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A case of Disseminated Herpes Zoster in a patient with Multiple Sclerosis on Glatiramer acetate

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ABSTRACT

We present a case of Disseminated Herpes Zoster in a 73 year old man who had been taking Glatiramer acetate for 8 years as treatment for Multiple Sclerosis. He presented to the emergency room with complaints of a painful skin lesions on his buttocks and was found to have a generalized papulo-pustular rash. He was treated with IV Acyclovir and concurrent Piperacillin-Tazobactam plus Vancomycin for disseminated herpes zoster with a necrotic bacterial superinfection on his buttocks.

Multiple Sclerosis is a chronic immune mediated disease of the CNS and is treated with immunomodulators and immunosuppressive medications. With more than 2 decades of Glatiramer acetate use, it is regarded as the safest immunomodulator without any associated reported infections. This is the first case of Disseminated Herpes Zoster associated with Glatiramer.

Introduction

Varicella-zoster virus is a human alpha herpes virus known to cause Chicken pox (Varicella) on primary infection and Shingles (Zoster) upon reactivation. Varicella most commonly affects children, is typically a self-limited pruritic, vesicular eruption. Herpes Zoster characteristically presents with a prodrome of burning pain followed by outbreak of vesicles distributed unilaterally within a single or adjacent dermatomes.

Varicella Zoster is caused by reactivation of VZV. Older adults and people with compromised or suppressed immune systems are more likely to be hospitalized. About 30 % of all people hospitalized with herpes zoster have compromised or suppressed immune systems. One study estimated that 96 deaths occur each year in which herpes zoster was the underlying cause (0.28 to 0.69 per 1 million population) [1].

It is hypothesized that the physiologic decline in varicella-zoster virus specific cell-mediated immunity among elderly and immunocompromised individuals helps trigger reactivation of the virus within the dorsal root ganglion [2]. Secondary complications of VZV infection include postherpetic neuralgia, bacterial superinfection progressing to cellulitis and visceral infection lead to increased morbidity and mortality. Disseminated cutaneous herpes zoster occurs almost exclusively in immunosuppressed patients [3].

This case is to make physicians aware that severe disseminated HZ infection can present atypically and that it can occur in individuals on Glatiramer acetate, a immunomodulator for Multiple Sclerosis. Clinicians should recognize atypical presentations of disseminated herpes zoster in order to initiate rapid treatment to decrease potential mortality and morbidity.

Case presentation

Patient is a 73 year old man with a past medical history of Multiple Sclerosis, Neurogenic Bladder andhypertension presented to the emergency department with a diffuse rash, fever and pain in his right buttocks. He reported that the skin lesions started on the buttocks as a “pimple” that was tender and eventually got worst with diffuse redness and drainage. Over the next several days he noted a vesicular rash all over his body. He also had subjective fevers and chills. He reported having had Chickenpox as a child.

He went to an urgent care facility and was told that he has cellulitis on his buttocks and was prescribed Clindamycin, but had no improvement in his buttock pain or lesions.

The patient had been on Glatiramer for 8 years for his MS. He was being managed by a Neurology specialist as an outpatient. He denied recent or prolonged use of steroids. He was never on other any other biologic medication.

Vital signs on initial presentation: Tmax: 101.5; Pulse Rate: 60, BP: 158/64 and RR: 16. Physical examination was significant for a diffuse papulo– vesicular rash with some pustules and crusting. The skin on the posterior-medial right thigh and right buttocks was erythematous with maculo-pustular lesions and tenderness on

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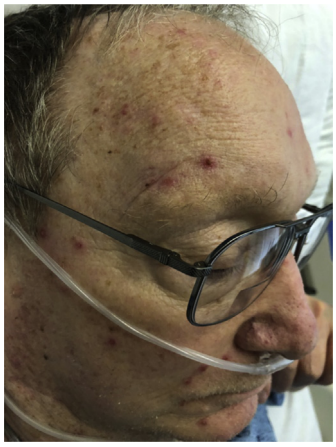
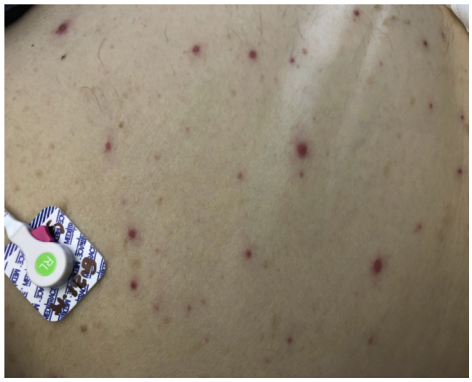
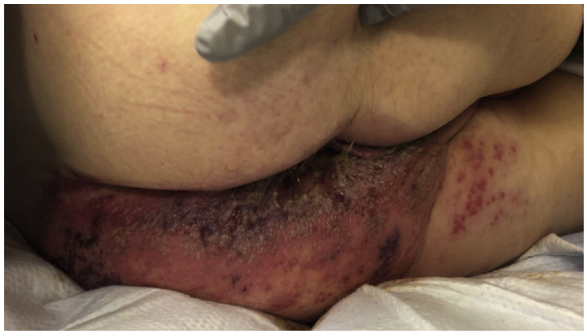
palpation. No oral lesions were noted. No rash was found on the hands or feet.





