*Journal of Pakistan Association of Dermatologists*. 2023;**33(3)**:1166-1172.

**Case Report**

# COVID-19 exanthem vs. drug induced maculopapular rash in a pediatric patient: Diagnostic challenge and management strategy

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**Abstract** Exanthem is a diffuse erythematous maculopapular skin eruption secondary to various conditions. Coronavirus disease-2019 (COVID-19) infections may manifest as maculopapular exanthem. A maculopapular rash can also be induced by medications. The distinction between viral exanthem and drug eruption may be challenging. A 4-month-old male infant was admitted in the pediatric department of a tertiary hospital in West Sumatera, Indonesia with diagnosis of post-craniotomy of cerebral abscess and a history of seizures. During admission, patient was consulted to the department of dermatology and venereology due to erythematous macules and papules of the face, trunk, upper and lower extremities without preceding prodromal symptoms. The patient was confirmed positive for COVID-19, almost concurrently with the eruption of maculopapular rash. Patient also get medications which of the drugs were high risk to induce allergic drug eruption, i.e. antibiotics and anticonvulsants. Patient was observed strictly during the administration of those essential drugs with desensitization method. Repetition of nasopharyngeal PCR swab after 2 weeks showed negative conversion, along with the recovery of maculopapular exanthem. Ascertaining a diagnosis of maculopapular exanthem caused can be established through anamnesis, prodromal symptoms, and appearance of cutaneous eruptions. However atypical symptoms often complicate the diagnosis. Dermoscopic, laboratory or histopathological examinations are not specific to rule out differential diagnoses. It has even been reported that viral infections and drugs can elicit cross-reactions that provoke maculopapular exanthem. "*Threating through*" combined with "*Wait and Observe*" methods can be considered in patients with maculopapular exanthem induced by COVID-19 and drugs.

***Key words***
Hypesensitivity reaction; SARS-Cov-2; Viral exanthem.

## Introduction

Coronavirus disease-2019 (COVID-19) is an acute respiratory disease caused by the SARSCoV-2 virus.[1,2] Based on data from the Ministry of Health, Republic of Indonesia until October 2022, there are 6,464,962 confirmed cases of COVID-19 in Indonesia. Globally, cases of COVID-19 in children tend to be lower than in adults. Data from the Indonesian Ministry of Health as of October 2022 shows that among all confirmed cases of COVID-19, 2.5% are children aged 0-5 years.[3]

Pediatric patient with COVID-19 may show nonspecific signs and symptoms. Clinical manifestations of COVID-19 in children can include systemic manifestations beyond respiration symptoms such as fever accompanied by diarrhea, vomiting, shock, involvement of the heart and other organs known as *multisystem inflammatory syndrome* in COVID-19. One of

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the clinical manifestations of Covid-19 on the skin that is often encountered is an exanthematous rash.[1] Maculopapular exanthem has been reported to occur in 47-70% patients due to COVID-19 infection.[4,5]

This report will describe a case of maculopapular exanthem in an infant who was hospitalized after undergoing a neurological surgical procedure, then received high risk medications to induce hypersensitivity reaction. The patient was also infected with COVID-19 during the hospitalization.

**Case report**

A 4-month-old boy was admitted to pediatric in-patient department of a tertiary hospital in West Sumatra, Indonesia. One month prior to admission, the patient had several episodes of fever which the highest temperature reached 39°C. The patient was treated by the pediatric department started on August 11, 2022, as a case of cerebral abscess. Craniotomy for the evacuation of cerebral abscess was carried out during the treatment period (dated August 15, 2022). He still experienced on and off episodes of fever during post-operative period.

On the 19$^{th}$ day of admission (August 29, 2022), the patient experienced erythematous macules and patches on the chest, abdomen, back, both arms and both legs accompanied with irritability and occasional sleep disturbance. The rashes initially appeared on the abdomen and chest area then increased in number and size to involve the face, back, both arms, and both limbs, hence referral to dermatology and venereology department. History of applying creams, lotions or herbal concoctions on patient's body was denied. The patient had a history of lactose milk allergy. Patient's mother denied any history of asthma nor allergic rhinitis in patient. Family medical history was noncontributory. Polymerase chain reaction (PCR) examination of nasopharyngeal swab showed positive COVID-19. During hospitalization patient were treated with various types of drugs with different initiation times and durations of administration, including: intravenous paracetamol; intravenous ampicillin, intravenous gentamycin, intravenous ceftriaxone, intravenous vancomycin, intravenous metronidazole; intravenous phenobarbital, intravenous phenytoin, oral clonazepam, oral acetazolamide, and oral carbamazepine.

