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Case Report

A young patient presents with fever and rash: ıs this an adverse effect of mrna vaccine, vasculitis, or rickettsiosis?

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A B S T R A C T

The aetiology may be complex in patients presenting with fever and rash. The differential diagnosis may include coronavirus disease 2019 (COVID-19) infection, an adverse effect of the COVID-19 vaccine, infection, and vasculitis. We reported a patient who presented with fever and vasculitic rash, which we hypothesized was an adverse vaccine effect. A 35-year-old male patient presented to the emergency department reporting headache, fever, rash, weakness, and myalgia. The first dose of the mRNA vaccine, COVID-19, had been administered five days before his presentation. A nasopharyngeal severe acute respiratory syndrome coronavirus two-challenge test was negative. Antinuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factor, and cryoglobulin were negative. No hypocomplementemia was detected. Skin biopsy was predominantly lymphocytic, with a vasculitic reaction with a few neutrophils. The *Rickettsia conorii* immunoglobulin M test examined using enzyme-linked immunosorbent assay (ELISA) was positive. COVID-19 should be excluded in patients with fever, rash, and headache. Symptoms that occur after vaccination may indicate adverse reactions. Even though we are in the pandemic phase, rickettsiosis should not be forgotten.

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Key Points

• COVID-19 is suspected first in the patient who applied to the emergency department with the complaints of fever and maculopapular rash during the pandemic era.

• Although the COVID-19 vaccine is widely used, possible side effects of the vaccine may raise doubts among physicians and patients.

• The preliminary diagnosis of a patient with a vasculitic rash who complains of fever and myalgia should be thought to be Rickettsiosis.

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INTRODUCTION

As of March 13th, 2022, coronavirus disease 2019 (COVID-19) is responsible for over 457 million cases worldwide and over 6 million deaths.[1] Fever, dry cough, sore throat, and muscle and joint pain are common symptoms of the illness.[2] In addition to pulmonary symptoms, dermatologic manifestations may be observed in patients with COVID-19. Skin lesions associated with COVID-19 can occur in three distinct patterns: vesicular, vasculopathic, and chilblain-like. Cases of leukocytoclastic vasculitis and rash following COVID-19 vaccination have been reported.[3] Vasculitic lesions are important in the differential diagnosis of rheumatologic, dermatologic, and infectious diseases.

Rickettsiae are a group of diseases caused by obligate intracellular Gram-negative coccobacilli and transmitted to humans by vectors such as lice, fleas, and ticks. Fever, headache, and rash are considered the classic triad. Lesions called eschars are seen at the entrance of the arthropods. The vasculitic lesions on COVID-19 can often resemble the eschars associated with rickettsiosis.[3,4] We aimed to present our patient who presented to the emergency department with fever and rash, in whom we investigated COVID-19 and other possible infectious pathologies, vasculitis, and vaccine adverse effects in the differential diagnosis.

CASE REPORT

A 35-year-old male patient presented to the emergency department, reporting a headache that had persisted for four days. The first dose of the mRNA COVID-19 vaccine was administered to the patient without known illness five days before admission. He had no previous known headache, and his discomfort began suddenly. His pain was relieved with ibuprofen. There were no prodromal symptoms, light or sound sensitivity, neurologic symptoms, fever, nausea, or vomiting. The patient was examined. The results of the laboratory tests were shown in Table 1. Cranial computed tomography (CT) noted no acute haemorrhage or oedema. He was discharged with a non-steroidal anti-inflammatory drug (NSAID) prescription and a recommendation for outpatient neurologic follow-up. A day later, he was again admitted to the emergency room because his headache was accompanied by maculopapular rash, weakness, and myalgia. His medical history included no allergy, regular drug use, new drug use, suspicious sexual intercourse, COVID-19-positive patient contact, and tick contact. On physical examination, he had a fever of 38.5 °C, his heart rate was 74 per minute, his blood pressure was 120/80 mmHg, his respiratory rate was 16 per minute, and oxygen saturation in room air was 98%. The patient's sclera and oropharynx were normal. There was no neck stiffness. There was no cervical lymphadenopathy. Pulmonary, cardiovascular and gastrointestinal system examinations were normal. We observed an erythematous, nonpruritic rash on the neck, trunk, back, and upper and lower extremities (Figure 1). There was a rash on the palmoplantar skin. Still, the face and mucous membranes were unaffected.