The pictures above are of the face and truck of the patient and show a mix of crusted and newly erupting erythematous rash. The picture below is the right medial thigh and buttocks with erythematous, necrotic tissue and a cluster of maculopapular crusted rash on the medial posterior are of the right thigh.



Laboratory evaluation revealed a white count of 7.26×10^3/microL. He had negative blood cultures. A CT scan of the pelvis did not show any perirectal or ischiorectal abscess. A presumptive diagnosis of disseminated herpes zoster with superimposed cellulitis was made and he was begun on IV Acyclovir, Vancomycin and Piperacillin-Tazobactam. A VZV PCR from one of the pustular lesions was positive. Serum HIV RNA and RPR were negative.

He received a total of 2 weeks of antibacterials and IV Acyclovir with resolution of his lesions.

Discussion

Disseminated herpes zoster when more than 2 contiguous dermatomes are affected, more than 20 vesicles are observed outside the initial dermatome, or involvement is systemic. DHZ is rare and most frequently occurs in immunocompromised host [4]. Multi-dermatomal zoster involves several adjacent dermatomes, while disseminated cutaneous herpes zoster (DCHZ) is defined as 20 or more vesicular lesions outside the primary and adjacent dermatomes. Generally, Disseminated Herpes Zoster remains limited to the skin, but extracutaneous or visceral disease can occur, with resultant pneumonia, encephalitis, meningitis, motor neuropathies and/or abdominal symptoms.

Multiple Sclerosis (MS) is an immune-mediated illness. It is a chronic inflammatory disease of the central nervous system responsible for substantial morbidity and mortality. Historically, T cells have been considered the main drivers in the pathogenesis of MS. This has been supported by observations including the higher number of T cells than B cells in MS lesions. However, it is now understood that B cells play a pivotal role throughout the course of MS [5].

Because of the importance of humoral and cell mediated immunity in the pathophysiology of MS, nearly all therapies involve modulation of the immune system with immunosuppressive agents. Immunomodulators include Interferon and Glatiramer acetate. Immunosuppressive medications that have been approved by the FDA to treat MS include monoclonal antibodies (Natalizumab, Alemtizimab and Ocreluzumab), chemotherapeutic agent (Mitoxantrone) and Small molecule oral agents (Fingolimod, Dimethyl fumarate and Teriflunomide).

Almost all of these immunosuppressive medications have been associated with severe reactivation of latent infections. Reactivation of TB has been associated with Alemtuzumab, due to its production of prolonged profound lymphocytopenia and effects on both humoral and cell mediated immunity [6]. Teriflunomide which is a dihydroorotate dehydrogenase inhibitor impairs lymphocyte proliferation which can increase risk for TB reactivation. Ocrelizumab and Alemtuzumab have the highest risk of Hepatitis B reactivation. Progressive multifocal leukoencephalopathy is a particular concern for Natalizumab [7]. Alemtuzumab, Natalizumab and Fingolimod give a higher risk of herpes virus reactivation [6].

Based on our review of literature, there have been no report of reactivation of latent infection or opportunistic infections reported with the use of Glatiramer Acetate.To our knowledge, this is the first case of Disseminated Herpes Zoster associated with Glatiramer Acetate. Since its release in 1996, it has not been associated with an increased risk of any specific infections.