Physical examination showed a moderately ill patient with a spastic posture. Vital signs were within normal limits. The patient's body weight was 7.3 kg and the body length was 63 cm. Nutritional status according to WHO was normal. General physical examination was unremarkable. Dermatological examination revealed erythematous papules and patches on the cheeks, chest, abdomen, upper and lower extremities with several area of xerosis **(Figure 1)**. Tidak ditemukan lesi pada konjungtiva, Lesions of the conjunctiva, oral or genital mucosa were absent.

Dermoscopy of the erythematous patches showed patchy erythematous areas, irregularly scattered brown-black dots, and fine scales **(Figure 2)**. Routine hematology examination denoted a normal eosinophil count and elevated segmented neutrophil count. Based on the history, clinical manifestation, physical, dermatologic and ancillary examinations, patient was diagnosed with exanthematous maculopapular rash probably induced by COVID 19 vs. drug reaction. Several medications such as: phenobarbital, clonazepam, phenitoin, ampicillin, gentamycin, ceftriaxone, vancomycin, metronidazole, and acetazolamide were suspected **(Figure 3)**.

Patient was treated with oral cetirizine 0.4 mg/kg

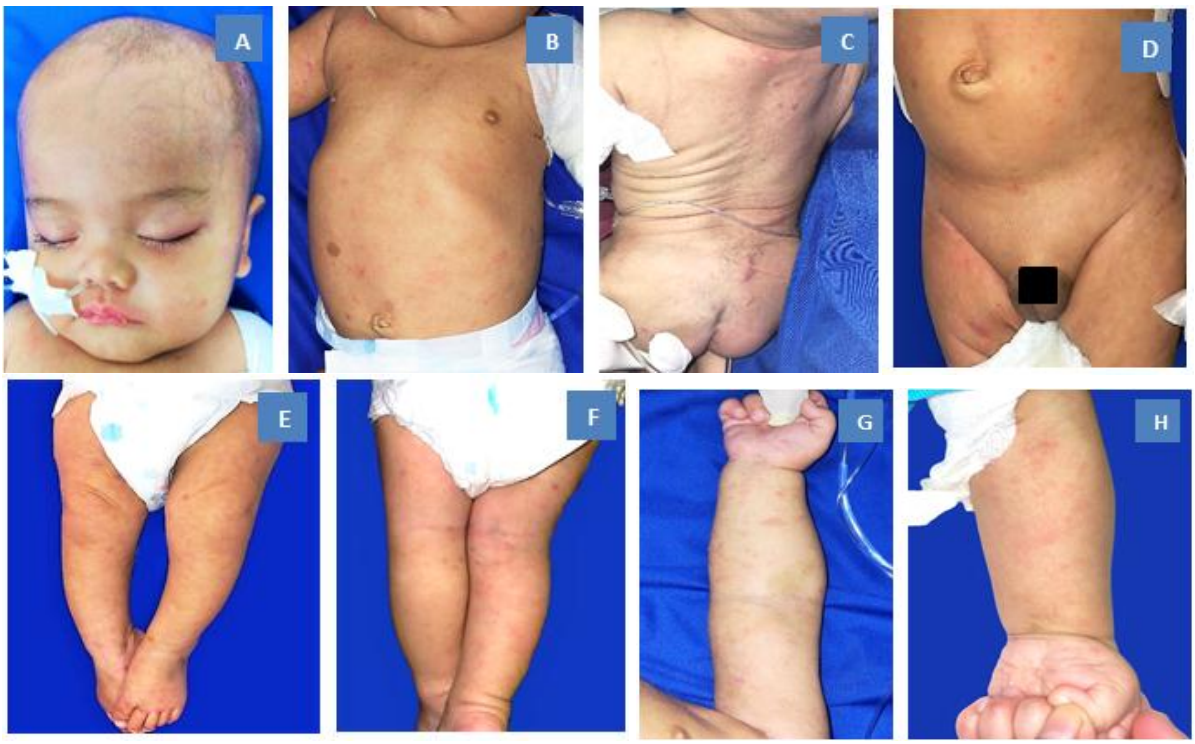


**Figure 1** Dermatologic findings showed multiple erythematous papules and patches with xerosis on the cheeks, chest, abdomen, upper and lower extremities.

