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Case report

Co-infection: Primary Varicella and COVID-19 - case report

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SUMMARY

Introduction: Primary varicella usually occurs in childhood and is generally self-limiting. In adults and immunocompromised individuals, it can have a more serious course. Obesity is one of the risk factors for a severe COVID-19 infection that can lead to immunosuppression among other systemic complications. This case report aims to present a rare co-infection with varicella-zoster virus and SARS-CoV-2 in an adult, as well as to evaluate the impact of this co-infection on the progression and severity of both diseases in order to highlight the significance of antiviral therapy in treating both infections.
Case report: We report the case of a 34-year-old obese woman with varicella-zoster virus and SARS-CoV-2 co-infection who was successfully treated with oral acyclovir and nirmatrelvir-ritonavir without developing significant complications.
Conclusion: Currently, there is not enough evidence to claim that co-infection with varicella-zoster virus and SARS-CoV-2 increases the chances of a more severe form of either of these infections. With effective antiviral therapy, it is possible to significantly reduce the chances of developing more severe forms of both infections, which physicians need to be aware of in case they come across it and respond promptly.

Keywords: **COVID-19, SARS-CoV-2, primary varicella, varicella-zoster virus**

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INTRODUCTION

The coronavirus disease of 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which led to a global pandemic that began in March 2020 (1, 2). COVID-19 is a primary respiratory disease with numerous systemic manifestations and complications. Skin changes, such as the appearance of a vesicular rash, are one of these manifestations. The majority of patients have a mild form of the disease, while about 5% of patients have a critical form of COVID-19, followed by acute respiratory distress syndrome (ARDS), multiorgan failure, and/or shock (2, 3).

Due to COVID-19 being a relatively new and understudied disease, people with underlying uncontrolled medical conditions such as diabetes, heart, lung, liver, and kidney disease, as well as cancer patients on chemotherapy and transplant recipients are at increased risk of severe form COVID-19 infection (4). In addition, obesity as chronic disease increases the risk of severe illness from COVID-19. Moreover, obesity is linked to impaired immune function (5), however is also associated with susceptibility to a number of infections (6).

Varicella-zoster virus (VZV) can cause two distinct forms of disease: primary varicella-zoster viral infection, or varicella (chickenpox), and herpes zoster (shingles). Varicella is characterized by the development of a vesicular rash on the head, face, and trunk, most often in childhood, and is usually self-limiting. Adults, neonates, pregnant women, and immunocompromised people are more likely to develop complications such as bacterial skin infections, pneumonia, thrombocytopenia, cerebellar ataxia, encephalitis, etc. (7, 8). Dysfunction of immune system and systemic immunosuppression can potentially be caused by SARS-CoV-2, so taken together it can possibly influence the course and severity of the varicella-zoster virus co-infection (9, 10).

The aim of this case is to present a rare but possible co-infection with SARS-CoV-2 and varicella-zoster virus in an adult, as well as the importance of prompt antiviral therapy in the treatment of both infections.

CASE REPORT

A 34-year-old woman was admitted to our hospital's emergency department unit due to high fever, malaise, sore throat, dry cough, pruritus, and the onset of a vesicular rash. The patient was in her usual state of health until approximately three days prior to hospitalization (Day 0), when she reportedly developed a high fever, malaise, and sore throat. On Day 1, a dry cough started, and she tested positive for SARS-CoV-2 using a nasal swab for rapid antigen testing (Abbott PanbioTM). The physician prescribed her oral acetaminophen in case of high fever, and home isolation measures were issued according to government orders. On Day 2, a new-onset pruritic rash appeared on the back of patient scalp and face. On Day 3, the rash spread to neck, trunk, and upper extremities, prompting her to visit our hospital's emergency department unit for evaluation. During these three days, she did not take any prescribed medication, instead relying on alcohol friction to treat a high fever that reached 37.3 °C. Her medical history included obesity, and she is not currently taking any medication. She had no history of drug allergies, tobacco or electronic cigarette use, alcohol consumption, or illicit drug use. The patient is a married woman who gave birth vaginally to two children without complications. She lives in an apartment and teaches at a local elementary school. She had a history of close contact with a varicella patient because, two weeks before hospitalization, her younger child developed varicella infection. She was neither vaccinated against the varicella-zoster virus nor against SARS-CoV-2, and she had no history of previous varicella infection. Her family history included hypertension in both parent.

