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REVIEW PAPER

# *Review of an Unusual Case of Chronic Relapsing (×6) Zoster Sine Herpete: Immediate Response to High-dose Oral Acyclovir Therapy: Efficacy of the Expedited Classic Therapeutic Trial in an Era of Digital Medicine*

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## *Abstract*

A 79-year-old retired physician with type II diabetes mellitus and hypercholesterolemia presented to his physician complaining of recurrent severe unilateral T10 thoracic pain. This report demonstrates the effect of early high-dose oral acyclovir therapy as a diagnostic, therapeutic challenge to assist in the early diagnosis of zoster sine herpete, herpes zoster infection without dermatomal skin rash (ZSH), a clinically covert form of the more recognized herpes zoster infection with both dermatomal pain and skin rash (HZ).

*Keywords:* Zoster Sine Herpete, Acyclovir Therapeutic Trial

The patient's unusual clinical course included five painful relapses over 13 months, each responsive to oral high-dose acyclovir. The clinical course is reviewed in the context of a diagnosis of chronic active zoster sine herpete. The index clinical presentation and second painful relapse were related to prior broad-spectrum antibiotic therapy, a known modulator of immunosuppression through microbiome dysbiosis. The concept of chronic active zoster is reviewed. The efficacy of the clinical therapeutic trial is demonstrated.

## *1. Case report*

A 79-year-old retired physician with an 11-year history of type II diabetes mellitus and a 7-year history of symmetrical peripheral "stocking-glove" neuropathy complained of a two-day history of severe left-sided posterior inferior thoracic pain. Close inspection of the regional skin revealed a subtle pink micro-papillary rash over the T10 left posterior dermatomal area that could not confidently be

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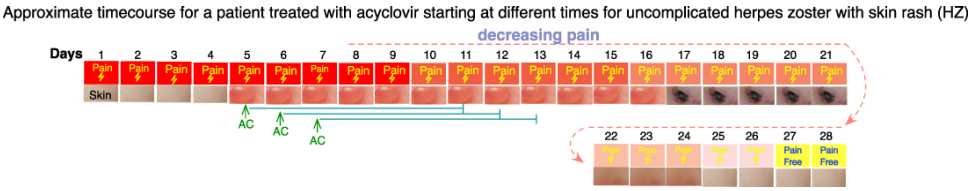


*Figure 1.* Textbook rendition of a usual clinical reactivation of the varicella-zoster virus (VZV) presenting as clinical herpes zoster (HZ). Note the evolution of skin rash and the variable time from first pain to the first rash to initiation of acyclovir therapy.

discriminated from the patient's chronic transient acantholytic dermatosis (Grover's disease). Family history included a brother with a history of herpes zoster. The patient initiated a course of high-dose oral acyclovir for seven days.

The unusual clinical course included five episodes of relapsing dermatomal pain without rash over 13 months. Each clinical relapse was treated with early administration of high-dose oral acyclovir (valaciclovir once). Significant pain relief was appreciated within 24–48 h of the start of each course of therapy. The patient appears to represent an unusual clinical presentation of chronic relapsing zoster sine herpete with retained sensitivity to acyclovir. It is speculated that high doses of broad-spectrum antibiotics may have contributed to immune suppression and activation/reactivation of varicella-zoster virus (VZV).

Figure 1 represents a general timeline for textbook clinical reactivation of the VZV presenting as clinical herpes zoster. Note the evolution of skin rash and the variable time from first pain to the first rash to initiation of acyclovir therapy.

Figure 2(A–F) displays the patient's initial presentation followed by five relapses, each treated with acyclovir (one treated with valaciclovir). Note the absence of a rash and the expedited initiation of acyclovir therapy.

