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Original article

Unusual extrapulmonary manifestations of covert COVID-19: a case series at a tertiary care hospital in Bali, Indonesia

Ida Bagus Suparyatha[1], Dyah Kanya Wati[1], I Nyoman Budi Hartawan[1], Vanessa Lini Gunawan[1], Andreas Dhymas Dhyna Martha Kelana[1], Ivy Cerelia Valerie[2]

[1]Department of Child Health, Faculty of Medicine, Udayana University/Sanglah General Hospital, Denpasar, Bali, Indonesia

[2]Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia

Abstract

One of the most challenging issues in facing the Coronavirus Disease (COVID-19) pandemic relies on the considerable uncertainty of the extent of its involvement. The wide spectrum of manifestations, ranging from generally milder manifestations to Multisystem Inflammatory Syndrome, and the concurrence with other disease entities substantially obscure clinical diagnosis. Diagnostic pitfalls persisted despite advancement in diagnostic criteria and modalities. We present a case series of confirmed COVID-19 cases in a tertiary hospital in Bali, Indonesia, with fever as the sole presenting feature and diagnostic hint.

Keywords

SARS-CoV-2, COVID-19, Multisystem Inflammatory Syndrome in Children, non-respiratory, Pediatric Emergency Medicine, Indonesia.

Corresponding author

Dyah Kanya Wati, Pediatric Consultant and PhD (Indonesia University, Indonesia), Department of Child Health, Faculty of Medicine, Udayana University/Sanglah General Hospital, Jalan Diponegoro Dauh Puri Klod, Denpasar, Bali 80113, Indonesia; telephone: +62361-227911; fax: +62361-227911; ORCID ID: 0000-0002-6633-7445; e-mail: dyahkanyawati@unud.ac.id.

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Introduction

The multisystemic nature of Coronavirus Disease 2019 (COVID-19) infection was first recognized in May 2020, at its extreme life-threatening form of hyperinflammatory shock developed in previously otherwise healthy children [1]. This distinct constellation of manifestations was further defined by the Centers for Disease Control and Prevention (CDC), Royal College of Paediatrics and Child Health (RCPCH), and World Health Organization (WHO), while the terminology Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 infection (PIMS-TS) or Multisystem Inflammatory Syndrome in Children (MIS-C) was coined [2-4]. Extensive researches were carried out to figure other plausible linkages to non-respiratory manifestations of COVID-19, although the majority of this search was still uncertain [5, 6].

Established definition for MIS-C required several advanced inflammatory parameters that are not routinely assessed and, therefore, may hinder the diagnostic investigation and timely treatment when a clinically suspected case presents in emergency settings [7]. The concurrent possibility of multisystemic and covert COVID-19 manifestations also contributes to the diagnostic enigma. We hereby report a case series of multisystemic manifestations in COVID-19 infected patients originating from local transmission areas presented in an emergency setting.

Case description

Case 1

A previously healthy 14-year-old female presented on the fifth day of intermittent fever with a peak temperature of 39°C. She also complained of abdominal pain with black, tarry, and dense stool, which she never experienced before (**Tab. 1**). Notable physical findings included right upper

Table 1. Demographics, clinical and laboratory features, and outcome of the three cases.

Parameters	Case 1	Case 2	Case 3
Age, sex	14 year, F	10 year, M	1 month, M
Symptoms	Fever, black stool	Fever, decrease of consciousness, seizure	Fever, decrease of consciousness, seizure
Diagnosis	Confirmed case of COVID-19	Dengue shock syndrome, dengue encephalopathy, confirmed case of COVID-19	Intracranial bleeding due to vitamin K deficiency secondary to cholestasis
Comorbidities	No	No	Yes
Glasgow Coma Scale	E4V5M6	E2V2M4	E2V3M4
Blood pressure (mmHg)	90/60	81/70	-
Heart rate (beats/min)	92	152	130
Respiratory rate (times/min)	16	31	38
Temperature (°C)	36.7	36.9	37.2
Oxygen saturation	95-98%	90%	100%
White blood count (10^3/μL)	4.11	10.04	18.10
Neutrophils (10^3/μL)	0.75	7.03	7.56
Lymphocytes (10^3/μL)	2.75	2.14	8.38
Neutrophils to lymphocytes ratio	0.27	3.29	0.90
Hemoglobin (mg/dL)	14.67	10.31	4.33
Platelets (10^3/μL)	42.48	122.8	559.001
Timing of first RT-PCR (from fever onset)	5th day	6th day	3rd day
First RT-PCR	Negative	Positive (Ct value: 33.53)	Positive (Ct value: 29.67)
Second RT-PCR	Positive (Ct value: 35.02)	-	Positive (Ct value: 32.22)
Anti-SARS-CoV-2 IgM	-	Positive	Negative
Anti-SARS-CoV-2 IgG	-	Negative	Negative
Anti-dengue IgM	Negative	Negative	-
Anti-dengue IgG	Positive	Positive	-
Outcome	Discharged	Death	Discharged