On examination during hospitalization (Day 3), the temperature was 37.3 °C, the blood pressure was 117/66 mmHg, the heart rate was 90 beats per minute, the respiratory rate was 18 breaths per minute and the oxygen saturation was 99% while the patient was breathing ambient air. The body mass index was 32.1. Maculopapular and vesicular lesions were present on the patient's head, trunk, and upper extremities (Figure 1). The remainder of the physical examination was unremarkable. The C-reactive protein level was 32.5 mg/l (the reference range is less than 5.0 mg/l), the white cell count was 3.6 K/μl (the reference range is between 4.0 and 10.0 K/μl), and the lymphocyte count was 1.06 K/μl (the reference range is between 1.18 and 3.74 K/μl). The serological test was negative for both VZV immunoglobulin (Ig) M and IgG. Other laboratory test results were in the reference range and are shown in Table 1. Chest radiography was performed, and it was normal. She declined further hospitalization, so she has been dis-

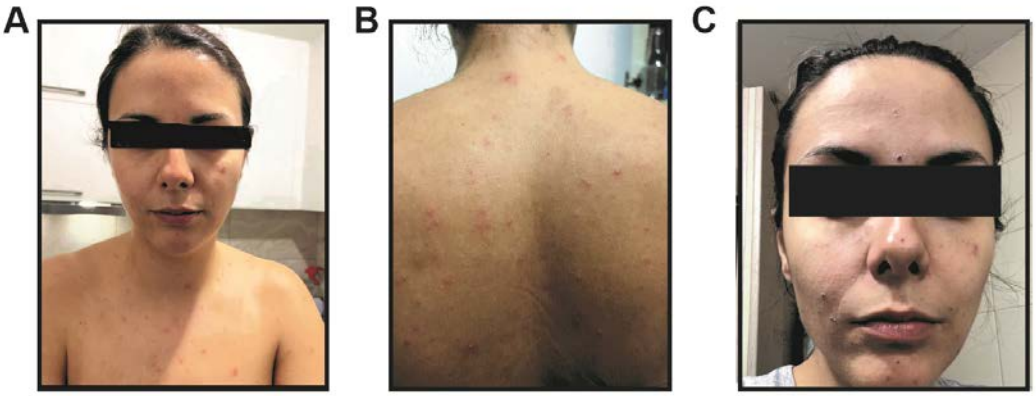

Figure 1. *Maculopapular and vesicular lesions. Vesicular rash on the patient face and trunk (Panels A and B); crusted vesicular lesions on the patient face (Panel C)*

Table 1. *Laboratory Data*

Variable	Reference Range, Adults*	Day 3	Day 8	Day 13
Hematocrit (%)	37 - 47%	39%	40.4%	40.3%
Hemoglobin (g/l)	115 - 155	130	132	132
Platelet count (K/μl)	140 - 400	271	274	293
Red-cell count (K/μl)	4.20 - 5.40	4.28	4.30	4.30
White- cell count (K/μl)	4.0 - 10.0	3.6	6.1	8.2
Differential count (K/μl)				
Neutrophils	1.56 - 6.13	2.10	3.24	4.40
Lymphocytes	1.18 - 3.74	1.06	2.15	3.13
Monocytes	0.24 - 0.86	0.34	0.54	0.44
Eosinophils	0.04 - 0.36	0.06	0.11	0.17
Basophils	0.00 - 0.10	0.02	0.03	0.02
C- reactive protein (mg/l)	0-5	32.5	10.3	3.2
Glucose (mmol/l)	2.6 - 6.1	4.9	5.1	5.0
Creatinine (μmol/l)	53 - 124	65.5	68.3	67.0
Urea nitrogen (mmol/l)	2.5 - 8.3	3.7	4.3	4.5
Lactate dehydrogenase (IU/l)	91 - 250	142	169	133
Alanine aminotransferase (U/L)	0 - 63	31	37	45
Aspartate aminotransferase (U/L)	0 - 33	19	11	16
d-Dimer (mg/l)	0 - 0.55	0.30	0.24	0.17
VZV IgM (U/ml)	< 10.0	7.0	47.0	-
VZV IgG (U/ml)	< 150.0	69.0	87.0	-

*Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Novi Pazar General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients

charged (Day 3) with oral acyclovir 800 mg five times per day, oral nirmatrelvir-ritonavir (Paxlovid) 300 mg plus 100 mg twice a day for five days, oral cetirizine 10 mg once per day, and oral acetaminophen as needed in case of high fever, along with the continuation of home isolation measures. The subsequent follow up examination was scheduled for five days or sooner if the condition deteriorated.

She appeared on the scheduled evaluation on Day 8 with a significant improvement in symptoms; she had had no fever for the past three days without using acetaminophen and cough has been stopped. Except for a couple of lesions on the abdomen, vesicular lesions were completely crusted (Figure 1C). The C-reactive protein level on Day 8 decreased to 10.3 mg/l, while the white-cell and lymphocyte counts increased to 6.10 and 2.15 K/μl, respectively. The serologic test yielded a positive result for VZV IgM, but a negative result for IgG. Other laboratory test results and the control chest radiography were normal (Table 1). We continued the same dosage of acyclovir for the next two days and scheduled a second follow-up examination in five days. At the subsequent examination on Day 13, the patient was free of symptoms and had crusts and hypopigmentation without vesicles. The C-reactive protein level was 3.2 mg/l, and the rest of the laboratory test results were normal (Table 1). She was discharged from our emergency unit with instructions to complete home isolation measures before returning to her normal activities.