## 1.1. First episode

The patient presented with a two-day history of severe left posterior T10 dermatomal pain (10 of 10) using the Visual Assessment Score [1]. The pain was unrelated to trauma, exacerbated by slight truncal movement, accompanied by allodynia, hyperesthesia, and questionable indistinct local skin changes. Two weeks before the episode, the patient finished a 5-day course of clindamycin (300 mg thrice daily) and Septra-DS (160 mg trimethoprim and 800 mg sulfamethoxazole) for a cutaneous right leg community-acquired Methicillin-resistant Staphylococcus aureus (MRSA) infection. Three days after the start of pain, the patient initiated therapy with acyclovir 800 mg five times a day for seven days. Remarkably, after the initiation of acyclovir, the patient rapidly experienced marked improvement in pain

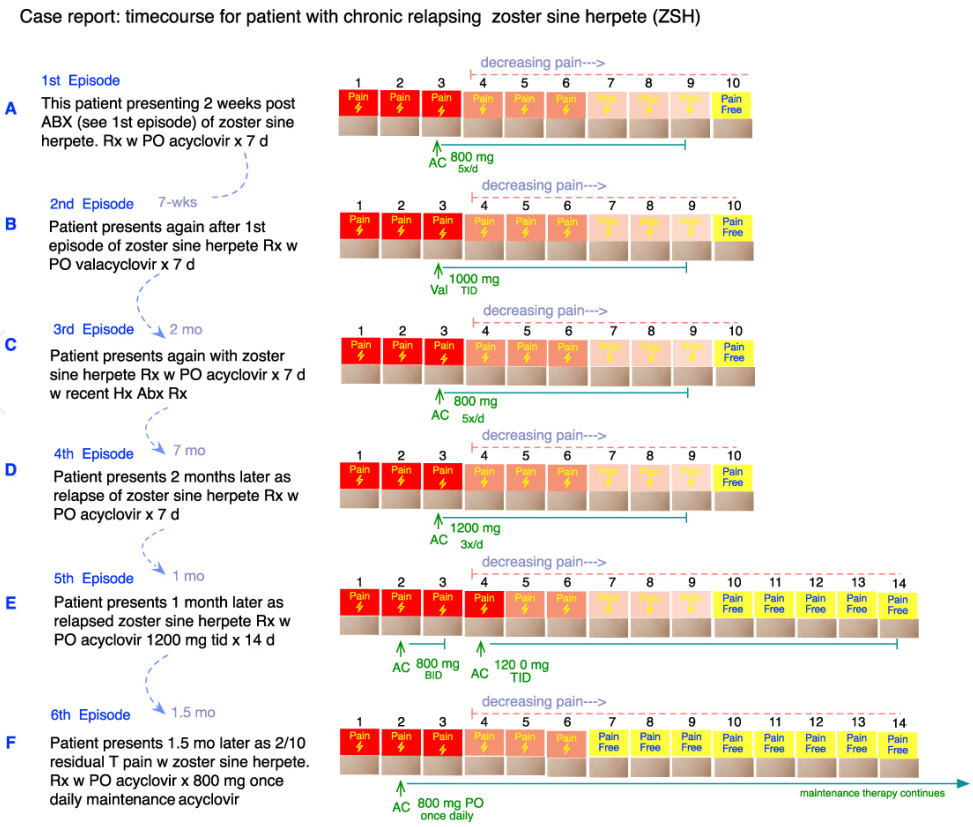


*Figure 2.* Patient's initial presentation followed by five relapses, each relapse except one was treated with high-dose acyclovir (one with valaciclovir). Note the absence of a rash and the expedited initiation of acyclovir or valacyclovir for each relapse induced rapid pain relief.

from pain score = 9 of 10 to 7 of 10 within 24 h. The rapidity of pain response was remarkable and discernable within the first 24 h. The pain continued to fade rapidly and was no longer perceptible by day ten, and a definitive dermatomal rash never appeared (figure 2A).

## 1.2. Second episode

The patient returned seven weeks later with recurrent pain (6 of 10) over the same dermatome without skin changes, and a course of valaciclovir 1000 mg three times daily for seven days was administered. The pain completely abated within seven days of therapy (0/10) (figure 2B).

