CASE REPORT

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Sepsis caused by Salmonella serovar paratyphi B in immunocompromised patient with kasabach-merritt syndrome in dr. Soetoro general academic hospital Surabaya: a case report

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ABSTRACT

Introduction: Salmonella species are recognized worldwide as a common cause of childhood infections, particularly gastroenteritis, bacteremia, and enteric fever. Some salmonella infection cases, especially those caused by Salmonella paratyphi B, which are rare, are reported to cause sepsis in children and neonates. The treatment of Salmonella paratyphi B-induced sepsis is challenging, particularly in immunocompromised babies as in Kasabach-Merritt Syndrome (KMS). This case report aims to report the case of a 1.7-year-old girl who had Salmonella serovar paratyphi B-induced sepsis and presented with KMS.

Case Description: A 1.7 years old girl has complaints of fever for 5 days prior to admission to the hospital with a history of a growing haemangioma in the abdominal area since the first 40 days since birth. The patient was diagnosed with KMS. During the period of hospitalization, there were no complaints of fever, therefore, the patient was discharged. The next day, the patient complained of persistent fever and general weakness.

Vital signs examination revealed tachycardia and hyperthermia. Laboratory results showed the hemoglobin was 8.7 gr/dL, leucocyte 20.640/uL, neutrophil 65%, lymphocyte 20.5%, platelet 14.000 uL, CRP 14.22 mg/dL. The patient was diagnosed with Kasabach-Merritt Syndrome (KMS) and has been in control as an outpatient and received oral therapy with methylprednisolone, propranolol and tranexamic acid. The patient was readmitted for chemotherapy with bleomycin and vincristine as part of the KMS treatment regimen. Empiric antibiotic (200 mg ampicillin i.v.) also administered as Salmonella sp. Bacteria was found on the blood culture.

Conclusion: Salmonella paratyphi B is a rare infection, the symptoms are typically mild. Rapid identification of bacterial infection and antimicrobial susceptibility testing is crucial for effective treatment.

Keywords: Sepsis, Salmonella paratyphi B, kasabach-merritt syndrome.
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INTRODUCTION

Kasabach-Merritt syndrome (KMS) is known as giant hemangioma with thrombocytopenia and consumptive coagulopathy. Kasabach first reported it and Merritt in 1940.[1–8] Kasabach-Merritt syndrome only develops as a side effect of tufted angioma (TA) and kaposiform hemangioendothelioma (KHE), which are uncommon, benign vascular tumors that generally manifest in infancy. Kaposiform hemangioendothelioma and TA are categorized as having moderate malignant potential since they are aggressive locally but not known to metastasize. Although the exact frequency of KHE and TA is unknown, they are stated to be rare and approximated to be 0.07/100,000 in one paper based on observed cases at a big center.[9] KMS accounts for only 1% of all cases of hemangiomas.[1,7] About 80% of these cases appear by the first year of age with mortality rates ranging from 10% to 37%.[1,2,4–8] However, KMS may impact up to 70% of all KHE patients and up to 10% of TA patients.[9] All races and all genders seem to be equally impacted. The average age of diagnosis in one case series for tumors was 2 months, with early infancy being the usual time of presentation. Kaposiform hemangioendothelioma rarely manifest in adults, and in adulthood, KMS is often not present.[3,10,11]

Vascular architecture in KHE and TA are complex, which probably contributes to the pathophysiologic processes of KMP. According to one theory, confined platelets in the lesion activate platelets and consume fibrinogen.[12] Positive immunohistochemical staining for the platelet marker CD61 inside the arterial lumen of lesions and localized consumption of radiolabeled fibrinogen both provide credence to this idea.[3,9] It has been found that the risk of KMP rises as the lesion's depth and its intrathoracic or retroperitoneal involvement increase. KMP has a significant morbidity and death rate, with recorded fatality rates as high as 30%.[3,11,13] A life-threatening hemorrhage, heart failure, or expansion of the underlying vascular disease into nearby tissues are the typical causes of

death. Increased mortality is linked to retroperitoneal lesions complication.[14]

