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Case Report

Diagnosis challenges of often-overlooked infectious mononucleosis in Indonesia: to what extent do we need to explore common viral exanthems further

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ABSTRACT

Although the diagnosis of viral exanthema is relatively common, the specific cause of them is rarely identified due to their benign natural history. Infectious mononucleosis (IM), one of the most common causes of viral exanthema, is frequently overlooked in Indonesia due to its nonspecific symptoms that mimic other much more common diseases such as dengue fever and bacterial infections, with a more unpredictable outcome. This diagnostic challenge is particularly pronounced in children, where overlapping clinical features complicate identification and management. We present a case of a young female with IM, which have previously been epidemiologically diagnosed with another condition. Our case highlights the need for increased clinical awareness and tailored treatment approaches to address the unique needs of paediatric patients, especially in a setting of individuals with diverse cultural and ethnical backgrounds. Individualized care is essential to improve outcomes and prevent complications, emphasizing the importance of accurate diagnosis and appropriate management in resource-limited settings.

Keywords: Infectious mononucleosis, Complications, Viral exanthemas

INTRODUCTION

Infectious mononucleosis (IM) is an acute viral infection, mostly caused by Epstein-Barr virus (EBV), which affects the mononuclear macrophage system.[1] This disease usually affects older children to young adults aged 15-25 years-old in developed countries, but it is more commonly found in infants and young children in developing countries. Due to its ubiquitous nature, data has shown that nearly 95% of adults worldwide have had EBV infection.[2] Data in Indonesia regarding infectious mononucleosis is still very limited. Clinical manifestation varies among individuals and age group since older children may possess a stronger host immune response.[1] Antibiotics are not indicated in the treatment of IM. However, some patients may have received antibiotics since IM may be misdiagnosed as bacterial infection. As a result, it increases the risk of patient developing skin rash.[3] Despite the advances in current medical knowledge, it is not unexpected that there is currently no international standard diagnostic procedure for the laboratory research and testing for IM. Generally, IM is a self-limiting disease. However, complications such as decreased liver function, airway obstruction, and splenic rupture may occur if patient is undertreated, which may lead to serious organ damage.[1,4]

CASE REPORT

A 12-year-old Caucasian girl was occupied with her mother to the office with chief complaint of non-itchy, non-tender rashes all over her body for 1 day prior to the

visit. The patient had fever and for 2 days which responded to antipyretics. She also had a partially resolving sore throat for 2 days being treated with syrup for rash. The patient was also given antibiotics for 1 day. The patient had not gone for a checkup for her current symptoms and were only given self-medications by her mother. History of nausea, vomiting, coughing, runny nose, red eye, joint pain, abdominal pain, and changes in bowel movements were denied. She was capable of peroral feeding. Immunisations were complete and up to date for her age.

The patient has had no similar symptoms before. The patient has no known allergies to food and drugs. History of atopy was denied. History of similar symptoms in the family were denied. History of similar symptoms of her friends in school were denied, although some of her peers were reported to had had sore throat. The patient does ballet and some contact sports at school. She was self-medicated with paracetamol 250 mg/5 ml syrup, 10 ml every 8 hours PO, betamethasone 0.25 mg+dexchlorpheniramine maleate 2 mg/5ml syrup, 5 ml every 8 hours PO, cefadroxil 250 mg/5ml syrup every 12 hours PO, and hydrocortisone 1% cream on rash areas topically, started 2 days prior to examination.

On examination, the patient appeared stable, and was 150 cm in height, 40 kg in weight. BMI was 20.4 (25th to 50th percentile by BMI-to-age according to WHO charts). Blood pressure was 112/68 mmHg, pulse rate 92 beats per minute, respiratory rate 18 times per minute, axillary temperature 36.8oC, oxygen saturation 98% on room air, pain score 1/10.