## 1.3. Third episode

Two months later, the patient experienced an infected ingrown right great toenail which was treated with four days of oral clindamycin 300 mg twice daily with the

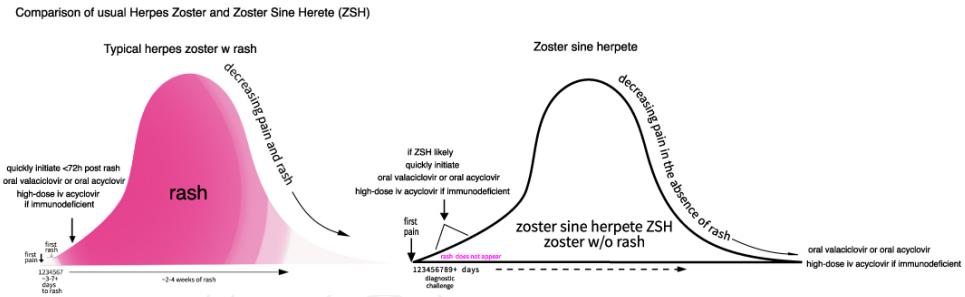


*Figure 3.* Timeline for symptoms and signs of common clinical herpes zoster infection with rash compared to zoster sine herpete (ZSH).

resolution of the infection. Three days after clindamycin discontinuation, the patient experienced recurrent T10 left dermatomal pain (9 of 10). A course of acyclovir was immediately initiated at a dose of 800 mg five times a day for seven days. The pain started to subside again within 24 h (7 of 10) and completely disappeared within a week of therapy, and the patient remained asymptomatic off acyclovir (figure 2C).

### 1.4. Fourth episode

Seven months later, there was a resurgence of identical severe left T10 dermatomal pain (5 of 10), and acyclovir was again initiated as 1200 mg three times a day, followed by rapid 3–4-day complete resolution of pain (figure 2D).

### 1.5. Fifth episode

One month later, the patient experienced a resurgence of identical dermatome pain (6 of 10) and initiated acyclovir therapy but at a reduced dose of 800 mg three times daily × 2d. The pain remained moderate for two days until the oral dose was increased to 1200 mg three times daily, and again the pain markedly improved (2 of 10) over 24 h and entirely resolved within two weeks. Therapy continued for 12 days (figure 2E).

### 1.6. Sixth episode

Six weeks later, because of a small amount of T10 residual pain (2 of 10), the patient restarted oral acyclovir at 800 mg once daily. Over the next five days, the pain completely disappeared. It is anticipated that the patient will remain on this dose while under close observation for an additional 1–2 months of therapy (figure 2F). After signs of acute reactivation have ended, the patient will initiate vaccine therapy (recombinant zoster vaccine, or RZV) for the prevention of herpes zoster (shingles) and related complications.

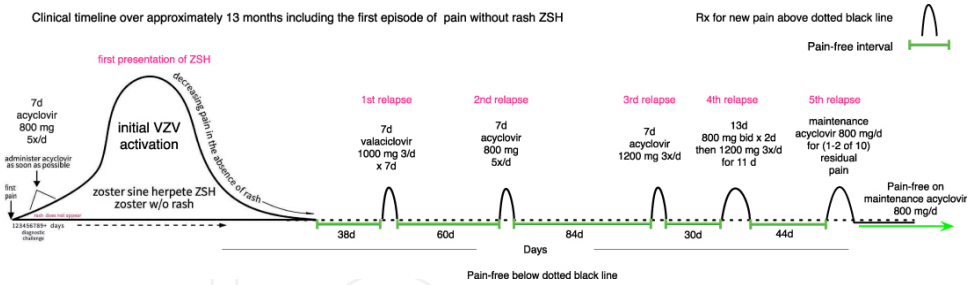


*Figure 4.* Timeline of initial Zoster Sine Herpete infection followed by five clinical relapses.

## 2. Clinical summary

The patient's clinical course over 13 months, figure 4, is unusual and included five episodes of symptomatic clinical recurrences of VZV manifest as ZSH. The variant timeline of the patient's ZSH infection contradicts most VZV reactivation infections where high dose oral acyclovir therapy is given as a 7- or 10-day course of therapy ("once and done") (figure 1). The chronicity and relapses in this elderly diabetic patient exposed to high doses of broad spectrum antibiotics therapy are discussed.

## 3. Discussion

Initial clinical diagnostic considerations for this patient's unilateral left T10 dermatomal pain included compressive radiculopathy, diabetic thoracic radiculopathy, and herpes varicella reactivation (zoster, herpes zoster, shingles). However, a definitive dermatomal rash was never precisely discerned, which added to the initial diagnostic dilemma.

