Bullous Herpes Zoster in a Lupus Nephritis Patient Treated with Rituximab: A Case Report

Amanda Christine F. Esquivel, MD,[1] Juan Raphael M. Gonzales, MD,[2]
Geraldine T. Zamora, MD[2] and Giselle Marie S. Tioleco-Ver, MD[1]

[1]*Department of Dermatology, Philippine General Hospital, University of the Philippines Manila*
[2]*Division of Rheumatology, Department of Medicine, Philippine General Hospital, University of the Philippines Manila*

ABSTRACT

Herpes zoster is a clinical syndrome associated with reactivation of varicella zoster virus (VZV), often occurring years after VZV infection, and characterized typically by painful grouped vesicles in a dermatomal distribution. Bullous herpes zoster, an atypical presentation of herpes zoster, is a relatively rare phenomenon; to the authors' knowledge, there have only been eight reports in worldwide literature. We present a case of a 59-year-old female with lupus nephritis who presented with multiple grouped vesicles evolving into large tender bullae filled with serosanguinous fluid on the lateral aspect of the right leg, and dorsal and medial aspects of the right foot, four days after the first dose of 1g of rituximab therapy. The diagnosis of bullous herpes zoster along L4-L5 dermatomes was made based on the clinical presentation and the presence of multinucleated giant cells on Tzanck smear. The giant bullae were drained and dressed, and the patient was treated with valacyclovir at the renally adjusted dose of 1g once a day for seven days and pregabalin 150 mg once daily. After seven days of antiviral treatment, there were no new bullae or vesicles, and the pain improved. Recognizing this atypical presentation of a common disease, especially in patients with an immunocompromised state, highlights the importance of prompt recognition and treatment.

Keywords: herpes zoster, bullous, lupus nephritis, rituximab, differential diagnosis, case report

Oral presentation – Korea Derma 2021, November 5-7, 2021, Seoul, Korea.

Poster presentations – Regional Congress of Dermatology 2022, October 26-28, 2022, Manila, Philippines; European Academy of Dermatology and Venereology Spring Symposium 2022, May 13, 2022, Ljubljana, Slovenia.

eISSN 2094-9278 (Online)
Published: September 30, 2024
https://doi.org/10.47895/amp.v58i17.7495

Corresponding author: Amanda Christine F. Esquivel, MD
Department of Dermatology
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: afesquivel@alum.up.edu.ph
ORCiD: https://orcid.org/0000-0003-1783-0097

INTRODUCTION

Herpes Zoster is a clinical syndrome associated with reactivation of varicella zoster virus (VZV), characterized typically by painful grouped vesicles in a dermatomal distribution. Bullous Herpes Zoster, an atypical presentation of herpes zoster, is a relatively rare phenomenon, with only eight reports in the literature. Occurrence of bullous Herpes Zoster in autoimmune diseases such as systemic lupus erythematosus (SLE) is even rarer.

CASE REPORT

A 59-year-old female diagnosed with systemic lupus erythematosus (SLE) underwent her first rituximab infusion (375 mg/m^2) for refractory lupus nephritis. During treatment, she was also on glucocorticoids (30 mg/day; 0.5 mg/kg/day) and hydroxychloroquine (200 mg/day). Four days after the rituximab infusion, she developed multiple vesicles and bullae on the right leg, eventually spreading to involve the dorsal and ventral aspects of the right foot. This was associated with severe pain which resulted in difficulty ambulating. The lesions were initially managed as a bacterial infection with a course of cloxacillin for one week. However, progression was noted, evidenced by enlargement of the existing bullae and development of new vesicles and bullae (Figures 1 and 2). On

follow-up, a course of clindamycin was given, still with little improvement. The patient was then referred to Dermatology.

The patient had varicella as a child, and a history of zoster in 2014. Family medical history, and personal and social history were unremarkable. She was awake, alert, and wheelchair bound. She had more than five well-defined tense bullae, the largest measuring eight by ten centimeters, and vesicles, some containing serosanguinous and hemorrhagic fluid, on an erythematous base, in a dermatomal L4-L5 distribution. The right leg was tender on palpation, with no associated warmth. There were no lesions anywhere else.

