronal necrosis accompanied by inflammations that cause neuropathic pain. Varicella zoster virus spreads from the ganglion to nerve endings and causes the typical skin manifestations of herpes zoster. Spread to the proximal part of nerve ganglion can cause the entry of the virus into the meninges and spinal cord, causing leptomeninges's, cerebrospinal fluid pleocytosis or segmental myelitis.[4,6]Infection and damage to posterior horn can cause persistent neuropathic pain known as post herpetic neuralgia (PHN), while infection of the motor neuron in the anterior horn causes motor disturbances that occur together with the appearance of rashes on the skin.[7]

Clinical Manifestation

Clinically, the course of herpes zoster is divided into 3 phases, namely the pre-eruptive phase, the acute eruptive phase and the chronic phase. The pre-eruptive phase is also known as the preherpetic neuralgia phase. This phase is dominated by prodromal symptoms involving discomfort or pain in the affected skin dermatome that precedes the appearance of the rash. These symptoms can appear for 3 to 7 days. Discomfort can be in the form of itching, paresthesia or a burning sensation. These uncomfortable sensations can mimic other pain such as brachial neuritis, angina or appendicitis. The pain can be continuous or intermittent. In some cases, the pain can be accompanied by malaise, myalgia, headaches, photophobia and fever.[3,7]

The acute eruptive phase occurs after the prodromal phase. This phase is characterized by the appearance of rashes on the skin. The rash caused by VZV has a typical clinical presentation. Usually begins as macula or erythematous papules which are localized according to the dermatome that is affected by VZV, clustered with a reddish skin base and occur unilaterally (not crossing the midline line). VZV initially infects the skin epithelium in the basal layer or stratum germinativum and stratum spinosum. Within 12 to 24 hours, the macula or papule develops into vesicles. This is caused by an increase in the number of infected epithelial cells and results in acanthosis, accumulation of intranuclear inclusion bodies and the formation of multinucleated giant cells.[3,6]The fluid accumulation lifts the uninfected stratum corneum layer and cause vesicle formation. In general, new vesicles will appear on days 1-4. Within 3 to 5 days, these vesicles become pustules. The pustules will dry out and form crusts within 7 to 10 days which will last for 2 to 4 weeks. In this phase, regional lymph nodes are often found. Scarring is uncommon unless there is bacterial superinfection.

A small portion of VZV infection also attacks the trigeminal nerve, especially the ophthalmic branch. If the nasociliary branch of the ophthalmic nerve is infected, the herpes zoster virus can infect structures in the eyeball. Signs of VZV infection in the nasociliary branch is the presence of Hutchinson's sign, unilateral conjunctivitis and impaired sensation of the cornea. This disorder can increase the risk of corneal ulcers and cause bacterial infections. VZV infection in the maxillary and mandibular branches of the trigeminal nerve can manifest as lesions in the mouth, pharynx and larynx. VZV infection of the facial nerve and its network with other cranial nerves can cause facial palsy, lesions in the ear canal or tympanic membrane and can cause vertigo or tinnitus. This condition is called Ramsay Hunt Syndrome. [3,9]

The chronic phase most often experienced by people with shingles is the occurrence of postherpetic neuralgia (PHN).

Workup and Laboratory Studies

Multinucleated giant cells with intranuclear inclusion bodies formed by the merging of epithelial cells that are infected with other cells that are adjacent to the base and edge of the vesicles is what distinguishes between skin lesions caused by VZV with other similar skin lesions. These cells can be observed using the Tzanck smear. Tzanck smear is done by examining the scrapings from the base of the vesicles under a microscope with hematoxylin and eosin or Giemsa staining.[10]

However, the best laboratory study to detect VZV is to do a polymerase chain reaction (PCR). PCR examination has a high sensitivity and specificity and is done in a relatively short time (less than 1 day). The best specimen for PCR examination is vesicle fluid butscrapes from the base of the vesicle or crusts and cerebrospinal fluid can also be used. PCR can distinguish between VZV and herpes simplex virus (HSV); and between wildtype VZV with Oka Vaccine strain. [3,7]

VZV isolation has low sensitivity and requires a longer time, about 1 week or more. However, VZV isolation is the only way to obtain VZV for further analysis. VZV isolation can only be done using samples from new vesicles, difficult to obtain if the lesions have become pustular and cannot be done using samples from the crust. In addition to PCR and virus isolation, another examination that can be done is immunofluorescent staining and immunoassay, but these two are no better than PCR in terms of sensitivity and specificity.[3,7]

Management

Until now, antiviral therapy used for VZV infection is a nucleoside analog group, namely: acyclovir, famciclovir, valacyclovir and brivudine by working to intervene in the synthesis of viral DNA by inhibiting viral DNA polymerase. Acyclovir and penciclovir are analogs of guanosine, which is phosphorylated by thymidine kinase from VZV, but not activated by thymidine kinase from other cells so it is not toxic to uninfected cells. [7,11]