VZV, the cause of childhood chickenpox, remains dormant or latent within neurons of cranial nerve ganglia, dorsal root ganglia, and enteric and autonomic ganglia after the resolution of clinical symptoms. According to the Hope–Simpson hypothesis [2], several years after the initial illness, an immunocompromised state may suppress both cellular and humoral immunity vs. latent VZV permitting reactivation of VZV[3], which may or may not become clinically symptomatic. A critical newly discovered factor found to have an essential role in maintaining VZV latency, VLT (VZV Latency-associated Transcript), was recently discovered [4]. The unique spliced VZV latency transcript represses expression of the viral transactivator gene 61 [5] and, by so doing, is responsible for maintaining VZV latency.

Clinically significant reactivation presents as either HZ or ZSH or as described by Lewis in 1958 [6] as a simultaneous or sequential mixture of both syndromes. The myriad of clinical signs and symptoms caused by zoster herpes virus (ZHV)

reactivation is more remarkable than generally appreciated and was elegantly reviewed in 1916 in a comprehensive descriptive report by Weber [7] and later by Nagel and Gilden [8].

A summary of the most common clinical sequelae of reactivation was presented by Gilden and includes the following: chronic pain (postherpetic neuralgia (PHN)) as well as meningitis or meningoencephalitis, cerebellitis, isolated cranial nerve palsies that produce ophthalmoplegia or the Ramsay Hunt syndrome (RHS), multiple cranial nerve palsies (polyneuritis cranialis), myelopathy, vasculopathy, and various inflammatory disorders of the eye, the most common of which is progressive outer retinal necrosis (PORN). Importantly, VZV reactivation may present as an acute episode of dermatomal pain with or without rash lasting weeks to a few months without residual or as a chronic and intermittent radicular pain syndrome with (HZ) or without rash (ZSH) [9]. The myelopathy or segmental peripheral episode of motor weakness that follows herpes zoster manifests as a segmental weakness frequently occurring around the zoster outbreak. Myelopathy may affect the legs and sphincter tone. Residual dermatomal pain after three months is functionally defined as PHN.

There is a strong association between age and PHN. At 60 years of age, approximately 60% of patients with shingles develop PHN, and at age 70 years, 75% develop PHN. Age is directly related to the frequency of PHN but indirectly related to immunocompetence, suggesting that advanced age and immune compromise may be involved with increased chronicity of both HZ and ZSH. PHN is the most common complication of HZ. Other risk factors include the severity of acute HZ or ZSH pain, greater extent of rash, and presence and longer duration of preherpetic neuralgia [10].

The lifetime risk of HZ in the general population ranges from 20–30%, but the risk increases after 50 years of age, with a lifetime risk reaching 50% at age 85 [11]. There is an absence of data to define the incidence of ZSH since its clinical presentation often masquerades as a diverse and unrecognized pain syndrome that may go undiagnosed. The incidence is considered significant [12]. Based on the literature review, I believe that many patients sent to the orthopedic clinic for evaluation of nerve root pain never raise a physician's suspicion of ZSH. Therefore, the patient may be sentenced to a prolonged battle with an unrecognized and thus untreated viral pain syndrome.

If allowed to progress untreated this may end in muscle wasting and dreaded PHN [9, 13]. It is generally recognized that early (<72 h post-rash) oral or intravenous anti-viral therapy is the treatment of choice for both HZ and ZSH. The dose and route of administration depend on the presence of severe immunocompromise [14].

### 3.1. Drug therapy

Both acyclovir and or valaciclovir (which yields three- to five-fold increases in acyclovir bioavailability) are recommended as initial anti-viral therapy. Oral valaciclovir may be the best oral acyclovir if given later within 48–72 h of the first rash [15], and valaciclovir given at 1000 mg three times daily for seven days was found to accelerate the resolution of pain while offering simpler dosing and higher blood levels of acyclovir while maintaining the favorable safety profile of high dose oral acyclovir [16]. Both drugs are reasonable initial therapy with minimal toxicity in the presence of renal competence. Intravenous acyclovir is recommended in the presence of pronounced immunosuppression, e.g., 10 mg/kg IV every 8 h for seven days; use ideal body weight for obese patients [17].