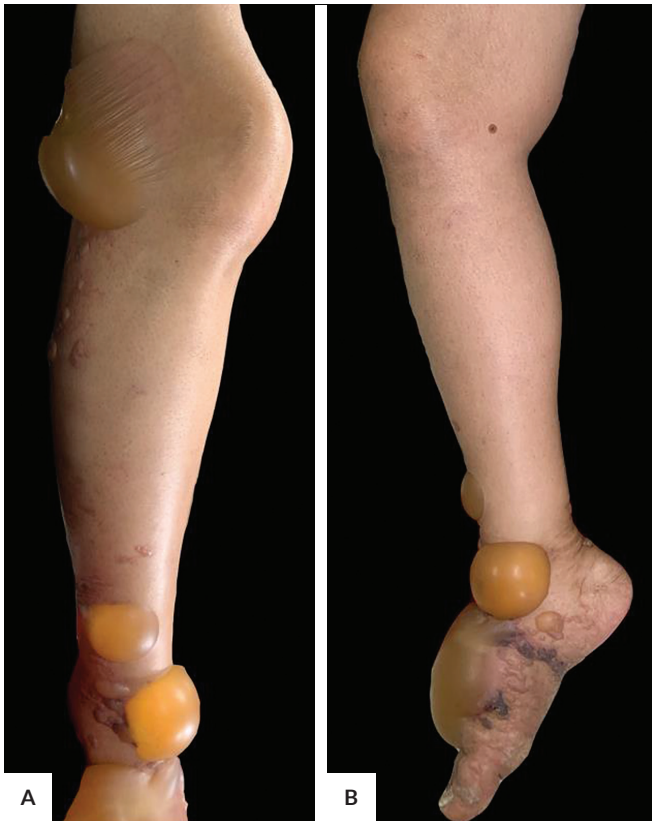

Figure 1. Clinical appearance of bullous herpes zoster showing lateral **(A)** and medial **(B)** aspects of the right leg.

Tzanck smear was done, revealing multinucleated giant cells (Figure 3). Biopsy was offered, but patient refused. Based on the clinical presentation of vesicles evolving into bullae in a dermatomal distribution, associated with pruritus and pain, and the results of the Tzanck smear, a diagnosis of herpes zoster in the right L4-L5 dermatome was made. She was given oral valacyclovir at the renally adjusted dose of 1 gram once daily, and oral pregabalin 150 milligrams once daily, for seven days. At the follow-up appointment seven days later, there were no new vesicles or bullae, and the patient's pain score had decreased.

Though the bullous herpes zoster resolved after the valacyclovir, two months later, she was admitted for complications from her SLE, and passed away.

DISCUSSION

Herpes Zoster (HZ) is a clinical syndrome associated with reactivation of VZV, often occurring years after VZV infection. It affects approximately 15% of immunocompetent and up to 50% of immunocompromised patients. The main risk factor is advanced age, however, immunosuppressed patients, such as those with malignancy, autoimmune diseases, human immunodeficiency virus infection, and solid organ and hematopoietic stem cell transplantations are also important risk factors.[1] It is characterized by painful vesicles

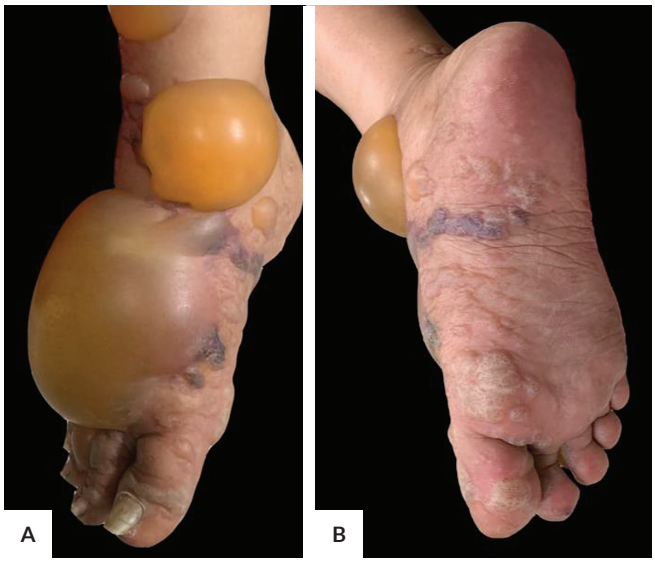

Figure 2. Clinical appearance of bullous herpes zoster showing dorsal **(A)** and ventral **(B)** aspects of the right foot.