In addition to nucleoside analogs, another antiviral group used is pyrophosphate analog, such as foscarnet, which inhibits herpesvirus replication by becoming a selective inhibitor at the pyrophosphate binding

site. Activation of foscarnet does not require phosphorylation of thymidine kinase, hence becoming a therapeutic choice for nucleoside resistant VZV, but is more toxic than nucleoside analogues. Valacyclovir and famciclovir are better than acyclovir because of their better bioavailability, higher levels in the circulation and because they require to be taken less often. The new antiviral group used to treat VZV infection is amenamevir. Amenamevir is a powerful helix primase inhibitor that can be used against VZV and HSV that are resistant to acyclovir. The dose of amenamevir used is a single dose of 400 mg.[7] The efficacy ofthe administration of antivirals more than 72 hours after the appearance of skin lesions is still being debated, but is still recommended, especially for herpes zoster infections involving the cranial nerve, for patients whose new vesicles are still appearing and for those who are elderly have immune problems. [10]The use of glucocorticoids in herpes zoster is still debated but is generally not recommended. The use of analgesics is preferable especially for pain reduction. [3,6]

Amitriptyline (a tricyclic antidepressant) is the only drug that shows a slight beneficial effect in the prevention of PHN. In a randomized double-blind controlled study in 72 patients aged over 60 years who were given amitriptyline 25 mg daily with antiviral drugs or with placebo in the first 48 hours since the onset of eruption. The main outcome of the study was the presence of pain at 6 months, where there was a reduction in pain in half of the patients in the therapy group. [7,10]

Other drugs used to treat PHN are calcium channel blocker anti-convulsant, namely gabapentin and pregabalin. The efficacy and safety of both gabapentin and pregabalin have been proven as PHN therapy in a randomized controlled trial. Both are classified as alpha-2-delta ligands which have been widely used and approved by the Food and Drug Administration (FDA). The mechanism of action of both in producing analgesic effects is thought to be selective binding on alpha-2-delta subunits on L-type calcium channels thereby reducing Ca2 + influx into presynaptic nerve endings which would inhibit the release of pronociceptive neurotransmitters such as glutamate and P substances that contribute to central sensitization.The use of gabapentin can reduce the degree of pain, improve sleep disorders, mood and quality of life significantly. The dose of gabapentin is 100mg, 3x per day with anincrement of 100-300mg every 5 days until 1800-3600mg per day. Side effects that are often found in the use of gabapentin are somnolence, dizziness, peripheral edema, impaired vision, gait or balance. The dose of pregabalin is 75 mg 2x per day with increased titration to 150 mg 2x per day in 1 week. The side effects of pregabalin are weight gain, dizziness and somnolence. [7,10]

Topical antiviral therapy has a very small (ineffective) role against varicella and shingles so it is not recommended. But in the acute phase, cold compresses or calamine lotion can reduce local symptoms and accelerate the drying of lesions. The use of ointments or creams or lotions containing corticosteroids is not recommended. [12]

Capcycin is an extract from *Capcisumfrustecans*, has been widely used for topical therapy in conditions that involve pain, pruritus and inflammation. It is commercially available in two kinds of cream preparations with concentrations of 0.025% and 0.075%. It's used 3-4 times a day. The mechanism of action of capcycin is by the release of substance P and other neuropeptides from nociceptive fibers (C-unelinated fibers). With repeated use, desensitization occurs in epidermal unmyelinated nerve fibers and reduce hyperalgesia. The use of capcycin is quite limited because of the discomfort and burning sensation associated with activation of the nociceptors at the beginning of the application. However, no systemic side effects were found in the use of capcycin so that it can be used for elderly PHN patients. The 8% capcycin patch was approved by the FDA in 2009 as a PHN therapy. [7,10]

Complications

The most common complication of herpes zoster is post herpetic neuralgia (PHN). Post Herpetic Neuralgia is a neurological complication after herpes zoster infection which is characterized by pain or burning sensation or sensation of puncture and / or allodynia that continues to be felt for 1 to 6 months after the rash disappears. The prevalence of PHN is around 5% -30% and is influenced by the immune system and age. [10]PHN can be caused by various mechanisms. Damage to the peripheral nerves, ganglion and nerves in the spinal cord and inflammation of the skin triggers the emergence of pain signals in the afferent pathway. Postmortem studies prove that herpes zoster patients with severe PHN experience atrophy in the posterior horn, losing axons, cells and myelin accompanied by fibrosis tissue formation in the sensory ganglion. This causes nerve cells to become too sensitive to peripheral stimulation and sympathetic stimulation. Excessive nociceptor activity and ectopic impulses can cause increased CNS sensitivity.[17]

Secondary Infection. Secondary infections by staphylococcal or streptococcal bacteria can occur both in patients with normal immune status and immunodeficiency, will slow healing and cause scarring. In immunodeficient patients, superficial gangrene can also occur.[13]