Brivudin is a thymidine nucleoside analog anti-viral with potent anti-VZV that inhibits DNA polymerases. Oral brivudin (125 mg once daily) is licensed for the treatment of HZ in several countries of the European Union. In a double-blind, randomized multicenter study, 48 immunocompromised patients with an HZ rash less than 72 h in duration received brivudin or intravenous acyclovir treatment. No significant difference was seen regarding cutaneous or visceral dissemination compared between the two therapies. Brivudin is not available in all countries and is not approved for anti-viral treatment in children and adolescents due to the absence of safety studies for that group.

In cases of drug resistance, foscarnet and cidofovir, both inhibitors of viral DNA polymerase, act independently of the viral thymidine kinase and are recommended [18].

A meta-analysis of five published randomized clinical trials on the use of acyclovir to prevent PHN has been reported. Oral acyclovir protocols varied between the five studies as (1) 4 × 200 mg, five times daily for 10 d, (2) 2 × 400 mg, five times daily for 7 d, (3) 2 × 400 mg, five times daily for 7 d, (4) 800 mg, five times daily for 10 d or (5) 800 mg, five times daily for 21 d [6]. The analysis concluded that treatment with oral acyclovir within 72 h of rash onset reduced the incidence of residual pain at six months by 46% in immunocompetent adults.

### 3.2. HZ and ZSH differences

HZ usually presents with a prodrome of pain or so-called preherpetic neuropathy (but not always) followed by dermatomal rash (figure 1).

ZSH presents with dermatomal pain without a following rash (figure 3). ZSH patients may not receive recommended expedited anti-viral therapy because the diagnostic challenge may require time-consuming confirmatory studies.

Clinically there are distinct differences other than rash between HZ and ZSH. Drago *et al.* [19] studied 16 consecutive patients with acute unilateral pain without

vesicular cutaneous eruption (ZSH) and compared them to 16 suffering from typical HZ with a skin eruption. ZSH patients averaged greater pain and used more opioids than those with HZ Compared with typical HZ patients; there was a higher rate of PHN development for ZSH patients.

### 3.3. Acute, chronic active (persistent active) and recurrent HZ and ZSH neuropathy

The histopathology of inflamed dorsal root sensory ganglia (DRG) or ganglionitis reveals dermatomal ganglion neuronal cell swelling and degeneration with associated mononuclear cell inflammation. Lymphocytic inflammation of neurons with associated vasculitis causes degeneration of motor and sensory roots and, if allowed to go unchecked, may spread into adjacent parts of the spinal cord and manifest as regional leptomeningitis and gray-matter necrosis and demyelination [20]. This VZV ganglionitis inflammatory response includes CD4+ T-cells, CD8+ T-cells, and Treg cells, amongst others. Ganglionitis is currently believed to be in significant part responsible for prolonged pain and potential irreversible neuronal damage leading to PHN [12, 21–23] and, in advanced cases, chronic myelitis [24], muscle wasting with loss of strength, hyperesthesia, paresthesia, burning dysesthesias, or pruritus involves the affected dermatomes.

### 3.4. Chronic ganglionitis

In his 1994 publication "zoster sine herpete, a clinical variant," Gilden closely outlined the chronic and recurrent nature of ZSH reactivation in two patients, both of whom suffered from severe recurring pain and responded on several occasions to both intravenous and or high-dose oral acyclovir. One patient required prolonged oral acyclovir administration for several months until completely pain-free [25].

In 2003 Gilden *et al.* published "chronic varicella-zoster virus ganglionitis—a possible cause of postherpetic neuralgia." He described a woman with multiple famciclovir responsive HZ infections over 11 years in that paper. A painful relapse closely followed each voluntary withdrawal of famciclovir, within one week. During each painful relapse, she was found to have VZV-associated DNA within circulating monocytes. Gilden felt chronic ganglionitis was the best explanation for the patient's multiple chronic painful relapses of PHN [26].

Other investigators have described patients with HZ and or ZSH who display chronicity of symptoms such as pain, rash, muscle weakness, keratitis, etc. [24, 27–29].

A cursory review of the literature seeking a precise definition for 'chronic active zoster infection' was difficult to pin down. Various publications discuss clinical cases of recurrent zoster reactivation several weeks to years after a first index case.