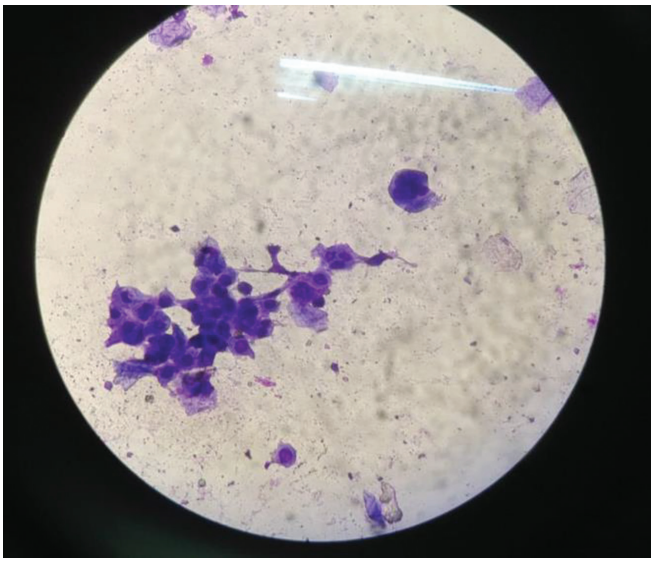

Figure 3. Tzanck smear showing multinucleated giant cells.

in a dermatomal distribution, and the skin eruption may be preceded by a prodrome of pain or paresthesia a few days prior to onset. The diagnosis is often made clinically, but atypical cases may require testing for VZV with polymerase chain reaction (PCR), viral culture, or Tzanck smear.

Bullous herpes zoster is a rare, atypical presentation of HZ. To the best of our knowledge, there have only been eight cases reported in literature. Five of these happened in immunocompromised individuals; the other three happened in otherwise healthy patients. Six were adults, with a mean age of 63; two were children.[1-8]

Bullae are vesicles greater than 1 cm in diameter, and may contain serum, blood, or lymph fluid. The differential diagnosis for bullae is broad, and includes infectious, autoimmune diseases, inflammatory conditions, drug reactions, genetic disorders, and physical injury.[9-11] In the general context of lupus and immunosuppression, the most common causes of bulla are likely to be infectious and autoimmune diseases.

Table 1 presents differentials for bullae, with particular note of distribution, location, and characteristics of the bullae, to help a clinician arrive at a correct diagnosis.[9-11] For this particular case, our bullae were acute, localized, and importantly, in a dermatomal distribution, and Tzanck was positive, making herpes zoster the primary consideration.

Certain physical maneuvers may aid the clinician in diagnosis. The Nikolsky sign, where lateral pressure to the skin results in bulla extension, and the Asboe-Hansen sign, where perpendicular pressure results in bulla extension, is positive in cases of flaccid bullae, like Steven Johnson Syndrome, Toxic Epidermal Necrolysis, and pemphigus vulgaris, and negative in cases of tense bullae, like bullous pemphigoid and linear IgA bullous dermatosis.[9,10]

Herpes zoster is reported as the most prevalent viral infection in patients with SLE. The incidence of zoster in patients with SLE varies from 5.1% to 46.6% in countries in the Asia-Pacific.[12] There are only a number of studies that look into the predictors of developing herpes zoster among SLE patients. The study by Chen supported the role of lymphopenia and high cumulative glucocorticoid doses (defined as greater than or equal to 30 mg of prednisone or its equivalent per day) in the occurrence of HZ.[13] Similar to our patient, their cohort who developed HZ also had a significantly higher proportion of active lupus and renal involvement.

Table 1. Differentials for bullae[9-11]

Distribution	Location / Characteristics	Differential	Clinical and Diagnostic Characteristics
Localized	Acral (Hands or Feet)	Dyshidrotic dermatitis	Intensely pruritic deep-seated vesicles or bullae notable on lateral aspect of digits
		Dermatophyte infections	Usually present on soles or between the toes May have other areas of the body with dermatophyte infection Potassium hydroxide (KOH) smear may help in distinguishing dermatophyte infections
		Friction blisters	Most frequently seen on heels and soles of feet due to friction from shoes while walking or running
		Erythema multiforme	Classic "target" lesions Commonly associated with herpetic or Mycoplasma pneumonia infection
	Dependent	Edema blisters	Location as clue – pressure and dependent sites
		Bullous LCV	Hemorrhagic vesicles or bulla with purpura Location as clue – pressure and dependent sites
	Dermatomal	Herpes zoster	Grouped eruption of painful vesicles in dermatomal distribution Tzanck smear, viral culture, or PCR can be useful to rule out herpes infections
	Grouped	Herpes simplex	Grouped painful vesicles Tzanck smear, viral culture, or PCR can be useful to rule out herpes infections
		Dermatitis herpetiformis	Erythematous vesicle symmetrically distributed on elbows, knees, buttocks, shoulders Skin biopsy reveals subepidermal split with collections of neutrophils in dermal papilla Immunofluorescence studies reveals (+) granular IgA at papillary tips
	Linear	Contact dermatitis	Intensely pruritic vesicles and bullae can occur in severe cases of contact dermatitis Usually with exposure to known irritant or contactant (i.e., poison ivy) Patch testing can be done
		Phytophotodermatitis	Vesiculation in linear distribution may occur after topical application of certain plant-derived substances (e.g., oil of bergamot, celery, lemon, limes) followed by sun exposure
	Photo-distributed	Polymorphous light eruption	Pruritic erythematous papules or plaques, can also have vesicles or bullae Photo patch testing
		Sunburn	Severe sunburns can result in blistering; check for history of sun exposure and inadequate photoprotection
		Phototoxic reaction	Usually occur after ingestion of a photosensitizing drug