DISCUSSION

Vesicular skin lesions are specific skin manifestations of COVID-19 infection with varied prevalence among studies ranging from 3.77% to 15% (11). In our case, the history of close contact with a varicella patient, the typical incubation period, and the typical clinical presentation led us to initiate antiviral therapy with acyclovir, empirically. Furthermore, during the course of the disease, we received serological confirmation that a primary varicella infection was the cause of the vesicular skin changes. In children, varicella is self-limiting disease, whereas in adults, it tends to have a more severe course. Compared with children, adult patients are 25 times more likely to develop varicella-related complications that lead to death, of which varicella pneumonia is the most frequent (12). Immunocompromised individuals with Severe Combined Immunodeficiency (SCID), Human Immunodeficiency Virus (HIV) infection, with high-dose corticosteroid therapy, chemotherapy, transplantation of solid organs, bone marrow transplantation, etc. have an increased risk of developing severe forms of varicella. Children with congenital or acquired deficiencies of cellular immunity as well as deficiencies of innate immunity such as abnormal natural killer (NK) cells are also more likely to develop a severe form of the disease (12, 13). Severe COVID-19 infection is associated with dysfunction of cellular immunity in the form of lymphopenia, CD4+ and CD8+ T cells functional exhaustion, a decrease in regulatory T cells, and a dysregulated interferon (IFN) response (10, 14, 15). Moreover, obesity is widely recognized as a risk factor for more severe forms of COVID-19 (16). There are only three published case reports (17 - 19) about co-infection with primary varicella and COVID-19, but no one used double antiviral therapy at the beginning of both diseases.

On December 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for ritonavir-boosted nirmatrelvir for the treatment of COVID-19. The EPIC-HR trial indicated starting ritonavir-boosted nirmatrelvir within 5 days of symptom onset in non-hospitalized adults with mild to moderate COVID-19 who were not vaccinated and who were at higher risk of progressing to severe disease (20, 21). Because nirmatrelvir-ritonavir has significant interactions with various drugs (20), we ensured there were no interactions between the prescribed medications and nirmatrelvir-ritonavir using the University of Liverpool COVID-19 interactions resource (www.covid19-druginteractions.org) (22). Moreover, acyclovir and its prodrug valacyclovir (the L-valyl ester of acyclovir) are the gold standard for the prevention and treatment of varicella-zoster virus-associated diseases (23). As we mentioned above, varicella is typically a self-limiting disease in children, however oral acyclovir should be considered for all healthy individuals over the age of 12 since this population is at increased risk for disease progression. Moreover, intravenous acyclovir is the treatment of choice for immunocompromised individuals. Acyclovir should be initiated within 24 hours of the onset of the rash because it has been shown to reduce the duration and severity of varicella (24). In our case, the patient is already suffered of obesity and therefore patient is with risk factors for severe forms of varicella and COVID-19

who has been treated at the onset of both diseases with effective antiviral therapy with a favorable outcome and without complications. This is the first documented report of usage double antiviral therapy in case of co-infection with varicella-zoster virus and SARS-CoV-2.

CONCLUSION

In the case of the appearance of a vesicular rash during a SARS-CoV-2 infection, physicians should always consider co-infection with varicella-zoster virus, especially in unvaccinated individuals and those who have not previously suffered from it. Based on the very limited evidence currently available, it is not possible to determine whether co-infection with varicella-zoster virus and SARS-CoV-2 increases the risk of more severe form of either infection. The potential immunosuppressive effect of the severe COVID-19 infection and its influence on the severity of the varicella infection could be prevented with specific and effective antiviral therapy; therefore, physicians should be aware of the potential situation in order to recognize and respond to it in a timely manner.

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Koinfekcija primarnom varičelom i virusom COVID-19: prikaz slučaja

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SAŽETAK

Uvod. Primarna varičela obično se javlja u detinjstvu i generalno je samoograničavajuća bolest. Kod odraslih i imunodeficijentnih osoba može imati ozbiljniji tok. Gojaznost je jedan od faktora rizika za teži oblik COVID-19 infekcije, koji može dovesti do imunosupresije i drugih sistemskih komplikacija. Ovaj prikaz slučaja ima za cilj da predstavi retku koinfekciju varičela zoster virusom i virusom SARS-CoV-2 kod odrasle osobe, da proceni uticaj ove koinfekcije na tok i težinu obaju oboljenja, kao i da naglasi značaj antivirusne terapije u njihovom lečenju.

Prikaz slučaja. Prikazuje se slučaj koinfekcije varičela zoster virusom i virusom SARS-CoV-2 zabeležen kod tridesetčetvorogodišnje gojazne žene, koja je uspešno lečena oralnim aciklovirom i nirmatrelevir-ritonavirom, bez razvoja značajnih komplikacija.

Zaključak. Trenutno ne postoji dovoljno dokaza za tvrdnju da koinfekcija varičela zoster virusom i virusom SARS-CoV-2 povećava šanse za teži oblik bilo koje od ovih infekcija. Efikasnom antivirusnom terapijom moguće je značajno smanjiti šanse za razvoj težih formi obeju infekcija; potrebno je da lekari to imaju u vidu u slučaju koinfekcije pomenutim virusnim oboljenjima i da, samim tim, reaguju pravovremeno.

Ključne reči: **COVID-19, SARS-CoV-2, primarna varičela, varičela zoster virus**