Recurrent zoster breakthrough pain appearing weeks or months after withdrawing or lowering effective anti-viral pain suppression suggests zoster chronicity. Are these cases 'chronic active zoster', or do they represent successfully suppressed episodes of VZV reactivation followed by subsequent new painful reactivations? Perhaps Gilden's group comes closest to offering clinical vignettes useful in loosely defining chronicity as follows. One feels that chronicity may involve a prolonged, possibly intermittent interaction between VZV activity and T-cell and other mononuclear cell activity with associated inflammation within the dorsal root ganglion.

Wolf *et al.* [30] in 2012 presented details of a patient with chronic active VZV infection. The patient was a 58-year-old insulin-dependent diabetic woman with a chronic active VZV infection. The patient's clinical course is unusually complicated. She presented with a 4-month delay between the onset of HZ and ZSH, involvement of nine dermatomes on the progression of right-sided HZ to left-sided ZSH, and she had both VZV DNA and anti-VZV immunoglobulin G (IgG) in the CSF. The patient developed zoster sine herpete involving several left-sided thoracic levels four months after typical HZ of the right side. Though therapy with valaciclovir for the right-sided HZ was ineffective for pain relief, it was found effective for pain relief of ZSH on the left side.

His group concluded that protracted zoster sine herpete in multiple dermatomes distinct from the site of the patient's initial HZ suggested she had a form of chronic active VZV ganglionitis and thus chronic active zoster sine herpete.

The group proffered that chronic VZV ganglionitis may present as prolonged pain without rash in individuals with no history of zoster, prolonged prodromal or preherpetic neuralgia before HZ, and as longstanding radicular pain due to an inflammatory ganglionic mass chronically infected with VZV. The patient's ZSH resolved after IV therapy with acyclovir. If active VZV infection is diagnosed in patients with PHN, IV treatment with acyclovir may be helpful, as it was for their patient [30].

Birlea, Nagel, Gilden, *et al.* [21] in 2014 published the paper "Varicella-zoster virus trigeminal ganglioneuritis without rash." They discuss in detail postmortem histopathological changes of the trigeminal ganglion and adjacent nerve root demonstrating chronic VZV ganglioneuritis.

Histology included: (1) dense lymphocytic-predominant inflammatory infiltrate surrounding neurons in the ganglion and inflammation in the adjacent nerve root. (2) CD4+ T cells predominated in the ganglion and nerve root, occasionally clustered around viable-appearing neurons. (3) CD8+ T cells were also frequently seen in the ganglion and nerve root, as well as CD68+ macrophages. (4) CD20+ B cells were occasionally seen in the ganglion. (5) VZV antigen was seen at the periphery of the left trigeminal ganglion, inside and outside the wall of a meningeal blood vessel, and the trigeminal nerve root after labeling with anti-VZV antibody, but not after labeling adjacent sections with anti-herpes simplex virus antibody [21].

The literature search revealed that chronicity of HZ and ZSH is frequently associated with severe immunodeficiency disorders such as occurs with HIV[31] infection and may occasionally present with other types of immunocompromise, e.g., T-cell deficiency [32], bone marrow transplantation [33] and ingestion of powerful immunosuppressive drugs. These clinical presentations are frequently but not always associated with cross-resistance between acyclovir, valaciclovir, and famciclovir. In such cases, drug susceptibility should be evaluated if a patient shows therapeutic failure within 7 to 10 days, and alternative drugs are required. Foscarnet and cidofovir, both inhibitors of viral DNA polymerase, act independently of the viral thymidine kinase and are recommended in such cases [18].

Historically there seems to be an attempt to tie clinical chronicity (PHN and/or episodes of anti-viral responsive multiple relapses) to chronic inflammation of dorsal ganglion neurons, so-called ganglionitis.

### 3.5. Frequency of zoster recurrences

Several authors point to the frequency of zoster recurrences. Dyer describes a 52-year-old black woman with an intact immune system with three episodes of recurrence [34]. Yawn's group reported that recurrences were significantly more likely in patients with 30 days or longer zoster-associated pain at the initial episode and in immunocompromised individuals. Women and anyone aged 50 years or older at the index episode also had a greater likelihood of recurrence [35]. Shiraki *et al.* note that of 16,784 patients observed in 10 clinics, 1076 (6.41%) experienced a recurrence of HZ, with 49 and 3 patients experiencing 3 and 4 recurrent episodes, respectively [36]. Frequent recurrences are difficult to distinguish from chronic active zoster.

