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Journal of Pediatric Nephrology

Case Report

Investigating the Disseminated Varicella Zoster Virus Infection After Rituximab Use in Nephrotic Syndrome: A Case Report

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Citation Seyedzadeh A, Tohidi M, Mohammadi Kamalvand M. Investigating the Disseminated Varicella Zoster Virus Infection After Rituximab Use in Nephrotic Syndrome: A Case Report. Journal of Pediatric Nephrology. 2023; 11(1):38-42. https://doi.org/10.22037/jpn.v11i1.41875

https://doi.org/10.22037/jpn.v11i1.41875

Article info:
Received: 05 April 2022
Accepted: 07 Nov 2022
Publish: 01 Jan 2023

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ABSTRACT

The infection with varicella-zoster virus in immune-deficient patients is an important and complex challenge in treating patients and requires decisions on an individual basis. Rituximab is an anti-CD20 positive B cells monoclonal antibody. Nowadays, it is frequently used in patients with idiopathic nephrotic syndrome and makes them susceptible to various infections. In this study, we report a 16-year-old male subject with steroid-resistant nephrotic syndrome who developed a severe and generalized form of chicken pox following rituximab administration.

Keywords: Nephrotic syndrome, Varicella zoster, Immune system deficiency

Introduction

Varicella zoster virus is a type of double-stranded DNA virus that causes chicken-pox in humans. In different communities, most children are infected with this disease [1, 2]. This virus remains hidden in the neurons of the human nervous system and causes shingles in adults. It is a skin disease with localized skin manifestations and severe pain [3, 4]. In most cases, chicken pox is a mild and self-limiting disease in children who do not have underlying diseases. It can be recognized by various symptoms, such as itchy blister rashes [5]; however, in children who (for various reasons) have a defect in their immune system, the severe form of the disease can occur and cause dangerous complications, including encephalitis, meningitis, and vasculitis [6, 7].

In various patients, including people with nephrotic syndrome, vasculitis, autoimmune diseases, and organ transplants, the use of immune system modulator drugs is common.

Drugs that modulate the immune system affect the immune system cells, including lymphocytes, macrophages, neutrophils, NK cells, and T cells, as well as the production of cytokines, and modulate the response of the immune system to internal and external stimuli [8].

The use of corticosteroids and monoclonal antibodies, such as rituximab in different patients puts the subjects at an increased risk of contracting infectious diseases by weakening their immune system, which can have various manifestations [9, 10]. In this article, we report a 16-year-old male subject with steroid-resistant nephrotic syndrome who developed a severe and generalized form of chicken pox following rituximab administration.

Case Report

The patient was a 16-year-old male with steroid-resistant nephrotic syndrome for 10 years. During hospitalization, the patient was on treatment with mycophenolate mofetil (1200 mg/m^2/day) and enalapril (5 mg/day). The subject received a single dose of rituximab (375 mg/m^2) and became exacerbated proteinuria 3 days after the rituximab treatment. The patient developed diffuse vesicular skin lesions on the face, trunk, and limbs which spread rapidly. The skin lesions of the patient started from the trunk and then spread to other parts of the body. There was no complaint of itching and burning in the area of the skin lesions, but the patient complained about severe pain in the lumbosacral region with poor response to analgesics. Also, the patient complained of weakness and lethargy but did not have a fever, headache, dizziness, vomiting, or diarrhea. There were no complaints of coughing or tears.

On physical examination, vesicular skin lesions with umbilicus and blisters with a size of about 3 mm were observed spreading throughout the trunk, face, earlobe, inside the mouth, and around the genital area; however, the patient's palms and feet were not involved. The patient had white exudate and vesicular lesions on the tonsils. There was no lymphadenopathy, organomegaly, petechiae, or purpura. Vital signs included blood pressure=130/80, pulse rate=90, respiratory rate=18, T=37.3, oxygen saturation (SpO_2)=96%. The patient's body mass index was calculated at 19, which was between 25 to 50 percentiles. Vaccination was done completely and according to the country's protocol (Figure 1).

The polymerase chain reaction (PCR) test for COVID-19 and monkeypox were negative. Abdominal and pelvic ultrasounds were normal, except for chronic kidney changes secondary to nephrotic syndrome. Then, specific chickenpox tests, including real-time PCR were performed, and the results were positive. Other viral diagnostic tests for human immunodeficiency virus (HIV) and herpes simplex virus (HSV) were also reported negative. Acyclovir 10 mg/kg/BID intravenous injection (IV) for 10 days was prescribed for the patient with an acceptable response. Also, because of the bacterial super-infection on skin lesions, clindamycin 40 mg/kg/day IV for 5 days was prescribed. Tizanidine 4 mg and gabapentin 100 mg for 5 days were prescribed for controlling the pain. Also, chloramphenicol drops and artificial tears were prescribed for dry eyes.

Over time, skin lesions gradually turned into a papule and pustule, and finally, the lesions were crusted over. The patient was discharged from the hospital with a good general condition. The above information is obtained and presented with the informed consent of the patient and permission to publish anonymously by the research center of Imam Reza Hospital in Kermanshah. The paraclinical examinations of the patient are listed in Table 1.

Discussion

Nephrotic syndrome is a clinical description of a set of findings that can be characterized by a large number of primary and secondary disorders. Rituximab is a monoclonal antibody against CD20 that its use has increased significantly in recent years [11]. Varicella infection is in the category of common childhood infections. In Iran, there are no accurate statistics on its annual incidence [12].