Table 1. Differentials for bullae[9-11] *(continued)*

Distribution	Location / Characteristics	Differential	Clinical and Diagnostic Characteristics
Generalized	Flaccid	SJS-TEN	Appears with epidermal sloughing of skin with involvement of mucous membranes; check for history of drug intake and prodromal period with flu-like symptoms Skin biopsy
		SSSS	Most common in infants and young children Associated with skin tenderness and characteristic red-orange wrinkled skin that subsequently desquamates Skin biopsy Bacterial culture
		Pemphigus vulgaris	Flaccid bullae that evolve into erosions With mucosal involvement Skin biopsy reveals suprabasal split Immunofluorescence studies reveals IgG and C3 in intercellular pattern ELISA reveals (+) Dsg 3 and Dsg1
		Pemphigus foliaceus	Flaccid bullae that evolve into crusted erosions Skin biopsy reveals subcorneal acantholysis Immunofluorescence studies reveal IgG and C3 intercellular pattern more superficially ELISA reveals (+) Dsg1
	Tense	Bullous pemphigoid	Common in older adults Urticarial plaques found on trunk and extremities Can be drug induced, but no recorded reports of rituximab causing Skin biopsy reveals subepidermal split with prominent eosinophils Immunofluorescence studies reveals (+) IgG and C3 at basement membrane zone ELISA reveals (+) BP180 and (+) BP230
		Linear IgA bullous dermatosis	Multiple erythematous annular or grouped papules, vesicles, and bulla Skin biopsy reveals subepidermal split with neutrophils Immunofluorescence studies reveals (+) IgA at dermo-epidermal junction ELISA reveals (+) IgA1
		Bullous systemic lupus erythematosus	Widespread tense subepidermal bulla in patients with SLE Skin biopsy reveals subepidermal split with neutrophils Immunofluorescence reveals linear or granular IgG, IgM, and IgA at BMZ ELISA reveals antibodies against Type VII collagen
		Epidermolysis bullosa acquisita	Tense bulla, scarring and milia formation are commonly associated features
		Dermatitis herpetiformis	Discussed above

Rituximab is a chimeric anti-CD20 monoclonal antibody that depletes B cells; it is used off-label for several autoimmune diseases, including lupus nephritis. Like other immunosuppressive agents, rituximab causes an increased risk for infections. Proposed mechanisms for the increased risk of infection with rituximab include prolonged B-cell depletion, B-cell–T-cell crosstalk, pan hypogammaglobulinemia, and late-onset neutropenia.[14]

Our patient was on a high glucocorticoid dose and had just been given rituximab, the role of which in the occurrence of HZ in SLE has not yet been studied. One study suggested that immunosuppressive therapy and severe manifestations of lupus may be risk factors for the development of zoster, although not necessarily at the time of disease flare or immunosuppressive therapy. The concomitant administration of other immunosuppressive agents such as mycophenolate mofetil and cyclophosphamide was not significantly different between groups.[13]

The mean time period from rituximab administration to onset of viral symptoms was found to be five months.[15] Our patient developed the symptoms a scant four days after one rituximab dose, therefore it is likely that the zoster was associated more with the general immunosuppression and underlying autoimmune condition. However, the contribution of rituximab to zoster development cannot be ruled out. Complete B cell depletion can occur within 72 hours of rituximab infusion, and this rapid depletion could have implications for the immune system and its ability to combat infections. Rituximab is also known to exert an influence on other immune cells, causing substantial T-cell depletion, which could help explain the higher risk of viral infections.[16]

CONCLUSION

Herpes zoster is easily diagnosed when it presents typically, however in immunocompromised patients like

our patient with an autoimmune condition, on chronic immunosuppressive therapy, and on monoclonal antibody therapy like rituximab, it can be a challenge when it presents atypically. Early recognition of bullous herpes zoster leads to earlier treatment and better outcomes for the patient. The differential diagnosis for bullae, and ways to differentiate them, have been discussed.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

None.