### 3.6. Early acyclovir therapy as a therapeutic trial

Being within the era of Covid-19, patient we report felt that his risk-benefit ratio was in favor of a self-therapeutic trial of high-dose oral acyclovir, which was started within two days of the initial severe, intractable left posterior T10 pain (figure 2A). He was surprised at the speed of substantial pain relief within only 24–48 h of the start of high-dose oral acyclovir suggesting therapy was appropriate and effective.

Figure 2(A–F): Outlines five distinct episodes of chronic and recurrent painful ZSH relapses within 13 months. Multiple recurrences of both HZ and ZSH, though infrequent, have previously been reported [25, 34, 36, 37].

This patient repeatedly enjoyed a rapid diminution of pain with each restart of high dose oral acyclovir. It is of interest that two of the reactivation episodes (the initial index reactivation ZSH and the third episode followed the use of broad-spectrum antibiotics for skin infections see figure 2(A,C).

### 3.7. Immune compromise

Gerada *et al.* reviewed VZV's extensive and complex modulation of components of the intrinsic, innate and adaptative immune response to ensure viral dissemination and the establishment of life-long latency [38]. A detailed discussion is beyond the scope of this presentation.

This patient's increased susceptibility to ZSH with five relapses may have been influenced by family history, a brother with a history of HZ [39], advanced age of 79 years [40], long-term use of statins [41, 42], diabetes mellitus [43, 44] and broad spectrum antibiotic use.

The risk of HZ associated with statins was found to be higher with advanced age: HR 1.39 in the over 70-year-olds ($p$ = 0.003). Statins inhibit interferon-$\gamma$-induced MHC-II expression and prevent antigen presentation to CD4+ T-cells. They also increase the immunosuppressive effects of regulatory Treg-cells. These activities acting in concert may add to the suppression of cell-mediated immunosuppression vs. VZV.

The microbiome, microbiota, dysbiosis, and systemic immunosuppression CD4+ T-cell cellular immunity is considered paramount above immunoglobulin response (IgM, IgG) in suppressing VZV reactivation [3, 12, 45]. Imbalances in the gastrointestinal (GI) microbiota (microorganisms), known as dysbiosis, can trigger several immune disorders through the activity of nearby T-cells or trafficking to distant sites. Changes in the microbiome are telegraphed through the shedding of immunoregulatory metabolites into the circulation, thereby affecting systemic cellular immunity [46, 47]. Systemically distributed immune cells within distal organs directly recognize circulating microbial-derived factors, and changes in microbiota-derived signaling molecules cause alterations in immune function that may lead to immunodeficiency [48].

An increasing body of evidence indicates that disruption of the homeostasis between the GI microbiome and the host immune system (dysbiosis) by broad-spectrum antibiotic therapy can adversely impact distant viral immunity [49–53]. The microbiome CD4+ T-cell is sensitive to antibiotic-mediated dysbiosis [54]. In separate laboratory experiments, the T-cell immune response vs. the VZV was compromised in diabetic patients [44].

The clinical significance of antibiotic dysbiosis was surprisingly exposed in cancer patients exposed to broad-spectrum antibiotics before receiving immune checkpoint inhibitors. Patients treated with antibiotics had significantly decreased overall and disease-free survival [55–59].

Other investigators have confirmed the paradigm of systemic instruction of cell-mediated immunity by antibiotic modulation of the intestinal microbiome [60].

Belkaid and Harrison, in an elegant review, reveal that all aspects of immunity, including systemic and regional, including humoral and cell-mediated, can be directly or indirectly controlled by the microbiota [61].

Armstrong *et al.* report that patients who received ≥4 antimicrobial prescriptions in the preceding year were at significantly increased risk of all types of meningitis, bacterial meningitis, and viral compared to their matched controls [62].