Patient was normocephalic, no anaemic conjunctivae and icteric sclerae were observed. There were no enlargements of cervical, subclavicular, and axillary lymph nodes. Pharynx appeared hyperaemic and oedematous bilaterally. Tonsils were normal with no detritus present. No strawberry tongue and Koplik spots were seen. Chest examination showed normal and regular heart sounds without murmurs. Equal vesicular sounds were heard on all lung areas, without rhonchi and wheezing. Abdomen was soft, bowel sounds were present and within normal limits, and there was a mild tenderness during palpation of the left lower quadrant of the abdomen. No hepatomegaly was observed. However, splenomegaly (Hackett stage I) was noted on examination. Extremities were warm with no oedema.

Table 1: Modified centor score (McIsaac).

Criteria	Score
Fever (> 38°C)	0
Absent cough	0
Painful and enlarged anterior cervical lymph node	0
Tonsillar hypertrophy and exudate	0
Age 3-14 years	1
Total score	1

Table 2: Initial laboratory examination results.

Examination	Patient's value	Reference value
WBC count	12,480/µl	4,500 -11,000/µl
Lymphocytes%	55%	20-40%
Eosinophils%	3%	2-4%
Neutrophils%	35%	40-70%
Haemoglobin (Hb)	12.5 g/dl	12.0-15.0 g/dl
Haematocrit (HCT)	37%	36 – 44%
Platelet count	140,000/µl	150,000-450,000/µl
RDW	13%	11.5-14.5%
Anti-EBV IgM	Negative	Negative
Anti-EBV IgG	Positive	Negative
AST	82 U/l	10–40 U/l
ALT	74 U/l	7–56 U/l
Anti-HIV	Non-reactive	Non-reactive
NS-1Ag dengue	Negative	Negative

Table 3: Follow-up laboratory examination results one week after initial examination.

Examination	Patient's value	Reference value
WBC count	8,200/µl	4,500-11,000/µl
Lymphocytes%	30%	20–40%
Eosinophils%	3%	2–4%
Neutrophils%	65%	40–70%
Haemoglobin (Hb)	12.8 g/dl	12.0 – 15.0 g/dl
Haematocrit (HCT)	39%	36 – 44%
Platelet count	188,000/µl	150,000-450,000/µl
RDW	12.8%	11.5-14.5%
Anti-EBV IgM	Positive	Negative
Anti-EBV IgG	Positive	Negative
AST	64 U/l	10-40 U/l
ALT	58 U/l	7-56 U/l

Dermatologic examination showed multiple erythematous macules-papules, well-defined margin, geographical in shape, some lesions confluence, 0.1×0.2–3×4 cm in size, in right and left extremities and anterior thoracoabdominal regions. No excoriation, scales, or ooze found on examination. A differential diagnoses of suspected infectious mononucleosis, dengue infection, and HIV infection were carried. A workup of laboratory examinations was ordered. The results are shown in Table 2. Working diagnosis of viral exanthemas due to infectious mononucleosis was carried. Supportive treatment of paracetamol was continued, but the rest of the other

medications were advised to be discontinued. Patient was asked to return for a follow-up one week after the initial examination. No new symptoms and rashes were present, and some of the rashes are getting better. Fever and sore throat have recovered. No new symptoms complained by the patient. All other medications were discontinued on the day of the initial visit, but paracetamol was discontinued two days after the initial visit.

On examination, the patient appeared stable. Blood pressure was 110/70 mmHg, pulse rate 88 beats per minute, respiratory rate 16 times per minute, axillary temperature 36.4℃, oxygen saturation 98% on room air, pain score 0/10. There were no new significant clinical findings found on physical examination compared to the previous visit. No abnormalities were found on head, chest, and extremities on physical examination.

Splenomegaly (Hackett stage I) was still noted on the follow-up examination. Dermatologic examination showed healing multiple erythematous macules, ill-defined to well-defined margin, geographical in shape, some lesions confluence, 0.1×0.2 cm–1×2 cm in size, in right and left upper extremities. No excoriation, scales, or ooze found on examination. Laboratory examinations on the follow-up examination can be seen on Table 3.

