

Herpes zoster-associated aseptic arthritis in adult patients: A case report

Dear Editor,

Aseptic arthritis can often be associated with viruses—in the Singapore context—dengue or chikungunya viruses. The association of varicella-zoster virus (VZV) with arthritis however, is rare. Few cases of aseptic arthritis associated with VZV have been documented in the paediatric literature in the past 50 years and fewer still in adults. To date, the exact mechanism, clinical presentation and treatment have not been well described in the literature. We describe here a case of aseptic arthritis associated with VZV reactivation and present a review of the published literature.

In December 2017, a 79-year-old Chinese man presented to our rheumatology clinic with left hand pain and swelling. Prior to this, the man had no history of joint complaints. He developed herpes zoster over the left C6 dermatome in September 2017. No antiviral treatment was prescribed when the patient first developed herpes zoster. Pain was worse when carrying or gripping objects but not worse in the morning. Stiffness lasted the whole day. The symptoms had persisted without improvement over 4 months and he remained unable to perform most of his daily activities with his left hand. He had no constitutional symptoms of fever, fatigue, anorexia or weight loss, and systemic review was otherwise unremarkable. His past medical history was significant for hypertension, atrial fibrillation, severe tricuspid regurgitation and moderate ischaemic mitral regurgitation.

Physical examination revealed a well-nourished elderly man, with tenderness over the proximal interphalangeal joints of his left index and middle finger. The entire left hand was puffy and oedematous, with a greatly reduced range of movement. He was unable to straighten his fingers fully or make a full fist, but clinical synovitis was not readily appreciated due to the swelling. His wrist was not swollen, and there were no signs of carpal tunnel syndrome. There was no remnant cutaneous sign of his previous herpes zoster, and no other joint swellings. Laboratory investigations showed negative rheumatoid factor and anti-cyclic citrullinated protein antibodies (Table 1). Anti-VZV immunoglobulin M and immunoglobulin G were not done as the herpes zoster had resolved 4 months ago. X-ray of the hand was normal with no evidence of chondrocalcinosis. Ultrasound revealed

grade 2–3 synovial hypertrophy of the proximal interphalangeal joints of the right thumb, left index, middle and little fingers, as well as mild osteoarthritic changes in both hands. There was no power Doppler signal visualised on ultrasound. Joint aspiration could not be done because of an absence of joint effusion on clinical examination and ultrasound.

He was diagnosed with an asymmetrical oligoarthritis of the hand, possibly zoster-associated arthritis. Due to the long duration of his symptoms, he was treated empirically with hydroxychloroquine 400mg daily and a short course of prednisolone (10mg for 1 week, followed by 5mg for 1 week). His symptoms and signs ameliorated 4 months later. The stiffness and swelling improved, his joints were no longer tender, and he was once again able to make a full fist with his left hand. Hydroxychloroquine was discontinued and the patient remained well.

From 1968–1993, 7 articles describing 8 cases of zoster-associated arthritis were reported in adults. Subsequently, only 1 case was reported in 2017. In contrast, although rare, arthritis is a well-recognised complication of primary VZV infection in otherwise healthy, immunocompetent children. From our literature review, the following clinical features are present in herpes zoster-associated arthritis: (1) small and large joint involvement; (2) synchronous onset; (3) joint involvement corresponding to dermatomal involvement; (4) neutrophil predominance on synovial fluid analysis; and (5) evidence of VZV in synovial fluid on laboratory testing (Table 1). As with most classification criteria in rheumatology, the presence of some but not all of the above features is suggestive of zoster-associated arthritis.