Laboratory tests revealed lymphopenia, elevated C-reactive protein (CRP), ferritin, and D-dimer (Table 1). A nasopharyngeal severe acute respiratory syndrome 2 (SARS-CoV-2) PCR test was negative. The chest CT was assessed as usual. The next day, he again contacted the emergency services because fever and cough were added to his symptoms. There was no dyspnea, sputum, tachypnea, or tachycardia. His physical examination revealed a fever of 39 °C, a heart rate of 84 per minute, a blood pressure of 125/85 mmHg, a respiratory rate of 16 per minute, and oxygen saturation in room air of 98%. Except for the persistent rash, there were no abnormalities. The results of the laboratory tests were shown in Table 1. The nasopharyngeal SARS-CoV-2 PCR test was negative. Thorax CT was unremarkable. The patient was discharged after being educated about the emergencies that might necessitate his visit to the emergency department and being prescribed acetaminophen, cetirizine dihydrochloride, and antitussives. Four days later, he stated that his fever rose to 40 °C and only decreased after he took acetaminophen and increased again within 2-3 hours. The patient lives in the city centre and is a pianist by profession. He did not report any trips to the countryside. He likes camping. He stated that he knew about ticks and had no recent contact with them. No new changes were noted during his interview and physical examination. On laboratory testing, AST increased to 190 U/L, ALT increased to 133 U/L, ferritin increased to 12,459 µg/L, D-dimer increased to 12.83 mg/L, and procalcitonin increased to 1.26 µg/L (Table 1). A nasopharyngeal SARS-CoV-2 PCR test was negative. There was no finding suggestive of pneumonia in lung CT, and the patient

Table 1. Laboratory data.

Post-vaccination time	**5th day**	**6th day**	**7th day**	**11th day[a]**	**12th day[b]**	**15th day[c]**	**25th day**	**3 months**
Presenting symptom	**Headache**	**Rash, weakness**	**Fever**					
SARS-CoV-2 swab test		Negative	Negative	Negative				
Leukocyte (K/µL)	7,450	5,650	5,770	12,050	16,140	15,600	10,850	8,020
Neutrophil (K/µL)	6,280	4,440	4,710	10,360	13,380	11,900	6,730	5,200
Lymphocyte (K/µL)	730	760	660	1,080	2,060	2,660	3,300	1,990
Hemoglobin (g/dL)	14.7	14.3	13.3	13.4	11.7	12.5	13.2	15.6
MCV (fL)	86.8	83.9	86.9	86.1	81.9	90.3	87.2	85.8
Platelet (K/µL)	157,900	144,500	136,300	116,400	119,800	363,000	351,700	298,400
Glucose (mg/dL)	133	118	116	103		126	77	93
Urea (mg/dL)	27	23	27	21	20	32	29	32
BUN (mg/dL)	12.6	10.7	12.6	9.8	9.3	15	13.6	15
Creatinine (mg/dL)	0.84	0.93	0.83	0.83	0.74	0.65	0.78	0.84
eGFR (mL/min/1.73 m^2)	113	106	114	114	114	126	117	113
AST (U/L)	25	40	33	190	172	65	18	30
ALT (U/L)	27	31	35	133	125	126	32	33
Total bilirubin (mg/dL)		0.8	0.5			0.9	0.64	0.82
Direct bilirubin (mg/dL)		0.3	0.23			0.4	0.27	0.25
Albumin (g/L)						37	45	50
Toral protein (g/L)							73	74
Uric acid (mg/dL)							5.7	7.1
LDH (U/L)						334	211	170
GGT (U/L)						62		
CK (IU/L)		13	409	555	263			301
Sodium (mmol/L)	128	127	135	124	132	134		135
Potassium (mmol/L)	3.4	3.7	3.5	3.2	3.2	4.65		4.49
Calcium (mg/dL)	8.6	8.7	8.8	8.2		8.2		9.6
Chlorine (mmol/L)	100	96	99	91	99	103		101
Magnesium (mg/dL)		1.8	2					
Amylase (U/L)		47		81				
Triglyceride (mg/dL)					797	272		
INR	1	1	0.9	0.9	1	1	0.9	0.96
ESR (mm/h)					3			4
CRP (mg/L)	96.7	121.1	126.1	66.3	79.6	30	< 2	2.8
Procalcitonin (µg/L)		0.29	0.43	1.26	0.86	0.11	0.01	
Ferritin (µg/L)		1,398	2,379	12,459	11,790		302	52
D-Dimer (mg/L)		4.56	1.64	12.83	4.41	1.13	0.83	0.23
Fibrinogen (mg/dL)							243.8	279