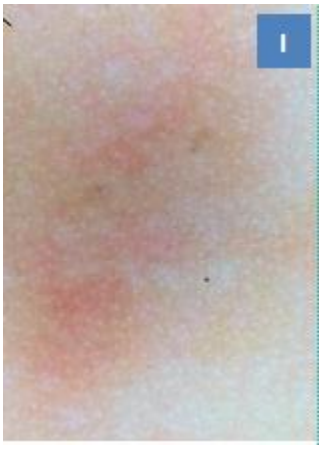


**Figure 2** Dermoscopy of the erythematous patches revealed patchy erythematous areas, irregularly scattered brown-black dots, and accompanied by a slight fine scale.

body weight/ day and 1% hydrocortisone cream applied 2 times a day on the erythematous papules and patches. Naranjo's score[8] indicated a score of +2 for vancomycin, ceftriaxone, phenytoin, klonazepam, phenobarbital, ampicillin, gentamicin, and acetazolamide, while for paracetamol and metronidazole it gave a Naranjo score of +1. These drugs are suspected (possible) to be the contributing factor of exanthem in patient.

During the observation period, there was noted several episodes of maculopapular rash eruptions, especially after the administration of ceftriaxone and vancomycin antibiotics. Thus, the two antibiotics were discontinued and substituted with meropenem administered intravenously with desensitization method. Systemic administration of corticosteroids was not performed to identify drugs that were suspected to play a role in causing exanthem in this patient.

PCR examination of the nasopharyngeal swab was repeated 2 times with an interval of 7 days. Negative results were obtained after 14 days from the initial test accompanied by improvement of exanthem symptoms in this patient.

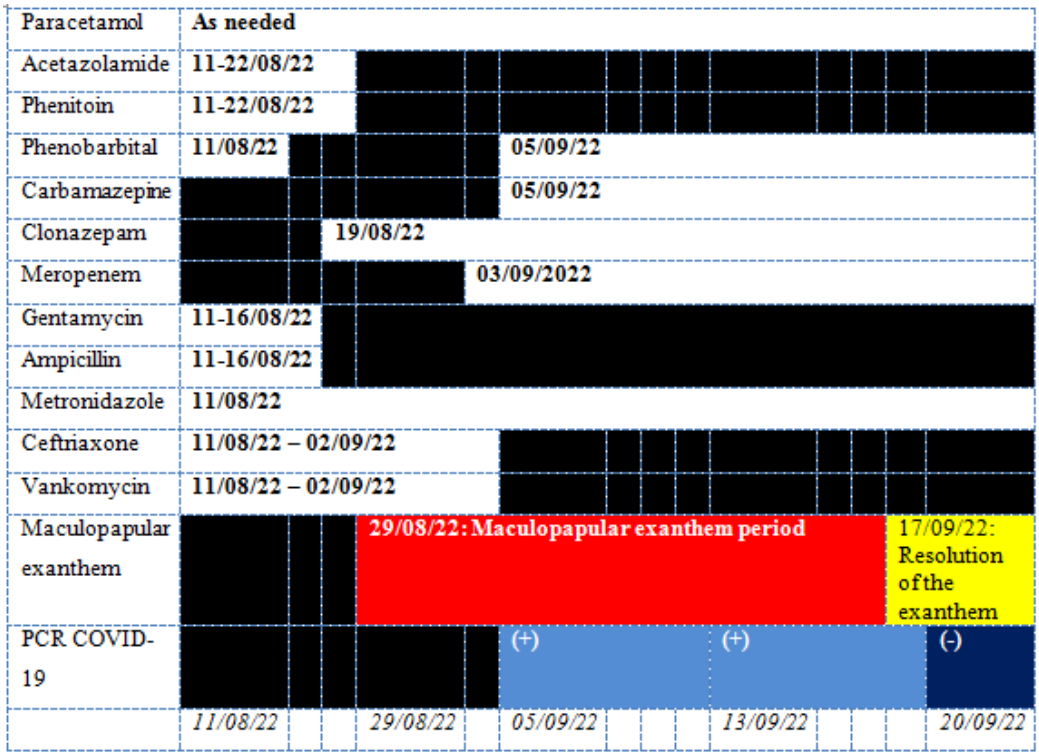


**Figure 3** Initiation time and duration of administration of suspect drugs vs. Onset and duration of maculopapular exanthem vs. COVID-19 PCR results.

## Discussion

We report a 4-month-old boy with cerebral abscess who experienced maculopapular exanthem on the 19th day of admission at our institution. The patient was confirmed positive for COVID-19 through PCR. During admission, patient was treated with various drugs. Viral exanthem is often difficult to distinguish from maculopapular type drug eruption. Exanthematous drug eruption also called maculopapular or morbiliform eruption may mimic myriad diseases such as viral exanthem with lower systemic involvement.[9]

Maculopapular rashes mostly appear in the prodromal phase or can also coincide with COVID-19 symptoms and have an average duration of 8.6 days. Some opinions consider maculopapular lesions not very useful for the diagnosis of COVID-19 due to their possible relationship with other causes, including drug reactions.[4] Patient in this report did not experience prodromal symptoms, making it difficult to distinguish from cutaneous drug reactions. However, the appearance of the rash almost coincides with the time of diagnosis of COVID-19 in this patient. The correlation between exanthema in this patient with COVID-19 infection is highly possible but the possibility of a drug-induced exanthem risk factor still exist.