COVID-19: Coronavirus Disease 2019; Ct value: cycle threshold value; F: female; M: male; RT-PCR: real-time reverse transcriptase-polymerase chain reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

abdominal tenderness with a negative tourniquet test. Laboratory findings revealed neutropenia and thrombocytopenia. Further laboratory investigations revealed elevated (0.7 μg/mL) D-dimer (normal value < 0.5 μg/mL) with normal C-reactive protein (CRP) and procalcitonin values. No abnormalities could be detected on her chest X-ray result (**Fig. 1**). There was no indication for more advanced supporting examinations. She tested negative on real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for COVID-19 conducted on admission day. Consequently, symptomatic management consisting of fluid replacement therapy and antipyretic agent was administered. However, on the third day of admission, or the ninth day of fever, the dengue serological test was positive for IgG and negative for IgM; while the second RT-PCR COVID-19 was positive with cycle threshold (Ct) value of 35.02. The final assessment for this case was confirmed COVID-19 case, and the patient was discharged after 12 days and with no sequelae.

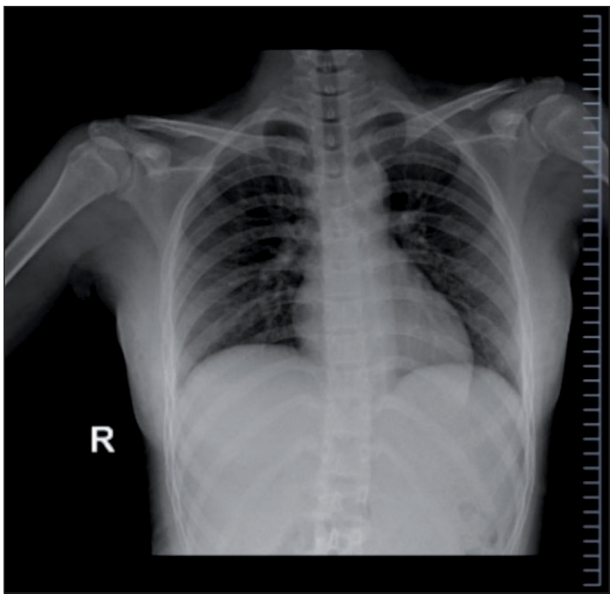

Figure 1. Case 1. Normal chest radiographic appearance.

Case 2

A 10-year-old male with no known comorbidities was referred due to decreased consciousness 11 hours before admission. He was reported to have a blank stare and did not respond to any stimulus with ensuing generalized involuntary jerky movements with upward eye deviation. He had an intermittent fever for 6 days, with the highest temperature of 38.5°C. Physical examination revealed a decrease of consciousness, hypotension, tachycardia, tachypnea, decreased oxygen saturation, and delayed capillary refill time (> 2 seconds) (**Tab. 1**). Prereferral (61-95 × 10^3/μL) and latest (122.8 × 10^3/μL) laboratory results demonstrated thrombocytopenia (normal range: 150-440 × 10^3/μL). He tested positive in IgM anti-Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) assay and IgG anti-dengue virus assay. He was diagnosed with dengue encephalopathy with decompensated dengue shock syndrome, whereas the COVID-19 status was not confirmed yet. He was admitted to the Pediatric Intensive Care Unit and given fluid resuscitation, antibiotics, and supportive therapy. His hemodynamic status deteriorated despite optimal treatment and this case, unfortunately, ended with mortality. The postmortem RT-PCR showed positive for COVID-19.