The demographic, clinical and biologic characteristics of the 9 patients are presented in Table 1. The median age was 67 years and 4 of them were male. Three patients were considered immunocompromised—2 had long-standing rheumatoid arthritis of more than 10 years and 1 had non-Hodgkin's lymphoma. Five had monoarthritis of the shoulder, hips or knees, with the herpes zoster eruption over the corresponding joint distribution. The median age of 67 years corresponds with the common age of VZV reactivation.¹⁻³

Joint involvement usually starts at the time of diagnosis of herpes zoster, the median onset time being 0 days (interquartile [IQR] range, -6.0–1.0)

Table 1. Summary of reported cases of herpes zoster-associated arthritis

	Age	Sex	Joint affected	Onset days ¹	Duration of arthritis	Herpes zoster dermatome	Blood	Synovial fluid	Synovial fluid	Others
							WBC (x10 ⁹ /L) ESR (mm/h) CRP (mg/L)	WBC (/mm ³), differential count	VZV	
Quin, ^a 1973	76	M	R shoulder			C5				
	91	F	R MCPJs, R 3rd PIPJ		7 months	T1				
Cunningham et al., ^b 1979	77	F	Both knees	+2	17 days	L T12 and L1	Normal WBC, ESR 101	L 9000, lymphocytes 5%, 90% PMN	VZV antigen in the cytoplasm of macrophages	
Devereaux et al., ^c 1983	18	F	R hip	-4	11 days	L2	Normal WBC, ESR	Not attempted	Not attempted	
Leventhal et al., ^d 1989	61	M	All MCPJs and PIPJs, wrists, elbows, shoulders, followed by L hip	-8	2 weeks	L2		Dry tap (L hip)	Dry tap (L hip)	15-year rheumatoid arthritis
Amoura et al., ^e 1993	67	M	R knee			L5	WBC 4.4, ESR 5	17600, lymphocytes 44%, 56% PMN	Positive immunofluorescence staining	
Aarons et al., ^f 1993	54	F	R knee	0	7 days	L1/2	WBC 6.3, Platelet 24	Moderate numbers of WBC	Electron microscopy and culture of synovial fluid for VZV negative	Non-Hodgkin's lymphoma
Senlis et al., ^g 2017	63	F	L hip			L3	CRP 22	3400	DNA (PCR) synovial fluid positive for VZV	11-year rheumatoid arthritis
Lee, et al., ^h 2021	79	M	L MCPJs, PIPJs	0	8 months	L C6	WBC 4.6, ESR 75, CRP 6			

CRP: C-reactive protein; DNA (PCR): DNA polymerase chain reaction; ESR: erythrocyte sedimentation rate; L: left; MCPJ: metatarsophalangeal joint; MTPJ: metatarsophalangeal joint; PIPJ: proximal interphalangeal joint; PMN: polymorphonuclear neutrophil; R: right; VZV: varicella-zoster virus; WBC: white blood cell
^a Quin CE. Paralysis and arthropathy in herpes zoster. *Rheumatol Rehabil* 1973;12:74-6.
^b Cunningham AL, Fraser JR, Clarriss BJ, et al. A study of synovial fluid and cytology in arthritis associated with herpes zoster. *Aust N Z J Med* 1979;9:440-3.
^c Devereaux MD, Hazelton RA. Acute monarthritis in association with herpes zoster. *Arthritis Rheum* 1983;26:236-7.
^d Leventhal LJ, Bomalaski JS. Articular presentation of herpes zoster eruption. *Arthritis Rheum* 1989;32:506-7.
^e Amoura I, Fillet AM, Huraux JM, et al. Isolation of varicella-zoster virus from the synovial fluid of a patient with herpes zoster arthritis. *Arthritis Rheum* 1993;36:1329.
^f Aarons EJ, Beeching NJ. Aseptic arthritis associated with herpes zoster. *J Infect* 1993;26:87-8.
^g Senlis M, Ottaviani S, Gardette A, et al. Varicella-Zoster virus hip arthritis in a rheumatoid arthritis patient. *Joint Bone Spine* 2017;84:241-2.
^h Lee WX, Yan GZ, Tay SH. Herpes zoster-associated aseptic arthritis in adult patients: A case report. *Ann Acad Med Singap* 2021;50:92-5.