REFERENCES

1. Jethwa T, Bertasi RAO, Kieneker L, Pattanaik S, Pujalte G. Bullous disseminated herpes zoster: an atypical presentation. Cureus. 2020 Jul;12(7):e9293. doi: 10.7759/cureus.9293. PMID: 32832290; PMCID: PMC7437097.
2. Veraldi S, Carrera C, Gianotti R, Caputo R. Bullous herpes zoster. Acta Derm Venereol. 2000 Jan-Feb;80(1):55. doi: 10.1080/000155500750012577. PMID: 10721839.
3. Haimi M, Ben-Arush MW, Kassis I, Postovsky S, Kra-Oz Z, Elhasid R. Bullous herpes zoster in a child with leukemia: case report and review of the literature. J Pediatr Hematol Oncol. 2004 Sep;26(9):587-90. doi: 10.1097/01.mph.0000139451.37585.01. PMID: 15342986.
4. Allu S, Ehrlich A, Lipman H. Herpes-Zoster presenting as giant bullae. J Am Med Dir Assoc. 2008 Mar;9B14.
5. Tsai MJ, Kuo HT, Chen HC. The clinical picture: multiple huge bullae after renal transplant. Cleve Clin J Med. 2009 Apr;76(4):221. doi: 10.3949/ccjm.76a.08066. PMID: 19339637.
6. Wong KJ, Osowicki J, Seaby E, Curtis N, Gwee A. Bullous herpes zoster. J Pediatr. 2014 Mar;164(3):667. doi: 10.1016/j.jpeds.2013.10.026. PMID: 24252791.
7. Chang KM, Galen BT. Shingles of the wrist with a bullous evolution. Mayo Clin Proc. 2019 Aug;94(8):1404-5. doi: 10.1016/j.mayocp.2019.03.024. PMID: 31378226.
8. Kakitha R, Shanmugam S. Bullous pemphigoid-like presentation of disseminated herpes zoster: a case report. Indian J Dermatol. 2020 May-Jun;65(3):234-5. doi: 10.4103/ijd.IJD_337_18. PMID: 32565574; PMCID: PMC7292458.
9. Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, et al. Fitzpatrick's Dermatology. 9th ed. McGraw Hill Education; 2019.
10. Generoso AJ, Goldman JA, Wolff AH. A 62-year-old man with new-onset bullae. Allergy Asthma Proc. 2021 Mar;42(2)175-9. doi: 10.2500/aap.2021.42.200055. PMID: 33685564; PMCID: PMC8133022.
11. Hull C, Zone J. Approach to the patient with cutaneous blisters. UpToDate [Internet]. 2023 [cited 2023 Oct]. Available from: https://www.uptodate.com/contents/approach-to-the-patient-with-cutaneous-blisters.
12. Sayeeda A, Al Arfaj H, Khalil N, Al Arfaj AS. Herpes Zoster infections in SLE in a university hospital in Saudi Arabia: risk factors and outcomes. Autoimmune Dis. 2010 Sep:2011:174891. doi: 10.4061/2010/174891. PMID: 21152215; PMCID: PMC2989732.
13. Chen D, Li H, Xie J, Zhan Z, Liang L, Yang X. Herpes zoster in patients with systemic lupus erythematosus: clinical features, complications and risk factors. Exp Ther Med. 2017 Dec;14(6):6222–8. doi: 10.3892/etm.2017.5297. PMID: 29285180; PMCID: PMC5740583.
14. Nixon A, Ogden L, Woywodt A, Dhaygude A. Infectious complications of rituximab therapy in renal disease. Clin Kidney J. 2017 Aug;10(4):455-60. doi: 10.1093/ckj/sfx038. PMID: 28852481; PMCID: PMC5570071.
15. Aksoy S, Harputluoglu H, Kilickap S, Dede DS, Dizdar O, Altundag K, et al. Rituximab-related viral infections in lymphoma patients. Leuk Lymphoma. 2007 Jul;48(7):1307-12. doi: 10.1080/10428190701411441. PMID: 17613758.
16. Furlan A, Forner G, Cipriani L, Vian E, Rigoli R, Gherlinzoni F, et al. COVID-19 in B cell-depleted patients after rituximab: a diagnostic and therapeutic challenge. Front Immunol. 2021 Nov;12:763412. doi: 10.3389/fimmu.2021.763412. PMID: 34804051; PMCID: PMC8595333.