

Skin manifestations of COVID-19 in a pregnant woman with premature rupture of membranes: A case report

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Case Report

ABSTRACT

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The number of COVID-19 cases, especially with pregnancy, remains a problem in the world and in Indonesia. The main clinical symptoms include fever (temperature $>38^{\circ}\text{C}$), cough, and shortness of breath. In addition, it can be accompanied by fatigue, myalgia, gastrointestinal symptoms such as diarrhea, and even recently found manifestations of skin disorders. Skin manifestations in COVID-19 pregnant patients are still a rare condition. Skin manifestations can be an early sign of such infection, which therefore requires clinicians' notice to allow them to conduct early COVID-19 screening in pregnant women for better outcomes of the mother and the baby. We present a 26-year-old primigravida at 39 weeks of gestational age with premature rupture of membranes and COVID-19 infection. Her complaints included itchy maculopapular rash and urticaria, then the pregnancy was terminated by a caesarean section, and the baby was born with good conditions. The skin lesions were given a mixture of corticosteroid cream and fusidic acid. The mother and the baby were discharged in a good condition.

Banyaknya jumlah kasus COVID-19 pada kehamilan masih menjadi masalah di dunia dan di Indonesia. Gejala klinis utama meliputi demam (suhu $>38^{\circ}\text{C}$), batuk, sesak napas. Selain itu, dapat disertai rasa lelah, mialgia, gejala gastrointestinal, seperti diare bahkan baru-baru ini ditemukan manifestasi pada kelainan kulit. Manifestasi kulit pada pasien hamil COVID-19 masih jarang ditemukan. Manifestasi kulit dapat menjadi tanda awal dari infeksi ini. Oleh karena itu perlu diperhatikan oleh dokter agar dapat melakukan skrining COVID-19 sejak dini pada ibu hamil untuk hasil luaran ibu dan bayi yang lebih baik.

Kami menyajikan kasus primigravida 26 tahun, usia kehamilan 39 minggu dengan ketuban pecah dini dan infeksi COVID-19, mengeluh gatal-gatal, ruam makulopapular dan urtika, kehamilan diterminasi dengan operasi caesar, dan bayi lahir dengan kondisi yang baik. Lesi pada kulit diberikan terapi racikan krim kortikosteroid dan asam fusidat. Ibu dan bayi pulang dalam kondisi baik.

INTRODUCTION

Coronavirus disease 2019 has become a global pandemic after WHO determined it on March 12, 2020. Since the first case was found in Wuhan, there has been an increase in the number

of COVID-19 cases in various other provinces in China, and it has become a global pandemic problem around the world.¹ Meanwhile, in Indonesia until February 2021, there were 1.17 million confirmed cases with 31,763 deaths.²

In Central Java, there were 136 thousand cases and 5,660 deaths were found.³ Indonesia has the highest mortality rate in Southeast Asia, reaching 8.9%.⁴

There is a large number of COVID-19 cases during pregnancy. Pregnant women and fetuses are a vulnerable and high-risk population.⁵ More than 193,000 deaths (as of April 24, 2020) occurred but no reports of maternal deaths have been published. In China, a total of 154 infected pregnant women were reported with a maternal morbidity of 1% and no maternal mortality. In America, 4-10% maternal morbidity was reported with no mortality.⁶ Pregnant women develop special immunological adaptations, which are necessary to maintain the tolerance of fetal semi-allografts. This suppressed state of immunity is modulated by the suppression of T-cell activity, while in pregnancy there is a predominance of the system by the T-helper 2 (Th2), which protects the fetus, thus making the mother vulnerable to viral infections.⁷ The COVID-19 infection in pregnant women has the same mechanism as the conditions without pregnancy, in which the ACE-2 receptor binds to the S protein from SARS-CoV-2. In addition, the entry of the virus is also influenced by the priming protein S with the protease cells on the host called Trans Membrane Protease Serine-2 (TMPRSS2).⁸

COVID-19 infection is characterized by an increase in the plasma interleukin 2 (IL-2), IL-7, IL-10, granulocyte-colony stimulation factor (G-CSF), interferon- γ -protein 10 induced protein, monocyte 1 chemoattractant protein, 1 alpha macrophage inflammatory protein, and tumor necrosis factor α (TNF- α) which is known as the cytokine storm.⁵ Pregnant women are prone to infections, especially in the pro-inflammatory state during the first and third trimesters, and the cytokine storm caused by SARS-CoV-2 can therefore lead to more severe inflammatory state.⁹