The diagnosis of viral exanthemas due to infectious mononucleosis was still carried. The patient is advised to stop symptomatic medications and to get plenty of rest and hydration. The patient and her parents were educated to exclude her from her extracurricular activities at school for one month after the onset, particularly ballet and other contact sports to avoid a complication of splenic rupture.

A second follow-up appointment was scheduled three weeks after the first follow-up visit. Teleconsultation services were provided because the patient was overseas. The patient has fully recovered, with no new complaints or symptoms, and the rashes were no longer visible. The patient was allowed to resume her usual activities, including ballet and contact sports that she enjoyed.

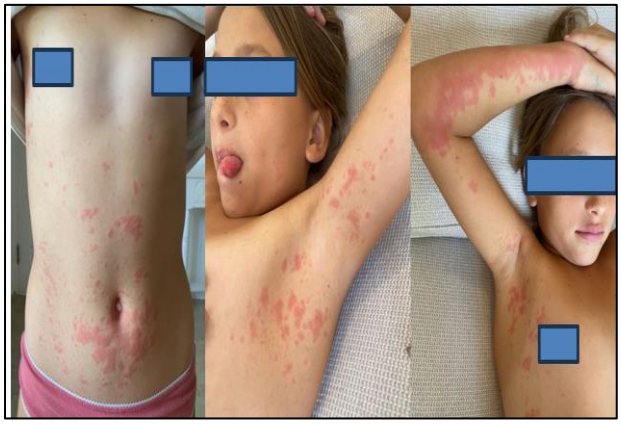

Figure 1: Clinical manifestation of the rash on initial examination.

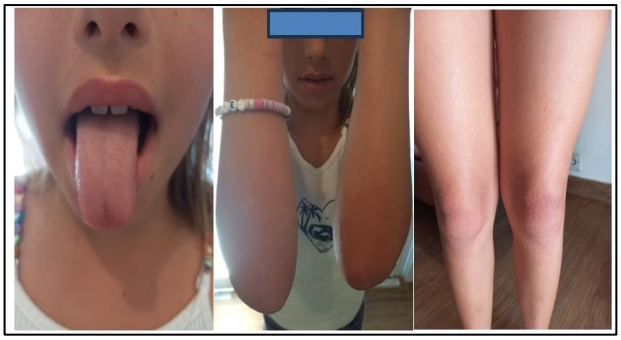

Figure 2: Clinical manifestation of the rash on follow-up, one week after initial examination.

DISCUSSION

Constellations of symptoms of IM might differ on different age groups. A recent meta-analysis reported that several signs and symptoms, particularly splenomegaly, palatal petechiae, posterior cervical lymphadenopathy, and axillary or inguinal lymphadenopathy are useful for ruling in IM.[5] Rashes, stomach ache, and neurologic issues are more common in young children than in adolescents and older adults. However, the clinical trial of fever, sore throat, and lymphadenopathy are still considered as main indicator for primary EBV infection.[6]

In some cases, IM may primarily be recognised due to its dermatological appearance. One of the most common dermatological manifestation of IM is a maculopapular rash occurring in almost all patients receiving antibiotics, primarily amoxicillin and ampicillin.[7] Although ampicillin was one of the first drug associated with skin eruptions in IM, other antibiotics such as cephalosporins, penicillin G, tetracycline, cephalexin, levofloxacin, erythromycin, and azithromycin have also been reported to cause symptoms.[3,8] A previous study has reported that while amoxicillin had a 29.5% antibiotic-induced rash, 15.4% of those treated with cephalosporins also present with cutaneous rash.[8] In our case, we calculated the modified Centor score for this patient, and with the score of 1, antibiotics were not necessary.

Interestingly, our patient initially presented with a rash following ingestion of antibiotics, although further history taking and physical examination revealed the underlying clinical triad present in the patient, raising a high suspicion of IM to the patient. This manifestation could be easily mistaken as viral exanthem, a diagnosis commonly made in Indonesia due to its limitation in resources for advance diagnostic techniques, especially in rural areas.