MCV: mean corpuscular volume, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, GGT: gamma-glutamyl transferase, CK: creatine kinase, INR: international normalized ratio, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.
[a]Admission to the Infection clinic, [b]transfer to rheumatology clinic, [c] discharge from hospital.

was admitted to the Infectious Diseases Clinic. Blood cultures, antibody tests for hepatitis B and C viruses, Epstein-Barr virus, cytomegalovirus, parvovirus, Lyme disease, brucella, and syphilis were negative. Human immunodeficiency virus testing with an enzyme-linked immunosorbent assay (ELISA) was also negative.

With fever, rash, elevated ferritin levels, and elevated liver enzymes, the patient was transferred from the rheumatology clinic with prior diagnoses of adult vasculitis and Still's disease. He reported occasional alcohol and cigarette use but no oral or intravenous drug use. He had no animals at home. When questioned further, he recalled visiting his friend's farm five days before vaccination and petting his dogs. He had not had any dental treatment recently. The *Rickettsia conorii* IgM test examined using ELISA was positive. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, rheumatoid factor, and cryoglobulin were negative.

Biopsies of the abdominal skin and anterior surface of the tibia were performed on the patient who presented to the dermatology department with preliminary diagnoses of drug eruption, cutaneous vasculitis, disseminated gonococcal disease, disseminated candidiasis, and meningococcal disease. A lymphocyte-dominant vasculitic reaction with sparse neutrophils was noted in a skin biopsy of the trunk and leg. When the findings observed in this case were evaluated with the patient's clinic, this suggested rickettsial infection. The cause could not be established because immunohistochemical staining could not be performed. It was additionally noted that it is recommended that connective tissue diseases such as lupus be included in the differential diagnosis.

On echocardiography, ejection fraction was 60%, wall motion was normal, pulmonary artery pressure was 18, and minimal tricuspid regurgitation was noted. Vegetation was not detected. Methylprednisolone 80 mg was administered intravenously. Azithromycin for rickettsiosis was administered because of the elevated liver enzymes. The patient's temperature was normal. Doxycycline 100 mg twice a day and prednisolone 15 mg/day was started in the patient whose enzymes regressed in the follow-up, and the patient was discharged. On the 10th day after discharge, the patient had no more symptoms. The improvement in laboratory test results was shown in Table 1. The patient's laboratory parameters were completely normal at the third-month follow-up. A *Rickettsia conorii* test was negative.