Pregnant women with COVID-19 infection show different symptoms ranging from mild to severe. Patients often have fatigue, dry cough, productive cough, sore throat, headache,

myalgia/atralgia, nausea/vomiting, chills, nasal congestion, diarrhea, abdominal pain, hemoptysis, conjunctival congestion, and skin manifestations. Skin manifestations are rarely seen among the symptoms of COVID-19. It was seen in 2 patients in China, but the characteristics and progression of these lesions were not clearly described. However, there are a number of studies that report patients with skin manifestations such as viral exanthem (i.e. morbilliform rash, petechial rash with thrombocytopenia, erythematous purpura, macular clots, extensive urticaria, and varicella-like vesicles) and skin manifestations associated with vasculopathy (i.e. peripheral cyanosis with dry bullae and gangrene, transient unilateral livedo reticularis, and red papules on the fingers that resemble chilblains).¹⁰ Since skin manifestations in COVID-19 pregnant patients are still uncommon, an integrated approach is required, especially for early detection, prediction, and evaluation of COVID-19 in pregnant women in terms of early recognition of symptoms and signs, diagnosis, and management, which are considered essential to improve the prognosis.⁹

CASE DESCRIPTION

We reported a case of pregnant woman with a confirmed COVID-19 infection, G1P0A0, 26 years old, 39⁺⁵ weeks of gestation. The patient came with a leaking amniotic fluid complaint experienced since the day before being admitted to the hospital. A regular contraction had been undergone for 8 hours prior to hospital admission, and blood mucus was also felt discharged. The patient had complained about and developed itchy spots all over the body for 5 days, but there were no fever, cough, or shortness of breath complaints. The patient also had a close contact with people with COVID-19.

Past medical history, such as hypertension, diabetes mellitus, asthma, allergies, and heart disease, was denied. History of routine antenatal care showed no abnormalities found in the mother and fetus. The results of the physical examination revealed that the general

condition of the patient was good and compos mentis. Vital signs examination resulted in 120/75 mmHg blood pressure, 86 times/minute pulse, 20 times/minute respiration, and a temperature of 36.4°C. The eyes did not look anemic or icteric, and the heart was within the normal limits without any additional sound found. The pulmo was also within the normal limits, and no additional sounds such as ronchi and wheezing were found. The abdomen was supple, no tenderness was found, there was a palpable single fetus, intrauterine, fetal back

on the right side, head presentation, fetal head entering the pelvis at 1/5 part, 148 times/minute and regular fetal heart rate of, 3 times of contraction in 10 minutes for 30 seconds, and 32 cm of fundal height (3,100 gr fetal weight). There were maculopapular rash and urticaria lesions on the upper and lower extremities as well as the back and lower abdomen (Figure 1). On the genital examination, the portio dilatation was 3 cm, and the Nitrazin test result was positive.

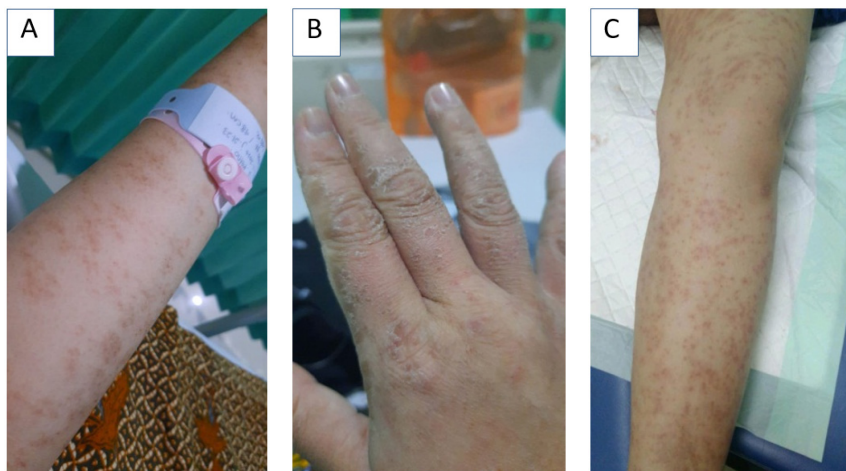


Figure 1. Maculopapular urticarial rash in the patient (A: arms, B: fingers, C: feet)

The blood laboratory test results on January 6, 2021 showed 11.4g/dL hemoglobin, 32.3% hematocrits, $19.64 \times 10^3/\mu\text{l}$ leukocytes, $254 \times 10^3/\mu\text{l}$ platelets, 3.94 million/ μl erythrocytes, 0.1% eosinophils, 0.2% basophils, 87.8% neutrophils, 8.0% lymphocytes, 3.9% monocytes, 11.10 NLR, 9.90 seconds of PT, 30.20 seconds of APTT, 0.66 INR, 106mg/dL random blood sugar, and non-reactive HbsAg, while bacteria (+1) found from urine examination. The chest X-ray showed bronchopneumonia, and from the anamnesis, physical examination, and laboratory finding, the patient was diagnosed with primigravida of 39-week gestational age with premature rupture of membranes, latent phase of birth, suspected COVID-19 infection, and skin manifestations of maculopapular rash and

urticaria.