Although studies have shown an increase in the frequency of infectious complications following rituximab within one year after completion of treatment, most infections either resolve or are treated without any major complications. In a study regarding infectious complications following rituximab treatment, 31% bacterial infections, 10% viral infections, and 1% fungal infections were reported [13].

Nephrotic syndrome with hypoalbuminemia treated with corticosteroids or other immunosuppressive drugs increases the risk of viral and bacterial infections in the mentioned patients. Primary infection with varicella and the reactivation of this infection (shingles) are common in immunocompromised patients and are associated with significant complications [14]. The results of various studies show significant differences in clinical manifestations and consequences of varicella infection in patients with acquired immunodeficiency [15]. The

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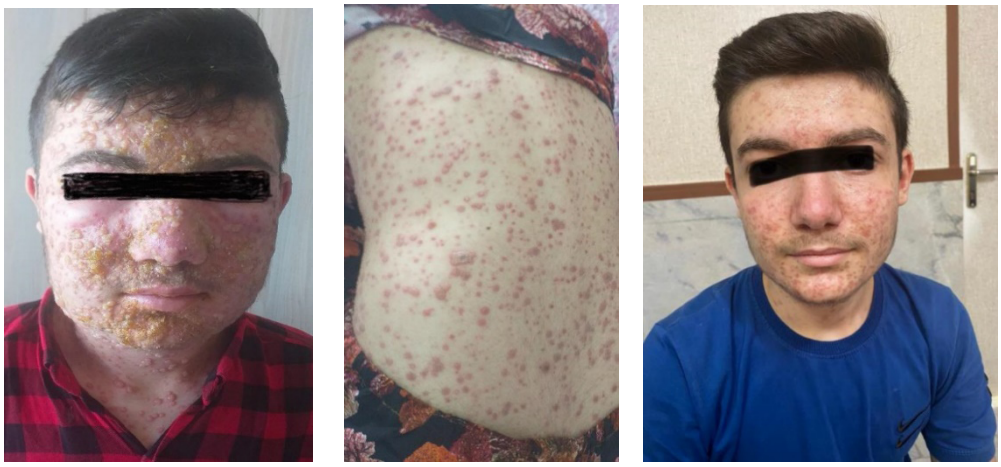

Figure 1. The course of the disease (from left to right)

Table 1. The results of the patient's paraclinical tests

Description	Normal Range	Results
White blood cell count x(10^9/L)	4-10×1000	6
Neutrophil count (%)		73
Lymphocyte count (%)		22.9
Monocyte count (%)		4.1
Hemoglobin g/dL	14-18	13.9
Platelet count x(10^9/L)	140-440×1000	173
Lactate dehydrogenase (IU/L)	225-500	353
Erythrocyte sedimentation rate (mm/h)	<15	45
C-reactive protein (mg/L)		3+
Creatine phosphokinase (micg/L)	5-200	48
Fasting blood sugar (mg/dL)	111	70-110
Aspartate transferase (U/L)	5-40	96
Alanine aminotransferase (U/L)	5-40	132
Urea (mg/dL)	17-43	38
Creatinine (mg/dL)	0.6-1.4	1
COVID-19 polymerase chain reaction		Negative
Anti-varicella zoster virus (IgG)	<9	1.5
Anti-varicella zoster virus (IgM)	<9	0.59
Varicella real-time polymerase chain reaction		Positive
HIV 1-2		Nonreactive
Monkeypox polymerase chain reaction		Negative

most common complications of chickenpox infection in immunocompromised patients include necrotizing pneumonia, viral hepatitis with acute liver failure, coagulopathy, and bacterial super-infections [16]. Kuwano et al. reported a case of nephrotic syndrome with different varicella zoster virus infections in a patient whose autopsy showed necrosis of various organs, such as the liver, kidneys, and digestive system [17]. In addition, Bastard et al. showed pulmonary and central nervous system involvement. Accordingly, researchers recommended the immediate start of antiviral treatment in such patients [15]. Rituximab has been associated with serious infections, including pneumocystis jiroveci pneumonia, the reactivation of HBV, and tuberculosis. Also, a report on 85 patients with membranous nephropathy who were given rituximab showed reactivation of herpes zoster in 1 patient [18]. The risk of infection appears to be the result of a variety of mechanisms, including prolonged B-cell depletion, B-cell and T-cell crosstalk pan hypogammaglobulinemia, late-onset neutropenia, and blunting of the immune response after vaccination. Andrew et al. reported that the risk of infectious complications following rituximab is related to the characteristic of the individual patients and the indications for the use of this medicine. Particular attention should be given to strategies to minimize the risk of infectious complications, including vaccinating against bacterial and viral pathogens, monitoring white cell count and immunoglobulin levels, prophylaxis against PJP, and screening for HBV and tuberculosis [13].

Conclusion

Patients with nephrotic syndrome treated with rituximab who are exposed to varicella zoster virus infection can experience severe side effects and complications, such as widespread skin rashes and failures of the lung, gastrointestinal tract, liver, and kidney. Rituximab can make the patient susceptible to various infections with intensified and unusual manifestations; therefore, the rapid initiation of antiviral treatment seems necessary for these patients.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors contributed equally to the preparation of this article.

Conflict of interest

The authors declared no conflict of interest.

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