DISCUSSION

Fever and rash are complex and important

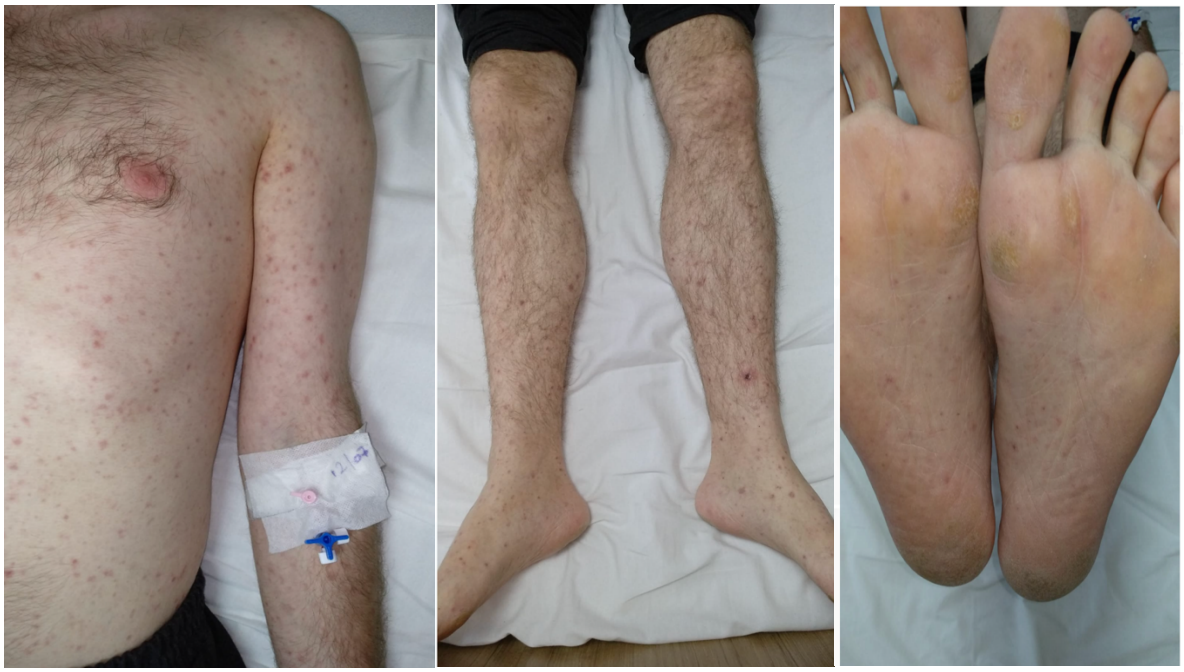

Figure 1. Rash and eschar on the trunk and extremities of the patient.

conditions for the patient and physician. Causes of fever include infections, rheumatic diseases, and malignancies. The differential diagnosis in an adult with fever and maculopapular rash is broad. In addition to infections, the differential diagnosis should include hypersensitivity reactions and vasculitides.[5,6] We presented our patient, whose differential diagnoses were hypersensitivity reactions, rheumatologic diseases, and infections.

Since the first coronavirus 2019 (COVID-19) case was reported in Wuhan in December 2019, it has rapidly spread to six continents and hundreds of countries. In patients presenting with fever, COVID-19 has taken its place in the first place in the preliminary diagnosis. COVID-19 disease can present as an asymptomatic or mild upper respiratory tract infection, or it can be severe and fatal, ranging from pneumonia to acute respiratory failure and death.[7] Accordingly, any patient reporting to the emergency department with a fever should have COVID-19 ruled out. In addition, COVID-19 has been associated with various skin manifestations. In the course of mild and fulminant COVID-19 disease, vasculitis of the skin can manifest as typical skin lesions.[8] SARS-CoV-2 directly infects endothelial cells and triggers a hyperinflammatory response, likely leading to immune complex deposition and vasculitis.[9] The vasculopathic lesions of COVID-19 may resemble those of scabs causing rickettsiosis.[3] Three nasopharyngeal SARS-CoV-2 swab tests were negative because our patient had a vasculitic rash. In addition, fibrin deposits and IgA deposits in the walls of small vessels characteristic of leukocytoclastic vasculitis were not observed on skin biopsy.