Another compelling finding in our case was that the rash appeared shortly after the initiation of cefadroxil, in contrast to the common culprit of amoxicillin being extensively correlated as a trigger of the maculopapular rash in patients with IM. Recent studies show that the risk of amoxicillin-induced rash is similar with other antibiotic group, including cephalosporins, in IM patients.[9,10]

There are several explanations to this finding. When amoxicillin is administered during infectious mononucleosis, maculopapular skin eruption is linked to the development of delayed-type hypersensitivity reaction, also known as type IV allergic reaction. Th2 T cells get activated during this response and release interleukins 4, 5, and 13, which cause inflammation of the eosinophils. Furthermore, B-cells may secrete IgE and IgG4 in conjunction with the previously described reaction, connecting type IV to a possible rapid allergic response (type I allergic reaction).

From a chemical perspective, penicillin is composed of a single-chain thiazolidine ring with a β-lactam ring connected to it. On the other hand, cephalosporins consist of a dihydrothiazine ring with two side chains connected to a β-lactam ring. The antigenic effect of the side chain, rather than the β-lactam ring itself, is increasingly being blamed for allergic reactions to cephalosporins. The likelihood of cross-reactivity and type IV allergic reaction with penicillin and its derivatives is further increased by the fact that the side chains of earlier cephalosporin drugs, including cefadroxil, resemble those of penicillin.[11]

When a proper diagnosis is determined, it is frequently the result of a thorough investigation based on basic understanding the illness: its aetiopathogenesis. This approach takes into account the fact that no two instances are exactly the same but that broad guidelines can be applied. Acute markers, in particular the detection of atypical lymphocytes can alert the clinicians to the need for further analysis and additional tests required to confirm the diagnosis.[2,12]

History and physical examination are usually sufficient to establish the diagnosis of infectious mononucleosis. Laboratory examinations can be ordered to support the diagnosis, especially in atypical cases. Diagnostic criteria for infectious mononucleosis (Hoagland criteria) include greater than 50% lymphocytes and at least 10% atypical lymphocytes with fever, pharyngitis, adenopathy, and a positive serologic test. The presence of atypical lymphocytes has a sensitivity of 75% and a specificity of 92%.

Other laboratory findings that could be suggestive of IM include transient neutropaenia, thrombocytopaenia, and elevated liver transaminases. Anaemia is considered a feature of complicated IM and is indicative of autoimmune haemolytic anaemia, splenic rupture, aplastic anaemia, and even disseminated intravascular coagulation.[13]

In our case, the patient had lymphocytosis and thrombocytopaenia, which supported the diagnosis of infectious mononucleosis. Epidemiologically, however, a differential diagnosis of dengue infection needs to be excluded as it may present with similar symptoms.[2,14] This patient was tested for NS1-Ag Dengue, however the test turned out negative. Furthermore, the patient did not exhibit classical symptoms of dengue, including the typical fever pattern. Heterophile antibodies are a characteristic feature of IM. A positive Monospot (rapid heterophile antibodies) test in the presence of dominating atypical lymphocytes in patients demonstrating distinct clinical symptoms is quite unequivocal in the diagnosis of IM. By the third week of sickness, up to 90% of patients with confirmed IM will show a positive heterophile test. Consequently, a negative heterophile test during the initial weeks of illness may occur; in this case, the false-negative rate may reach 25%, necessitating further testing.

With the use of more sensitive assays that identify viral capsid antigens for IgM and IgG antibodies, IM can be definitively diagnosed.[2,13] Initially, this patient presented with a negative Anti-EBV IgM and a positive Anti-EBV IgG antibodies, which was interpreted as a past exposure, or a latent infection. The negative initial Anti-EBV IgM test was most likely to be caused by insufficient titres of the EBV in the first week of infection. This was further proved by a positive Anti-EBV IgM antibodies on a subsequent follow-up testing one week after the initial visit.[2] The diagnosis of IM is rarely established in Indonesia.