The patient was given an emergency caesarean section. A male baby was born with a birth weight of 3000 grams and 8-9-10 APGAR score. On January 7, 2021, a nasopharyngeal PCR swab was performed on the mother with a positive result followed by a diagnosis of confirmed COVID-19 infection and skin manifestations (maculopapular and urticaria). The therapy for the skin manifestations was desoximetasone cream with fusidic acid.

DISCUSSION

SARS-COV2 infection enters the cells via the Angiotensin Converting Enzyme 2 (ACE-2) receptor on the cell surface.¹¹ In the human body, ACE-2 receptors can be found in the lungs, small intestine, kidneys, heart, blood vessels, spleen,

bone marrow, muscles, brain, large intestine, liver, adipose tissue, adrenal glands, and also on the skin. It is found in the basal stratum of the epidermis and eccrine glands, and the surface of damaged skin can be a port of entry for the virus to reach the ACE-2 receptor on keratinocytes. This relates to the clinical symptoms of SARS-COV2 virus infection.¹²

The percentage of patients with skin manifestations in COVID-19 is 1% to 20%.¹³ Manifestations of skin lesions occur because the virus induces vascular dysfunction directly or indirectly, such as livedo reticularis, petechiae, or cutaneous acro-ischemia. From numerous cases, most have reported lesions or rash of maculopapular exanthema/vesicular exanthema and urticarial lesions.¹⁴

The manifestations of COVID-19 on the skin vary from maculopapular rash (77.8%), urticaria (16.7%), vesicular purpura (5.6%), Covid toes, Livedo racemosa, to androgenic alopecia.¹⁵ Maculopapular or morbilliform rash is one of the rashes that is often found in patients with COVID-19.¹⁵ There were several cases of patients with COVID-19 who developed morbilliform rash as reported by Recalcatti in Italy with 14 out of 18 cases.¹⁶ In addition, Hunt et al. in New York also reported a morbilliform rash in a man who had a diffuse morbilliform rash in the trunk and lower limbs.¹⁷ The morbilliform rash can be caused by microorganism infection and partly caused by the virus.^{15,16} In the research by Sachdeva et al., maculopapular rash was found in 36.1% cases, and 47% in the study by Casas et al.^{13,18} The rash is resulted from diffuse microvascular vasculitis due to complement activation. Another theory indicates the finding of a high lymphocyte count without eosinophils, edema in the papillary stratum of the dermis, epidermal spongiosis, and lymphohistiocytic infiltrates.¹⁹ A maculopapular rash is often seen in severe COVID-19 disease with a mortality rate of up to 2%, lasting for 7-9 days, and more than 50% cases is accompanied by itching.

Most of the rash is found on the extremities, trunk and mucosa. In addition, the maculopapular rash in some cases appears to resemble lesions

on erythema multiforme.¹⁹ The rash may occur with itching as well as pain. Itching usually appears on the third day and disappears within 8 days.¹⁹ A case report in Indonesia by Putra found a rash or maculopapular lesions on the patient's extremities which was accompanied by pain. These complaints appeared on day 4 and 5 after the fever disappeared.²⁰

Rashes can also occur due to drug allergies, but in this case there had been no history of drug consumption since the previous 15 days. Some diseases could be present with maculopapular lesions, including viral exanthema, scarlet fever, rubella, drug eruptions, and secondary syphilis.¹⁴ The number of different diagnoses of maculopapular rashes presents a challenge for medical personnel to determine the correct diagnosis. Therefore, during the COVID-19 pandemic, it is important to be able to differentiate the etiology of skin rashes to avoid misdiagnosis.

Urticaria was present in 19% of the cases in a study in Spain. These lesions are found in many elderly patients with COVID-19. Lesions are usually accompanied by itching and associated with severe disease with a mortality rate of 2%. Urticaria can appear on the head, trunk, extremities, and palms of the hands and feet. The biopsy finds perivascular lymphocyte infiltrates, eosinophils, and edema in the upper dermis.²¹ Research by Wollina, et al. and Casas, et al. found an association of urticaria lesions with disease severity.²² However, urticaria can also be a clinical manifestation of various other diseases, such as allergic reactions, anaphylactic reactions, and angioedema, or autoimmune diseases, such as lupus erythematosus. Urticaria with fever needs attention because it can be a sign of infection with COVID-19.¹⁵