In recent years, the world has been facing an incomparably deadly pandemic characterized by its high contagiousness and mortality rate. For this reason, scientists have developed vaccines to prevent the transmission of COVID-19 infection and control the infection.[10] Vaccines developed for this purpose include the RNA-based vaccines BionTech and Moderna, the viral vector-based vaccines Sputnik V (Gamaleya) and AstraZeneca (Oxford), and the inactivated virus vaccine Sinovac.[11] More than 6.5 billion doses of the COVID-19 vaccine have been administered worldwide.[12] Our country used the inactivated virus vaccine Sinovac and the mRNA vaccine BionTech. Adverse events after COVID-19 vaccination consist mainly of typical vaccine-related events. Symptoms include pain at the injection site, chills, fever, arthralgia, myalgia, and headache.13 The occurrence of headaches in the days after vaccination, followed by additional malaise and rash, suggests possible adverse effects of the vaccine after ruling out COVID-19 infection. Cases of leukocytoclastic vasculitis following vaccination with COVID-19 have been reported in the literatüre.[14,15]

Rickettsiae are intracellular pathogens that bind to the membrane of vascular endothelial cells and integrate their genome into host DNA, thereby inhibiting apoptosis of endothelial cells. They cause necrotizing vasculitis by proliferating in the cytoplasm of endothelial cells, capillaries, arterioles, and smooth muscle cells of small arteries. Scabs form when these vascular lesions are accompanied by capillary thrombosis and necrosis. Rickettsiae can infect the body after bites from arthropods such as fleas, lice, ticks, and mites. They occur suddenly and are accompanied by fever, headache, weakness, muscle pain, and in almost all cases, a characteristic rash that lasts for one or more weeks.[16,17] A blackish, crusty lesion 1 cm in diameter, called an eschar, is typical of the bite site. An eschar lesion was also seen on the anterior leg of our patient.

Mediterranean spotted fever (MSV) is an infectious disease endemic to our country caused by Rickettsia conorii. Vasculopathy of small or medium vessels, thrombocytopenia, myositis, myocarditis, encephalopathy, and possible tick exposure should indicate rickettsia. Vasculitis is characteristic of this disease. Findings include a maculopapular rash that begins peripherally, often affecting the palms and soles, and later spreads centrally. Small vessel vasculitis involves bleeding into the skin from small blood vessels, and petechial or purpuric lesions may occur. Platelet adhesion to the damaged endothelium classically results in thrombocytopenia.[16]

Serology positivity begins two weeks after illness. Therefore, if rickettsiosis is clinically suspected, treatment should be initiated immediately. Antibiotics such as doxycycline and tetracycline are used for treatment.[18,19] Our patient's therapy with doxycycline resulted in a dramatic response; his fever decreased, and his skin rashes resolved.

CONCLUSIONS

As a result, skin infestations may be an important manifestation of COVID-19 and rickettsiosis.

Even during the pandemic, rickettsiosis should be considered in patients who complain of fever and rash, especially in areas where rickettsia is endemic during summer.

Conflict of Interest

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Authors' Contribution

Study Conception: BNÇ, HA; Study Design: BNÇ, ED, YP, HA; Supervision: YP, ED, HA; Literature Review: BNÇ; Critical Review: BNÇ; Data Collection and/or Processing: BNÇ, NL, CS; Manuscript preparing: BNÇ.