Case 3

A 1-month-old male was referred for a decrease of consciousness. He had a history of 2 episodes of generalized tonic seizures lasting less than 1 minute each and was documented to have projectile vomiting. Three days prior to admission, he had intermittent fever with the highest temperature of 38.5°C, with accompanying spontaneous bleeding in his right ear. Any history of trauma was denied by his mother. His mother reported a history of yellow discoloration of his sclera for 3 weeks after birth. He was born spontaneously with midwife assistance, measuring 3,200 grams in weight and 51 cm in length. The history of vitamin K administration was unclear. The physical examination showed large bulging fontanelle, eye discharge and conjunctival pallor, and pale skin. Positive Babinski reflex was found in routine neurologic examination. From the laboratory parameters, elevated levels of white blood count and platelet were observed (**Tab. 1**). Cholestasis was confirmed with elevated total (2.2 mg/dL) and direct (1.41 mg/dL) bilirubin levels. His liver function and coagulation test values were within the normal limit. The CRP (8.39 mg/L), lactate dehydrogenase (LDH) (994 U/L), and D-dimer (0.87 μg/mL) levels were increased, despite normal procalcitonin level. Two separate RT-PCR tests turned out positive. Imaging study by chest X-ray was not suggestive of any focal infection (**Fig. 2**) and head computed tomography (CT) scan without contrast revealed intracranial hemorrhage (**Fig. 3**). He was assessed with intracranial bleeding with suspected vitamin K deficiency secondary to intrahepatic cholestasis, severe anemia, and

Figure 2. Case 3. The focus of infection was not identified clearly in chest radiograph.

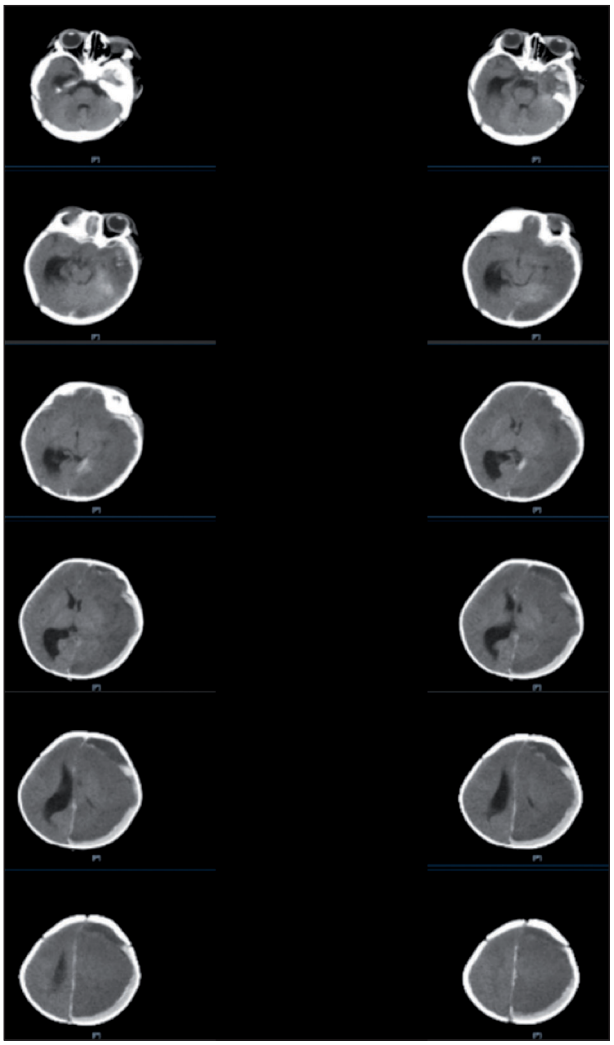

Figure 3. Case 3. Head computed tomography (CT) scan without contrast revealed acute on chronic subdural hematoma on left fronto-temporo-parieto-occipital regions to interhemispheric fissure that caused compression on left lateral ventricle and right midline shift (± 6.6 mm), subarachnoid hemorrhage of left temporal lobe, cerebral edema, and right bilateral ethmoidal and maxillary sinusitis.

confirmed COVID-19, and was given supportive therapy and planned to undergo subdural tapping after clinical improvement and stabilization. He was hospitalized for 9 days in the isolation ward and de-isolated after the de-isolation criteria were fulfilled.