(Table 1). In terms of symptom duration, it was interesting to note that although most cases of zoster-associated arthritis resolved in a median of 2.2 weeks (IQR 1.4–35.0), 1 patient experienced persistent arthritis that lasted for 7 months.⁴ Our patient was similar in that he experienced joint swelling as well as skin and subcutaneous oedema of his left hand that took 8 months to resolve. It is worth noting that despite prolonged arthritis, all cases that have been reported thus far resolved eventually. Other viruses like parvovirus B19 can also induce chronic inflammatory arthritis that lasts for months, but mainly affecting women rather than men.⁵

In the immunopathogenesis of herpes zoster-associated arthritis, it has been noted that there is a predominance of neutrophils in the synovial fluid rather than lymphocytes. This is in contrast to primary VZV-associated arthritis and other virus-associated arthritis, which is associated with a predominance of lymphocytes. This may have implications when speculating on the role of neuro-immunological communication in the occurrence of herpes zoster-associated arthritis. It has been described that nociceptors suppress the recruitment and surveillance of neutrophils.⁶ Pain in herpes zoster and post-herpetic neuralgia is due to inflammation-induced sensitisation of nociceptor endings and later, deafferentation due to destruction of the sensory neurons in the affected dorsal root ganglion.⁷ Hence, the involvement of the dorsal root ganglion and subsequent destruction of nociceptors in herpes zoster may explain the neutrophilic predominance in herpes zoster-associated arthritis and not arthritis associated with primary VZV infection.

The joints are innervated by peripheral sensory afferents originating from spinal sensory neurons, whose cell bodies originate within the dorsal root ganglia.⁶ This suggests that VZV may spread along the nerves to the joints, similar to how it spreads to the skin in disseminated herpes zoster. In some cases where pain rather than swelling was the predominant presentation, joint pain may also be contributed largely by nerve root involvement. However, some of the patients had widespread joint involvement beyond the dermatome affected by herpes zoster reactivation. This suggests a different pathophysiology, perhaps a generalised inflammatory response to viral immune activation.

Similar to the syndrome of aseptic meningitis, we elected to adopt the terminology of “aseptic” to describe zoster-associated arthritis since there is synovial fluid pleocytosis in the absence of a positive Gram stain and

culture.⁸ Of the 9 cases, 5 had synovial fluid assessment, and 3 were positive for VZV, although all 3 were tested using different methods. Polymerase chain reaction (PCR) test is the most sensitive method for the detection of VZV DNA in clinical samples (e.g. fluid from vesicles, cerebrospinal fluid) and together with its rapid turnaround time, has largely superseded traditional methods of obtaining a microbiological diagnosis such as viral culture and immunofluorescent techniques.⁹

Antiviral therapy is recommended for use in herpes zoster, ideally within the first 72 hours of infection. Immune complications of herpes zoster requiring immunosuppression have also been reported. The use of adjuvant glucocorticoids in complicated herpes zoster infections (e.g. herpes zoster ophthalmicus and Ramsay Hunt Syndrome) as well as immunologic complications of VZV (e.g. transverse myelitis) has been reported to be beneficial.¹⁰ Our patient received a short course of oral prednisolone and hydroxychloroquine with good response. Hence, immunosuppression can be considered for use in treating zoster-associated arthritis once septic arthritis has been appropriately excluded. It is important to consider other differential diagnoses such as septic arthritis, crystal arthritis and flare of existing inflammatory arthritis, as zoster-associated arthritis is relatively rare. Arthrocentesis can also be helpful in distinguishing between these differential diagnoses.¹¹

In summary, in patients with herpes zoster-associated arthritis, we suggest PCR test on the synovial fluid to look for VZV DNA, treatment with antiviral therapy such as acyclovir, and to consider the use of glucocorticoids if not otherwise contraindicated. Most cases are self-limiting but chronic inflammatory arthritis requiring prolonged immunosuppression may be required.

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