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CASE REPORT

Daratumumab-associated varicella-zoster virus meningoencephalitis in relapsed refractory multiple myeloma

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ABSTRACT

Daratumumab is a widely-used monoclonal anti-CD38 antibody both in newly-diagnosed and relapsed refractory multiple myeloma. CD38 is expressed on the surface of NK, regulatory B, and T cells. Therefore, patients receiving the drug are prone to decreased immunity, especially against herpes virus infections. Varicella-zoster virus is one of the herpesviruses, and reinfection typically occurs in immunocompromised individuals, including multiple myeloma patients, by reactivation of endogenous latent infection within the sensory ganglia. This type of infection (herpes zoster) usually presents in a dermatomal skin area. Here, we report a patient who developed varicella-zoster virus meningoencephalitis under daratumumab treatment.

Keywords: daratumumab, herpes zoster infection, multiple myeloma, immunoglobulin, reactivation.

INTRODUCTION

Daratumumab, a human anti-CD38 antibody of the immunoglobulin (Ig)G1 isotype, is widely used in multiple myeloma (MM) and other plasma cell disorders for its antibody-dependent cellular cytotoxicity, as well as its Fc-dependent complement-dependent cytotoxicity and antibody-dependent cellular phagocytosis [1]. MM patients have a 14.8-fold risk of herpes zoster infections, which are the leading cause of infections in these patients, and daratumumab use may facilitate the development of herpes infections by disrupting immune responses via the depletion of natural killer (NK) cells and other CD38-expressing immune cells [1,2]. Here, we report an MM-diagnosed patient who developed varicella-zoster virus (VZV) meningoencephalitis under daratumumab treatment.

CASE PRESENTATION

A 68-year-old female patient was diagnosed with IgG lambda type MM in 2018. A bortezomib–lenalidomide–dexamethasone (VRd) regimen was initiated, together with acyclovir 800 mg/day twice a week for herpes prophylaxis. She refused to proceed with high-dose therapy with autologous stem cell rescue. After eight cycles of VRD treatment, she continued treatment with lenalidomide/dexamethasone for 4 years. After she relapsed, her treatment was switched to pomalidomide/dexamethasone as oral therapy to restrict hospitalization during the COVID-19 outbreak. Unfortunately, she had progressive disease, and a few months later, daratumumab monotherapy with dexamethasone was initiated, at 16 mg/kg weekly for 8 weeks. After 2 months, she was admitted to hospital because of new-onset confusion and fever. She did not have neck

stiffness. Hematological findings were as follows: leukocytes, 8720/mm3; neutrophils, 4850/mm3; lymphocytes, 2380/mm3; hemoglobin, 8.7 g/dL; and platelets, 43,000/mm3. Her IgG, IgM, and IgA levels were 41.55 g/L (6–15), 0.16 g/L (0.5–2.5), and 0.17 g/L (0.5–4), respectively. Lumbar puncture was performed. Direct microscopic examination detected 30 erythrocytes/mm3, 10 leukocytes/mm3, and no plasma cells, and Gram staining revealed no microorganisms. Cerebrospinal fluid analysis showed protein and glucose levels of 38 g/L (15–40) and 79 mg/dL (50–80), respectively. No bacteria were produced on culture. A rapid meningitis viral panel including herpes simplex virus type 1 and 2, human parechovirus, enterovirus, and VZV, and employing polymerase chain reaction, detected VZV positivity. In her serum, VZV IgG level was positive at 20.1 NovaTec units (NTU) (0–0.9); however, IgM level was negative at 0.15 NTU. Her HIV status was negative. On magnetic resonance imaging, bilateral high-signal foci were observed in the periventricular and supraventricular white matter on T2-FLAIR, some of which tended to coalesce in the subcortical area (Figure 1). Acyclovir treatment, intravenously at 10 mg/kg twice a day, was initiated and continued for 3 weeks. The patient never developed skin findings suggestive of VZV involvement before the central nervous system infection or during the treatment. She experienced significant benefits from the treatment and recovered without neurological sequelae.

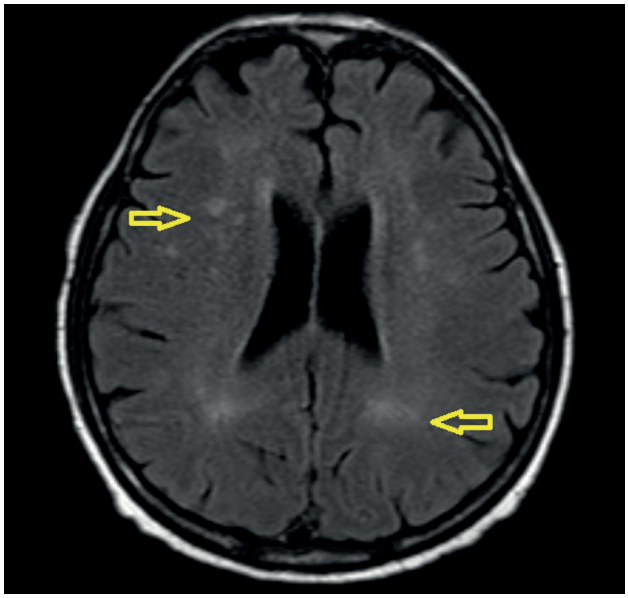

Figure 1. Bilateral high-signal foci in the periventricular and supraventricular white matter, some of which tended to coalesce in the subcortical area (arrows, FLAIR sequence MRI)

DISCUSSION

MM patients are prone to infections because of B cell dysfunction such as hypogammaglobulinemia, as well as abnormalities in T, dendritic, and NK cells. Daratumumab may reactivate viral infections by inhibiting CD38, which is expressed on the surface of NK, regulatory B, and T cells [2]. This is more prominent in MM patients heavily treated with prior lines. In addition, daratumumab is suggested to decrease CD4 T and NK cells and cause a low CD4/CD8 ratio, which makes the patient prone to viral reactivations [3]. Furthermore, limited data suggest that daratumumab penetrates the central nervous system (CNS), although this should be supported by extensive research. This may render the patient prone to the development of infections and reactivation of herpes virus in the CNS [4].

A meta-analysis by Vassilopoulos et al., examined the cumulative risk of infection in MM patients receiving anti-CD38 monoclonal antibody-based therapy and reported no increase in VZV infections due to daratumumab, despite an almost 30% higher risk of overall infections [5]. However, pharmacovigilance data from the Food and Drug Administration Adverse Events Reporting System report an increased risk of VZV reactivation when comparing patients receiving daratumumab with patients receiving other anti-myeloma treatments [6]. Drugs from other groups, such as proteasome inhibitors and/or dexamethasone, which are often used in combination with daratumumab, also increase this risk [5].

Our case was a relapsed refractory MM case who had previously received three lines of treatment. It should be emphasized that since dexamethasone was used together with daratumumab, the development of this infection should not be attributed to daratumumab alone. To our knowledge, our patient is the first case of daratumumab-associated herpes zoster meningoencephalitis reported in the literature. Thus, particular attention should be paid to the possibility of daratumumab causing viral infections in the CNS region, especially in heavily treated MM patients.

Author contribution

Study conception and design: AT, İY, AZB; data collection: AT, İY; analysis and interpretation of

results: AT, İY; draft manuscript preparation: AT. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

Since this is a case report, it does not require ethical committee approval. The informed consent was obtained from the patient for the participation and publication.

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Conflict of interest

The authors declare that there is no conflict of interest.

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