Whether broad-spectrum antibiotic dysbiosis-associated immunocompromise added to other immunosuppressive stresses for the subject of this case report is purely speculative. However, two of six episodes of VZV reactivation closely followed the administration of broad-spectrum antibiotics (figure 2(A,C)).

## *4. Summary*

This elderly diabetic patient initially presented as a diagnostic challenge with what appeared to be T10 nerve root pain. Differential diagnoses included compression radiculopathy, diabetic thoracic radiculopathy, and herpes varicella reactivation. The physician–patient initiated a self-therapeutic trial of high-dose oral acyclovir and experienced a rapid onset of pain relief. The patient's subsequent clinical course was compatible with the unusual syndrome of chronic, frequently relapsing acyclovir sensitive zoster sine herpete (chronic active zoster sine herpete). After an extraordinary five episodes of painful relapse, he remained pain-free on a modified oral dose of acyclovir 800 mg daily for an additional six weeks.

It is suggested that physicians faced with common as well as perplexing pain syndromes always be mindful that ZSH is a master of disguise and missing an early opportunity to diagnose and treat properly may commit the patient to a lifelong burden of PHN pain management. This case report suggests we include the patient history of prior statin and antibiotic therapy when presenting dermatomal pain syndromes with or without an associated rash and consider that some patients may follow a course of chronic active zoster which may span over several months and possibly years if anti-viral therapy is delayed by just a few days.

NOTE: Classical laboratory diagnosis of VZV infection is time-consuming. Though the diagnosis of chicken pox or herpes zoster is typically clinical when in doubt, laboratory tests can be performed. PCR to detect VZV DNA is the first choice, most reliable, and sensitive lab test. Direct immunofluorescence (DFA) to detect VZV antigen is the second choice; sensitivity is only 60–70% of cases detectable by PCR. Other methods to confirm VZV infection do not enhance accuracy. The viral culture of VZV is possible but is insensitive.

In cases of acyclovir-resistant VZV, detections of mutations in thymidine kinase can be determined by PCR and sequence analysis. MRI may be helpful if myelitis,

meningitis, or encephalitis is suspected. Lumbar puncture may be helpful if signs suggest myelitis, meningitis, or encephalitis. Under these circumstances, clinical suspicion should guide immediate emergency use of intravenous acyclovir therapy. Central Nervous System (CNS) involvement with VZV infection may cause severe and irreversible damage. Time is of the essence. Acyclovir is the treatment of choice, supplemented with aggressive hydration to avoid kidney injury. Emergency room empiric intravenous acyclovir therapy while awaiting laboratory results of lumbar puncture (4–5+ days for PCR testing) is generally considered safe relative to risk.

It is not unreasonable to conjecture, and it has been hypothesized that some emergency room and pain clinic patients may be suffering from occult ZSH (acute or chronic). As with classical herpes zoster, initiation of empiric high-dose acyclovir therapy should be entertained at the first suspicion of the more occult ZSH. Some have suggested that the pain from ZSH may last longer and is of greater intensity than that of HZ High-dose acyclovir therapy for patients with chronic PHN syndromes remains controversial. ZSH is likely to be missed or misdiagnosed, and patients may not receive timely anti-viral treatment. This causes continuous activation of the VZV, which may induce persistent herpetic neuralgia, and even PHN if chronic damage affected nerve ganglia.

NOTE: This patient was planning to get vaccinated with the RZV therapy after the sixth episode of intercostal pain. However, within the context of the confusion of the Covid 19 epidemic and potential overlapping clinical symptoms shared between RZV and Covid-19 infection, he declined to do so. He currently remains free of all intercostal pain for the past 20 months and has no longer taken anti-viral medication.

The RZV is not a treatment for active herpes zoster (shingles), zoster sine herpete, or active PHN and should not be given during active disease [63] RZV was studied in two pre-licensure clinical trials that found efficacy against shingles was 97% for persons 50–59 years of age, 97% for persons 60–69 years of age, and 91% for persons 70 years and older. Among people 70 years and older, vaccine efficacy was 85% four years after vaccination. In clinical trials, RZV reduced the risk of PHN by 91%. For more information regarding the RZV, go to the following CDC link: https://www.cdc.gov/vaccines/vpd/shingles/public/shingrix/index.html.

## *Conflict of interest*

The author declares no conflict of interest.

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