Systemic Complication

Herpes zoster virus infection can also cause complications in various organs due to its spread to other nerve ganglions or through the bloodstream. This spread can cause the appearance of new lesions in different skin dermatomes. Various systemic complications of shingles are as follows:

1. Disseminated Herpes Zoster. This is a form of herpes where the lesion appears in areas unrelated with the dermatome and can resemble varicella. It often occurs in patients with impaired immune status such as long-term use of corticosteroids, chemotherapy patients, post-organ transplant patients and patients with malignancy. [8] Disseminated herpes zoster has a high prevalence in post-organ transplant patients (solid organ transplant / SOT) which occurs in 40% of patients. The mortality caused is

also high at 12.5-34% even though therapy has been given. [8,18,19]

2. Ramsay Hunt Syndrome. Complications of VZV infection in the ENT fieldis Ramsay Hunt Syndrome (RHS), which is characterized by peripheral type facial palsy accompanied by the appearance of herpes rashes on the outer ear canal, scalp and mucosa of the oropharynx. RHS involves the geniculate ganglion and also several cranial nerves, one of which is often involved is the vestibulocochlear nerve which causes tinnitus, vertigo and unilateral hearing loss. Also, in 50% of cases, the patient loses the sense of taste on the anterior 2/3 of the tongue.[14]

3. Ophthalmic Herpes Zoster. Herpes Zoster Ophthalmicus (HZO) can decreased vision and decreased sensation in the cornea and can cause neurotropic keratitis which can lead to corneal ulcers followed by bacterial infections. HZO also often shows clinical ophthalmoparesis / plegia (ophthalmospasm) that occurs up to 2 months after the appearance of the herpes itself. In addition, HZO can also cause contralateral hemiplegia and aphasia. [15]

4. Vasculitis and Stroke. VZV infection in the cranial nerve can spread to the blood vessels of the brain can cause vasculitis and cause stroke with contralateral hemiplegia that occurs within a few weeks to several months (with an average of 7-8 weeks) from the initial lesion, usually occursafter HZO, but can also occur in herpes zoster that infects other cranial nerves. Vasculitis / angiitis can also cause temporal arteritis, myocardial infarction and aortic aneurysm, and can indirectly cause subarachnoid and intra-parenchymal bleeding. [6.16]

5. Encephalitis. As mentioned earlier in the pathogenesis section of herpes zoster, infection to the proximal portion of the ganglion can cause an infection in the central nervous system. Encephalitis is a rare but possible complication of herpes infection, especially in the cranial nerves. Symptoms depend on the part of the brain affected, but in general those affected will experience headaches, vomiting, fever, sensory disorders and seizures. Another symptom that is often encountered is cerebellar ataxia. In addition to encephalitis, VZV infection can also cause aseptic meningitis, polyneuritis, multiple cranial neuropathy and Reye's syndrome.[16]

6. Myelitis. If herpes zoster infection occurs in the vertebral ganglion especially in the thoracic part, spread towards the proximal part of theganglion can cause myelitis. Symptoms include paraparesis, decreased sensory function, sphincter disorders and Brown-Sequard syndrome, usually felt about 2 to 3 weeks after the appearance of herpes lesions. [6]

7. Complications in Visceral Organs. Complications of shingles can also occur in visceral organs, depending on the dermatome of the infected skin. Herpes zoster in the gastric mucosa can be found following VZV infection in the thoracic ganglion, hemi cystitis can be found in VZV infection in the sacral ganglion. Herpes zoster can also cause esophagitis, pleurisy, peritonitis. [6]

Varicella zoster virus can interfere with the intestinal function and sphincter in the gastrointestinal tract and cause ileus. Several studies report that said patients came acute abdominal complaints, without skin lesions or clear neuropathic pain. The diagnosis of intra-abdominal VZV infection is difficult to establish and, in some cases, it can only be established after the patient isdeceased. In said cased a broad infection in several intra-abdominal organs could be found. Symptoms that may occur besides acute abdominal pain are signs of bleeding from the gastrointestinal tract and reactive hepatitis that is not caused by hepatitis virus infection. Research by Rommelaere et al. in 2012, about 31% of post-kidney transplant patients had disseminated herpes zoster with hepatitis complications.[8,18]

8. Complications in the Genitourinary System. In addition, VZV infection can also affect the genitourinary system. Symptoms that appear in the form of impaired kidney function without skin lesions and without typical neurological symptoms. Varicella zoster virus can also cause sphincter disorders in the urogenital tract and bladder which result in urinary disorders. Several studies have written that VZV infection plays a role in causing bladder cancer. [1.18]

More severe complications are experienced in immunodeficient patients in which patients have disseminated herpes zoster on both the skin and visceral organs such as the lungs, liver and brain. Recurrent VZV infection in AIDS patients can manifest as hyperkeratotic chronic verruca lesions or eczematous lesions caused by acyclovir resistant VZV.

CONCLUSION

VZV infection is no longer just an infection that attacks the skin and peripheral nerves. Various studies have proven that VZV infection is an infection that attacks systemically and causes various kinds of organ disorders.

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