The broader diagnosis of viral exanthemas is extensively used, without addressing the specificity of the causative agent. Although it may seem that specifying the aetiology does not change the management plan and prognosis, it is essential in providing an individualised yet holistic treatment approach. Furthermore, heterophile antibody tests are not widely available to be used. In this case, the patient enjoys ballet and sports at school. Providing a definitive diagnosis of IM, rather than viral exanthema, is helpful to provide necessary education to prevent complications. In patients with IM, splenomegaly needs to be addressed and watched out for, especially for patients favouring contact sports, as a morbid complication of splenic rupture may be imminent.[13]

CONCLUSION

Infectious mononucleosis is frequently overlooked in Indonesia due to its nonspecific symptoms and its ability to mimic other common diseases. This diagnostic challenge underscores the importance of heightened clinical awareness and thorough evaluation, particularly in paediatric patients, where accurate diagnosis is crucial for optimal management. Treatment strategies must be individualized, taking into account the unique needs and potential complications in children, to ensure effective care and better health outcomes.

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REFERENCES

1. Ming Y, Cheng S, Chen Z, Su W, Lu S, Wang N, et al. Infectious mononucleosis in children and differences in biomarker levels and other features between disease caused by Epstein-Barr virus and other pathogens: a single-center retrospective study in China. Peer J. 2023;11:15071.
2. Naughton P, Healy M, Enright F, Lucey B. Infectious Mononucleosis: diagnosis and clinical interpretation. Br J Biomed Sci. 2021;78(3):107–16.
3. Ónodi-Nagy K, Bata-Csörgő Z, Varga E, Kemény L, Kinyó A. Antibiotic induced cutaneous rash in infectious mononucleosis: overview of the literature. J Allergy Ther. 2015;6(5):1000222.
4. Wu Y, Ma S, Zhang L, Zu D, Gu F, Ding X, et al. Clinical manifestations and laboratory results of 61 children with infectious mononucleosis. J Int Med Res. 2020;48(10):300060520924550.
5. Cai X, Ebell MH, Haines L. Accuracy of signs, symptoms, and hematologic parameters for the diagnosis of infectious mononucleosis: a systematic review and meta-analysis. J Am Board Fam Med. 2021;34(6):1141–56.
6. Alli A, Nabil F, Ortiz JF. Infectious mononucleosis: a case report with unusual features and abnormal laboratory findings. Cureus. 2021;13(5).
7. Ciccarese G, Trave I, Herzum A, Parodi A, Drago F. Dermatological manifestations of Epstein-Barr virus systemic infection: a case report and literature review. Int J Dermatol. 2020;59(10):1202–9.
8. Chovel-Sella A, Ben Tov A, Lahav E, Mor O, Rudich H, Paret G, et al. Incidence of rash after amoxicillin treatment in children with infectious mononucleosis. Pediatrics. 2013;131:1424-7.
9. Zhang JX, Xie J, Fan L, Zhao HY, Xiong SJ, Qian X, et al. Evaluation of the association between the use of antimicrobials and the risk of rash in patients with infectious mononucleosis: systematic review and meta-analysis. Chin J Hosp Pharm. 2022;42:281–7.
10. Zhang R, Mao Z, Xu C, Wang W, Kwong JSW, Xu M, et al. Association between antibiotic exposure and the risk of rash in children with infectious mononucleosis: a multicenter, retrospective cohort study. Antimicrob Agents Chemother. 2023;67(6):24923.
11. Vlastarakos P V, Michailidou E. How Safe is It to Prescribe Cephalosporins in Patients with Infectious Mononucleosis? Implications for Clinical ENT Practice. Turkish Arch Otorhinolaryngol. 2018;56(3):183–4.
12. Sylvester JE, Buchanan BK, Silva TW. Infectious mononucleosis: rapid evidence reviews. Am Fam Physician. 2023;107(1):71–8.
13. Becker JA, Smith JA. Return to play after infectious mononucleosis. Sports Health. 2014;6(3):232–8.
14. Boyd K, Harrison JM, Kavanaugh MJ. False-Positive Monospot in a Returning Traveler with Dengue Fever. Mil Med. 2018;183(3–4):235–6.

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