Discussion

The emerging COVID-19 pandemics remains a significant diagnostic challenge for clinicians worldwide. This is especially true for pediatric cases presenting in emergency settings with fever and negligible clue for respiratory system involvement. The milder manifestation of COVID-19 in the pediatric population was well-observed, yet the possible combination with various non-respiratory manifestations and severe progression to MIS-C would render the overall clinical spectrum of COVID-19 unclear [5]. The unaddressed gap in COVID-19 perplexing clinical diagnosis is even more pronounced in emergency cases where risk-benefit balancing management strategy is at stake. We reported three cases of confirmed COVID-19 without evident respiratory symptoms and their unique diagnostic challenge.

The current case series highlighted intermittent fever as the sole clinical feature leading to the diagnosis of COVID-19. It supported the finding in a recent review by Ali et al. [8], which reported the frequent occurrence of fever and respiratory symptoms, despite the fact that they are not considered the hallmark of this disease. Due to the relatively delayed presentation of these cases, the fever had subsided by the time of admission, and the absence of unremitting fever reduced the likelihood of extreme inflammation [9]. This finding justified the role of fever in triage and as one of the indications for screening of severe disease [10, 11]. Laboratory parameters, including RT-PCR and serology tests, were consistent for case positivity and disease resolution based on increasing Ct values and IgM and IgG level dynamics [12, 13].

Consideration of dengue infection in hyper-endemic areas like Indonesia is an integral part of febrile patient assessment, particularly taking into account the shared characteristics and possible interactions between dengue and COVID-19 [14, 15]. Both cases tested for anti-dengue virus antibody showed the identical result of single reactive IgG without IgM reactivity. Careful interpretation of this result yielded two possibilities: dengue infection or serological cross-reactivity with COVID-19 [16, 17]. Given the limitation of the circumstances, a

confident conclusion could not be drawn for this context, and management was adjudicated on clinical grounds.

Unusual gastrointestinal and neurologic manifestations were reported in prior studies concerning severe COVID-19 [18, 19]. The gastrointestinal symptom was reported as the prominent clinical feature of MIS-C. Only two cases of melena were reported in a recent systematic review of MIS-C cases [20], while a case series described that this phenomenon is self-limiting in adult patients [21]. Existing evidence on altered mental status and seizure in severe COVID-19 were conflicting, and it was not clear whether viral encephalitis and cerebrovascular disease reported were directly related to COVID-19 [6].

There were some noteworthy multisystemic involvements as implied in both clinical and laboratory findings in the aforementioned cases. We closely followed the most recent national protocol [22] and, in spite of partially fulfilled criteria of MIS-C, further investigations were hampered by resource availability and the discrepancy between variable immediate circumstances and guideline scope. The combinations of clinical and supportive investigations were not fully explained by uncomplicated COVID-19, main differential diagnosis, nor the underlying disease. These case series were expected to supplement existing evidence and improve the awareness of important non-respiratory findings in the constantly evolving understanding of COVID-19.

Conclusion

We reported three cases of confirmed COVID-19 with non-respiratory manifestations as the predominant presenting symptoms. Future epidemiological and clinical studies are required to confirm possible extrapulmonary involvement of COVID-19, as it would greatly enhance the screening algorithm, specifically in emergency settings.

Ethical clearance

Ethical approval was obtained in this study and protocols were approved by the Ethical Committee of Medical Faculty of Udayana University/ Sanglah General Hospital.

Declaration of interest

The Authors have nothing to disclose. The Authors have no support or funding to report.