Maculopapular drug eruptions mostly appear within 7-10 days (ranged 5–21 days) after exposure to the suspected drug.[7,10] Drugs that often cause maculopapular eruption are the β-lactam class antibiotics and sulfonamides, phenytoin, carbamazepine phenobarbital, pyroxicam, allopurinol, nevirapine, etc.[11] In this patient, suspected drugs that possibly induce maculopapular eruptions in this patient was administered within 10 to 18 days before the exanthem appear so that the possibility of rashes

caused by drugs cannot be ruled out.

The eruption of drug-induced exanthem starts from the trunk then spreads to the face and both extremities. This sentimental pattern is different from viral exanthema disease which has a centrifugal pattern and exanthema is rarely accompanied by pruritus.[12] In a case report by Freeman, *et al.*, maculopapular exanthem in COVID-19 are usually localized in the trunk and extremities, and are often accompanied by pruritus.[13] Patient in this case report showed a centrifugal pattern of disease spread similar with the pattern in drug-induced exanthem. Unfortunately, subjective complaints such as pruritus could not be assessed in this patient due to patient's age.

Dermoscopic features of maculopapular exanthem induced by COVID-19 have not been reported. Dermoscopy image in this patient showed a vague picture of erythema with a hint of evenly distributed brown-black dots accompanied by fine scales. Brown-black dots, describe melanin in the epidermis, while erythema describes the presence of vasodilation. Drug-induced maculopapular exanthem dermoscopy picture shows a nonspecific picture of erythema.[14] Dermoscopy has a low specificity to distinguish maculopapular exanthem caused by viral infection vs. drug eruption.

The histological findings of the drug induced exanthem are also often indistinguishable from the exanthem of the virus. Various studies have evaluated certain histopathological features for drug- and virus-induced exanthema, but the results are not pathognomonic.[7,10] Thus histopathological examination was not carried out in this patient.

The link 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 pathomechanisms. First, the clinical picture of the viral exanthem is the immune response to the viral nucleotide, and secondly, the skin eruption is the result of systemic consequences caused by COVID-19, which causes vasculitis and thrombotic vasculopathy. In addition, skin manifestations of viral infection are obtained by direct inoculation of the virus, the spread and reactivation of the virus from other sites, or the interaction of the virus with the immune system in general as a cellular and humoral immune response to certain viral lymphocytes and antibodies.[9]

Maculopapular rash is a common clinical manifestation of drug allergy which is similar to viral exanthem. Several additions of viral infection entities are included for drug-induced exanthem ("*rubeola-like*" or "*measles like"* exanthemas) and the differences are difficult to be determined during the acute phase. Discontinuation of highly suspected medications that have the potential to cause severe symptoms are usually essential, although *"threating through"* strategy can be considered also as an option while still administering the essential live saving suspected drugs with close monitoring is important.[9] Patient in this report was managed with *"threating through"* method, where administration of essential suspected drugs (i.e. antibiotics and neurologic drugs) with desensitization methods and strict observation of the possible severe allergic reactions were performed.

Viral infections are also reported as co-factors for immune stimulation. A number of clinical observations suggest that viral infections as a predisposing factor or aggravating factor of drug-related skin rashes. The interaction between immunity to the virus and drug hypersensitivity is complex. The drug can induce the formation of neo-antigens recognized

by virus-specific memory T cells. These memory T cells can cross-react with haptenated endogenous peptides on HLA (Human Leukocyte Antigen), or drugs that bind to T-cell receptors and/or MHC (Major Histocompatibility Complex). Virus has been shown to cause cell damage, enhance inflammatory responses, induce production of specific antibodies, provoke changes in antigenic expression, and stimulate T-cell replication. In addition, the drug can increase viral replication, which can then result in an eruption in the skin.[9] The presence of cytokine storms in COVID-19 can facilitate drug reactions, known as slow-type hypersensitivity reactions that are mainly mediated through TNF-α and interleukin-12.[15]

Management of maculopapular exanthem caused by COVID-19 varies according to clinical severity. Topical corticosteroids can be sufficient in most cases, systemic corticosteroids that are worth giving only in a more severe and extensive presentation.[12] Management of maculopapular exanthema caused by drug eruptions is supportive therapy. Pruritus can be treated with topical steroids, emollients, or oral antihistamines.[16] Patient in this case was treated with "threating through" and also "wait and observe" strategy. Oral antihistamines and topical steroids were also added as a supportive therapy.