REFERENCES

1. COVID-19 coronavirus pandemic. Avaliable at: https://www.worldometers.info/coronavirus/. Accessed 22 October, 2021.
2. Elrobaa IH, New KJ. COVID-19: Pulmonary and extra pulmonary manifestations. Front Public Health. 2021 Sep 28;9:711616. doi: 10.3389/fpubh.2021.711616.
3. Almutairi N, Schwartz RA. COVID-19 with dermatologic manifestations and implications: An unfolding conundrum. Dermatol Ther. 2020 Sep;33(5):e13544. doi: 10.1111/dth.13544.
4. Mittal A, Elias ML, Schwartz RA, Kapila R. Recognition and treatment of devastating vasculopathic systemic disorders: Coronavirus disease 2019 and rickettsioses. Dermatol Ther. 2021 Jul;34(4):e14984. doi: 10.1111/dth.14984.
5. Muzumdar S, Rothe MJ, Grant-Kels JM. The rash with maculopapules and fever in adults. Clin Dermatol. 2019 Mar-Apr;37(2):109-18. doi: 10.1016/j.clindermatol.2018.12.004.
6. Anderson CW, Shah PA, Roberts JR. Adult-onset Still's disease: Is this truly a diagnosis of exclusion? Hawaii J Med Public Health. 2017 Nov;76(11 Suppl 2):3-6.
7. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020 May;109:102433. doi: 10.1016/j.jaut.2020.102433.
8. Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, Navarro Fernández I, Ruiz-Villaverde R, Falkenhain-López D, Llamas Velasco M, García-Gavín J, Baniandrés O, González-Cruz C, Morillas-Lahuerta V, Cubiró X, Figueras Nart I, Selda-Enriquez G, Romaní J, Fustà-Novell X, Melian-Olivera A, Roncero Riesco M, Burgos-Blasco P, Sola Ortigosa J, Feito Rodriguez M, García-Doval I. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020 Jul;183(1):71-7. doi: 10.1111/bjd.19163.
9. Cohen SR, Prussick L, Kahn JS, Gao DX, Radfar A, Rosmarin D. Leukocytoclastic vasculitis flare following the COVID-19 vaccine. Int J Dermatol. 2021 Aug;60(8):1032-3. doi: 10.1111/ijd.15623.
10. World Health Organization. Coronavirus diseaese (COVID-19) pandemic [Internet]. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=Cj0KCQjwnoqLBhD4ARIsAL-5JedKWHzI1FP1nJxgYfvBgqnPcPJ-vL7KzKDjn-8TOtkyjlr9wlIu--5SgaAlgWEALw_wcB. Accessed 25 October, 2021.
11. Soleimanpour S, Yaghoubi A. COVID-19 vaccine: where are we now and where should we go? Expert Rev Vaccines. 2021 Jan;20(1):23-44. doi: 10.1080/14760584.2021.1875824.
12. Coronavirus (COVID-19) Vaccinations [Internet]. Available at: https://ourworldindata.org/covid-vaccinations?country=TUR. Accessed 25 October, 2021.
13. Centers for Disease Control and Prevention-Safety of COVID-19 Vaccination [Internet]. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/safety-of-vaccines.html. Accessed 25 October, 2021.
14. Fritzen M, Funchal GDG, Luiz MO, Durigon GS. Leukocytoclastic vasculitis after exposure to COVID-19 vaccine. An Bras Dermatol. 2022 Jan-Feb;97(1):118-21. doi: 10.1016/j.abd.2021.09.003.
15. Bostan E, Gulseren D, Gokoz O. New-onset leukocytoclastic vasculitis after COVID-19 vaccine. Int J Dermatol. 2021 Oct;60(10):1305-6. doi: 10.1111/ijd.15777.
16. Walker DH, Ismail N. Emerging and re-emerging rickettsioses: endothelial cell infection and early disease events. Nat Rev Microbiol. 2008 May;6(5):375-86. doi: 10.1038/nrmicro1866.
17. Bechelli JR, Rydkina E, Colonne PM, Sahni SK.

Rickettsia rickettsii infection protects human microvascular endothelial cells against staurosporine-induced apoptosis by a cIAP (2)-independent mechanism. J Infect Dis. 2009 May 1;199(9):1389-98. doi: 10.1086/597805.
18. Brouqui P, Parola P, Fournier PE, Raoult D. Spotted fever rickettsioses in southern and eastern Europe. FEMS Immunol Med Microbiol. 2007 Feb;49(1):2-12. doi: 10.1111/j.1574-695X.2006.00138.x.
19. Antón E, Font B, Muñoz T, Sanfeliu I, Segura F. Clinical and laboratory characteristics of 144 patients with mediterranean spotted fever. Eur J Clin Microbiol Infect Dis. 2003 Feb;22(2):126-8. doi: 10.1007/s10096-002-0879-x.