References

1. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395(10237):1607-8.
2. Centers for Disease Control and Prevention. Emergency preparedness and response. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Available at: https://emergency.cdc.gov/coca/calls/2020/callinfo_051920.asp, date of publication: 19 May 2020, last access: 09 February 2021.
3. Royal College of Paediatrics and Childrens Health. Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Available at: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf, last access: 09 February 2021.
4. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19. Available at: https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19, date of publication: 15 May 2020, last access: 09 February 2021.
5. Pousa PA, Mendonça TSC, Oliveira EA, Simões-e-Silva AC. Extrapulmonary manifestations of COVID-19 in children: a comprehensive review and pathophysiological considerations. J Pediatr (Rio J). 2020 Sep 22. [Epub ahead of print].
6. AlSamman M, Caggiula A, Ganguli S, Misak M, Pourmand A. Non-respiratory presentations of COVID-19, a clinical review. Am J Emerg Med. 2020;38(11):2444.
7. Simon Junior H, Sakano TMS, Rodrigues RM, Eisencraft AP, de Carvalho VEL, Schvartsman C, Reis AGADC. Multisystem inflammatory syndrome associated with COVID-19 from the pediatric emergency physician's point of view. J Pediatr (Rio J). 2020 Sep 11. [Epub ahead of print].
8. Ali AS, Al-Hakami AM, Shati AA, Asseri AA, Al-Qahatani SM. Salient conclusive remarks on epidemiology and clinical manifestations of pediatric COVID-19: Narrative review. Front Pediatr. 2020;8:584694.
9. Gul MH, Htun ZM, Inayat A. Role of fever and ambient temperature in COVID-19. Expert Rev Respir Med. 2020;2020:17476348.2020.1816172.
10. Zhang J, Zhang L, Yin Y, Lu Q, Hong JG, Zhang XB, Zhou XJ, Wang LB, Zhang JH, Lu M, Dong XY, Shao J, Lu YM, Yu J, Gu L; Respiratory Disease Group, Pediatric Committee of Shanghai Medical Association, Shanghai, China. Best practice for infection prevention in pediatric respiratory clinics during the COVID-19 epidemic. World J Pediatr. 2020;16(4):326-32.
11. DeLaroche AM, Stankovic C, Ehrman RR, Noble J, Arora R, Maksimowski K, Ruffing RP. Emergency department screening for multisystem inflammatory syndrome (MIS-C) in children. Am J Emerg Med. 2020 Sep 29. [Epub ahead of print].

12. Rao SN, Manissero D, Steele VR, Pareja J. A narrative systematic review of the clinical utility of cycle threshold values in the context of COVID-19. Infect Dis Ther. 2020;9(3): 573-86.
13. Carlotti APCP, de Carvalho WB, Johnston C, Gilio AE, de Sousa Marques HH, Ferranti JF, Rodriguez IS, Delgado AF. Update on the diagnosis and management of COVID-19 in pediatric patients. Clinics (Sao Paulo). 2020;75:e2353.
14. Harapan H, Michie A, Mudatsir M, Sasmono RT, Imrie A. Epidemiology of dengue hemorrhagic fever in Indonesia: Analysis of five decades data from the National Disease Surveillance. BMC Res Notes. 2019;12:350.
15. Harapan H, Ryan M, Yohan B, Abidin RS, Nainu F, Rakib A, Jahan I, Emran TB, Ullah I, Panta K, Dhama K, Sasmono RT. Covid-19 and dengue: Double punches for dengue-endemic countries in Asia. Rev Med Virol. 2020;2020:e2161.
16. Raafat N, Blacksell SD, Maude RJ. A review of dengue diagnostics and implications for surveillance and control. Trans R Soc Trop Med Hyg. 2019;113(11):653-60.
17. Lustig Y, Keler S, Kolodny R, Ben-Tal N, Atias-Varon D, Shlush E, Gerlic M, Munitz A, Doolman R, Asraf K, Shlush LI, Vivante A. Potential antigenic cross-reactivity between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and dengue viruses. Clin Infect Dis. 2020;2020:ciaa1207.
18. Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis KG. Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children that is related to coronavirus disease 2019: A single center experience of 44 cases. Gastroenterology. 2020;159(4):1571-4.e2.
19. Panda PK, Sharawat IK, Panda P, Natarajan V, Bhakat R, Dawman L. Neurological complications of SARS-CoV-2 infection in children: A systematic review and meta-analysis. J Trop Pediatr. 2020;2020:fmaa070.
20. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, Acosta S, Naqvi R, Burmeister-Morton F, Burmeister F, Tarriela A, Petershack M, Evans M, Hoang A, Rajasekaran K, Ahuja S, Moreira A. Multisystem inflammatory syndrome in children: A systematic review. EClinicalMedicine. 2020;26:100527.
21. Barrett LF, Lo KB, Stanek SR, Walter JW. Self-limited gastrointestinal bleeding in COVID-19. Clin Res Hepatol Gastroenterol. 2020;44(4):e77-80.
22. Indonesian Society of Respirology; Indonesian Heart Association; Indonesian Society of Internal Medicine; Indonesian Society of Anesthesia and Intensive Therapy; Indonesian Pediatric Society. Concise COVID-19 management protocol. Available at: https://www.kemkes.go.id/article/view/20092400001/buku-saku-protolol-tatalaksana-covid-19-di-indonesia.html, date of publication: 23 September 2020, last access: 09 February 2021.