## Conclusion

Distinguishing viral exanthema with maculopapular drug reactions is a challenge in establishing a diagnosis. Laboratory tests and histopathology do not help much. Some research suggests that viral infections can also play a role as a predisposing factor or intensifying drug-related skin rashes. Strict observation management strategies, supportive therapy and drug desensitization are recommended in patients with maculopapular exanthema who suffer from COVID-19 and receive various medicamentous therapies that are at high risk of causing allergic reactions.

## References

1. Burhan E, Susanto AD, Nasution SA, Eka G, Pitoyo W, Sssilo A, *et al*. Tatalaksana Covid-19 pada Anak, Remaja, dan Neonatus. In: Burhan E, Susanto AD, Nasution SA, *et al*., ed. Pedoman tatalaksana COVID-19. 4 ed.;2022:91–145.
2. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Published 2022. Diakses Oktober 20, 2022. https://covid19.who.int/
3. Kementrian Kesehatan Republik Indonesia. COVID 19 Indonesia. Published 2022. Diakses Oktober 20, 2022. https://covid19.go.id/id/peta-sebaran
4. Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, *et al*. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol*. 2020;**183(1)**:71–77. doi:10.1111/bjd.19163
5. De Giorgi V, Recalcati S, Jia Z, Chong W, Ding R, Deng Y, *et al*. Cutaneous manifestations related to coronavirus disease 2019 (COVID-19): A prospective study from China and Italy. *J Am Acad Dermatol*. 2020;**83(2)**:674–675.
6. Hina A, Masood S, Jamil S, Tabassum S, Jalil P, Ghulam U. Prevalence of Clinical Spectrum of Cutaneous Adverse Drug Reactions in Patients Presenting at a Tertiary Care Hospital in Pakistan. *Cureus*. 2021;**13(4)**: e14568. doi:10.7759/cureus.14568
7. Khandpur S, Ahuja R. Drug-Induced vs. Viral Maculopapular Exanthem-Resolving the Dilemma. *Dermatopathology*. 2022; **9(2)**:164–171. doi:10.3390/dermatopathology9020021
8. Naranjo C, Busto U, Sellers E, Sandor P, Ruiz I, Roberts EA, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981; **30(2)**:239–245.

9. Anci E, Braun C, Marinosci A, Rodieux F, Midun E, Torres MJ, *et al*. Viral Infections and Cutaneous Drug-Related Eruptions. *Front Pharmacol*. 2021;**11**:586407. doi:10.3389/fphar.2020.586407
10. Tsabouri S, Atanaskovic-Markovic M. Skin eruptions in children: Drug hypersensitivity vs viral exanthema. *Pediatr Allergy Immunol*. 2021;**32(5)**:824–834. doi:10.1111/pai.13485
11. Heelan K, Sibbald C, Shear NH. Cutaneous Reactions to Drugs. In: Kang S, Amagai M, Bruckner AL, *et al*., ed. Fitzpatrick's Dermatology in General Medicine 9th ed. 9th ed. McGraw-Hill; 2019:749–764.
12. Genovese G, Moltrasio C, Berti E, Marzano AV. Skin Manifestations Associated with COVID-19: Current Knowledge and Future Perspectives. *Dermatology*. 2021;**237(1)**:1–12. doi:10.1159/000512932
13. Freeman EE, Mcmahon DE, Lipoff JB, Rosenbach M. The spectrum of COVID-19eassociated dermatologic manifestations: An international registry of 716 patients from 31 countries. *J Am Acad Dermatol*. 2020;**83**:1118–29.
14. Rossi G, Da Silva Cartell A, Marchiori Bakos R. Dermoscopic Aspects of Cutaneous Adverse Drug Reactions. *Dermatol Pract Concept*. 2021; **33(1)**:e2021136. doi:10.5826/dpc.1101a136
15. Ergun T, Ergenç İ, Seven S, Seçkin D, Özer EC, Aktaş M, *et al*. Drug eruption: A mimicker of Coronavirus disease-2019 rash. *Turkderm Turkish Arch Dermatology Venereol*. 2022;**56(1)**:34–38. doi:10.4274/turkderm.galenos.2021.29904
16. Crisafulli G, Franceschini F, Caimmi S, Bottau P, Liotti L, Saretta F, *et al*. Mild cutaneous reactions to drugs. *Acta Biomed*. 2019;**90(Suppl 3)**:36-43. doi:10.23750/abm.v90i3-S.8159.