The relationship between skin manifestations and COVID-19 infection remains unclear. However, there is an opinion regarding the skin manifestations of COVID-19 patients in terms of their pathomechanism. First, the clinical picture of viral exanthema is an immune response to viral nucleotides, and second, skin eruptions are a result of systemic consequences caused by

COVID-19, which lead to vasculitis and thrombotic vasculopathy.²³ In addition, skin manifestations of viral infection are obtained by direct inoculation of the virus, spread and reactivation of viruses from other sites, or interaction of viruses with the immune system in general as a cellular and humoral immune response to specific virus lymphocytes and antibodies. The onset of skin lesions is associated with viremia, and the onset of general symptoms can also be a feature of the pathophysiological skin manifestations in COVID-19 patients. In some cases, skin lesions precede generalized symptoms or may even be the only sign for infection, where it can serve as an important early indicator of a disease or an indicator that the person is a carrier of the virus but asymptomatic. On the other hand, if the skin symptoms occur late during infection or even after resolution of the main symptoms, it is an indicator that the virus is still not clear and includes a cascade of immune response caused by the virus. Viremia often precedes the typical symptoms of COVID-19, and specific viral virology may be false-negative and false-positive due to the cross-reactivity against other types of coronavirus, but it can provide important information about whether or not infection is acute through IgM and IgG analysis.²⁴ As a comparison, the diagnosis of both a rash in COVID-19 or a rash caused by drug eruptions has clinical and histological similarities, making it often difficult to distinguish.¹⁵ Morbilliform rashes on the acral areas can also be caused by vasopressor drugs, hydrochloroquine, or azithromycin. Consequently, in COVID-19 patients who have received a lot of therapy, it is difficult to determine whether the skin manifestations are caused by drug eruptions or because of the actual manifestations of COVID-19. Therefore, evidence that supports both viral causes and drug eruptions is essential.^{15,25}

In this patient, the initial symptom of COVID-19 was the maculopapular rash on the upper and lower extremities as well as the back and lower abdomen. This is similar to the finding of the research by Sachdeva et al., in which maculopapular rash results from diffuse

microvascular vasculitis due to complement activation. A rash may occur with pruritus, pain, or itching. The rash can also occur due to drug allergy.^{13,25} In this case, the patient denied any previous history of drug taking, thereby indicating that the maculopapular rash appeared as a manifestation of COVID-19. This was supported by the results of the nasopharyngeal swab in the patient, which showed a positive COVID-19 result. The cause of skin eruptions that occur in patients with COVID-19 must be distinguished whether they are caused by infection from the virus, systemic consequences, or the drugs they are receiving. Early recognition of cutaneous signs in patients with severe complications and appropriate management is important in patient recovery.¹⁵

This patient also had premature rupture of membranes. Premature rupture of membranes is a rupture of the membranes without signs of labor.²⁶ This can occur in about 10% pregnancies. The cause remains difficult to determine, but some theories suggest that premature rupture of membranes is induced by, among others, the weakness of the amniotic membranes and increased distension pressure in multiple pregnancy, polyhydramnios, macrosomia, and abruption of the placenta.²⁶

COVID-19 infection can cause 8% premature rupture of membranes just as in this patient due to an increase in IL-6 by the activation of macrophages which can lead to increased cytokines.²⁷ The risk factor of the premature rupture of membranes in this case was an infection, which was based on the patient's pain complaint when urinating and results of routine urine examination that show the presence of bacteria. Urinary tract infection can ascend and cause premature rupture of the membranes through the mechanism of elevated cytokines and prostaglandins in the amniotic fluid due to the influence of increased production of pro-inflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor TNF alpha (TNF- α).²⁸

The management of patients with premature rupture of membranes at a gestational age of more than 34 weeks is performed by termination

of the pregnancy to prevent maternal and fetal complications due to premature rupture of membranes.²⁰ The maternal complications, especially chorioamnionitis, can lead to sepsis (3.5-6.4%), while fetal complications can include umbilical cord prolapse, prematurity, and neonatal infection. The choice of per-abdominal termination in this patient was due to the premature rupture of the membranes at term and the patient's COVID-19 condition. To reduce the morbidity and mortality of both the mother and fetus, emergency pregnancy termination becomes the appropriate therapy option for the patient to ensure good outcomes.

CONCLUSION

This patient is a pregnant woman with COVID-19 infection and rare skin manifestations in the form of maculopapular rash and urticaria. For COVID-19 cases with mild symptoms, the manifestation of skin lesions may serve as diagnostic clues for the early detection of infection to obtain better outcomes for the mother and the baby.

CONFLICT OF INTEREST

The authors state that there is no conflict of interest related to this study, the author, and the publication of this article.

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