Glatiramer acetate is a mixture of random synthetic polypeptides composed of 4 amino acids (glutamate, lysine, alanine and tyrosine). It was initially developed at the Weizmann Institute in Israel as a chemical and immunologic analog of Myelin Basic Protein (MPB) to indice experimental autoimmune encephalomyelitis. Surprisingly, it was not encephalotigenicand did not induce encephalitis in animal models. Theoretically, it is thought to interfere with immune surveillance of infectious agents. It's mechanism of action is its ability to skew the balance from proinflammatory to anti-inflammatory response [8]. During treatment there is a shift from T helper type 1 (Th1) to Th2 cells which is passes freely into the blood brain barrier. This shift leads to the increased production of anti-inflammatory cytokines: IL-4, IL-6, IL-10. Conversely, there is reduction of pro-inflammatory cytokines such as IL-12 [9]. Glatiramer acetate additionally promotes regulatory $CD8^+$ cells and, via the conversion of conventional $CD4^+CD25^+$ T cells to regulatory $CD4^+CD25^-$ T cells [10]. Glatiramer acetate also alters the profile of circulating B cells in patients with MS. It has been shown to reduce the total frequency of B cells (as a percentage of all lymphocytes), plasmablasts, and memory cells [11]

Based on the clinical experience over more than 20 years, Glatiramer acetate is considered to be one of the safest MS

therapies [7]. Its principal side effects include local injections reactions, allergic reactions, local lipoatrophy and regional lymphadenopathy [11].

Disseminated HZ has potential life threatening complications. As such, an understanding of prevention and treatment modalities for VZV infection among immunocompromised patients is critical. Vaccination remains a potential strategy to reduce the incidence of Herpes Zoster in this patient population. Questions about chemoprophylaxis for patient who are taking Glatiramer acetate can't be answered at this time due to the rarity of case. Based on our case, closer monitoring of patients on Glatiramer and the recognition of potential opportunistic infections may be warranted.

Source of funding

None.

Consent

'Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request".

Author contribution

Dr. Carol Halasan:researcher and writer (fellow)
Dr.Carmen Isache: edited
Dr.Michael Sands: researcher and writer and edited as well.

Declaration of Competing Interest

None.

References

[1] Shingles surveillance. https://www.cdc.gov/shingles/surveillance.html.
[2] Weinberg A, Levin MJ. VZV T cell-mediated immunity. In: Abendroth A, Arvin A, Moffat J, editors. Varicella-zoster virus. Current topics in microbiology and immunology, vol 342. Berlin, Heidelberg: Springer; 2010.
[3] McCrary Monica L, Severson Jessica, Stephen K. Tyring, varicella zoster virus. J Am Acad Dermatol 1999;41(1), doi:http://dx.doi.org/10.1016/S0190-9622(99)70398-1 Pages 1-16,ISSN 0190-9622.
[4] Stratman E. Visceral zoster as the presenting feature of disseminated herpes zoster. J Am Acad Dermatol 2002;46:771–4 doi:S0190962202710104 [pii].
[5] Winkelmann A, Loebermann M, Reisinger EC, Zettl UK. MS treatment and infection. Clin Exp Immunol 2014;175:425–38, doi:http://dx.doi.org/10.1111/cei.12226.
[6] Epstein DJ, Dunn J, Deresinski S. Infectious complications of multiple sclerosis therapies: implications for screening, prophylaxis, and management. Open Forum Infect Dis 2018;5(8), doi:http://dx.doi.org/10.1093/ofid/ofy174 ofy174. Published 2018 Jul 16.
[7] Grebenciucova E, Pruitt A. Curr Neurol Neurosci Rep 2017;17:88, doi:http://dx.doi.org/10.1007/s11910-017-0800-8.
[8] Duda PW, Schmied MC, Cook SL, Krieger JI, Hafler DA. Glatiramer acetate (Copaxone) induces degenerate, Th2-polarized immune responses in patients with multiple sclerosis. J Clin Invest 2000;105(7):967–76, doi:http://dx.doi.org/10.1172/JCI8970.
[9] Ziemssen Tjalf, Schrempf Wiebke, Acetate Glatiramer. Mechanisms of action in multiple sclerosis, International review of neurobiology, Volume 79. Academic Press; 2007, doi:http://dx.doi.org/10.1016/S0074-7742(07)79024-4 Pages 537-570, ISSN 0074-7742, ISBN 9780123737366.
[10] Kuerten S, Jackson LJ, Kaye J, Vollmer TL. Impact of glatiramer acetate on B cell-mediated pathogenesis of multiple sclerosis. CNS Drugs 2018;32(11):1039–51, doi:http://dx.doi.org/10.1007/s40263-018-0567-8.
[11] Rommer PS, Milo R, Han MH, et al. Immunological aspects of approved MS therapeutics. Front Immunol 2019;10:1564, doi:http://dx.doi.org/10.3389/fimmu.2019.01564 Published 2019 Jul 11.