The underlying concept of KMS treatment is to accelerate haemangioma regression and to regulate coagulopathy.[4,7] A variety of interventions recommended include the use of steroids, compression, embolization, interferon use, laser therapy, sclerotherapy, chemotherapy, radiotherapy and surgery.[1–8] Corticosteroids are the traditional first-line therapy when surgery is not a choice of treatment. Vincristine is a chemotherapy drug that has been proven its efficacy in the treatment of KMS. While the use of vincristine and corticosteroids as first-line treatment for KMS has been reported to be effective, the combination of bleomycin and corticosteroids also show clinical improvement.[2,7]

Enteric fever is a non-specific systemic infection caused by S. *typhi* or S. *paratyphi A, B* or *C*.[15–17] Transmission of *Salmonella* is often associated with consumption of contaminated water and food of animal origin (eggs, meat, dairy products) usually associated with poor hygiene conditions.[15,16,18,19] The World Health Organization (WHO) estimates that 16 to 33 million cases of typhoid fever caused 500.000 to 600.000 deaths worldwide each year.[20] According to worldwide surveillance, countries in south-central and southeast Asia (e.g. Bangladesh, India, Indonesia, Nepal, Pakistan, and Vietnam) and southern Africa have the highest incidence of typhoid fever with an estimate of around more than 100 cases per 100,000 population per year.[15,20]

Emerging data from several Asian countries including India, Indonesia, Pakistan, and China show the role of S. paratyphi as a major pathogen that causes enteric fever. Paratyphoid fever is widely spread throughout Asia by S. paratyphi A, while it is less common in Europe by S. paratyphi B. S. paratyphi C is the rarest and has no specific geographical spread.[21,22] This case report aims to report the case of a 1.7-year-old girl who had Salmonella serovar paratyphi B induced sepsis and presented with KMS.

CASE DESCRIPTION

A girl, 1.7 years old, was brought by her parents on December 22, 2021 to the Emergency Department at RSUD Dr. Soetomo Surabaya with complaints of fever for 5 days prior to admission to the hospital. The patient has a history of a growing haemangioma in the abdominal area that appeared in the first 40 days since birth. The patient was diagnosed with Kasabach-Merritt Syndrome (KMS) since June 2021 and had an embolization procedure performed in July 2021. The patient has been in control as an outpatient and received oral therapy with methylprednisolone, propranolol and tranexamic acid. The patient was readmitted on December 7 to 17 for chemotherapy with bleomycin and vincristine as part of the KMS treatment regimen. During the period of hospitalization, there were no complaints of fever, therefore, the patient was discharged. The next day, on the December 22, the patient complained of persistent fever which could only be managed with antipyretics acompanied by general weakness. There were no complaints symptoms with urinary or gastrointestinal involvement. On admission to emergency room, physical findings revealed the child as conscious with general weakness, vital signs examination revealed tachycardia (heart rate of 120 beats per minute) and hyperthermia (temperature > 39^{0}C). Laboratory results shows haemoglobin 8.7 gr/dL, leucocyte 20.640/uL, neutrophil 65%, lymphocyte 20.5%, platelet 14.000 uL, CRP 14.22 mg/dL. The patient received an empiric antibiotic treatment of 200 mg intravenous Ampicillin for 6 hours. The chest X-ray examination showed that there were no abnormalities in the cor and pulmonum while abdominal ultrasound shows a haemangioma in the both upper abdominal quadrant to the supraumbilical with a size of ± 8.29 x 3.47 x 7.20 cm, minimal ascites in the pelvic cavity and right paracolic.

Blood culture of the patient was obtained on December 23, and is then incubated on Bactec. Positive result of Bactec Incubation was obtained in 1x24 hours, with Gram staining revealing Gram negative rods (Figure 1). Blood culture was also conducted and tested on Blood Agar (BA), Chocolate Agar and MacConkey Agar. Results show single colony growth, with MacConkey Agar revealing the organism to be a Non-Lactose Fermenter (NLF) (Figure 2). Colonies from BA undergo subculture (SC) into an SS Agar media. After incubation of 1x24 hours at 37^{0}C, the SS Agar shows colorless NLF colonies with a black center on each colony (Figure 3). In addition, other test including IMVIC test, SIM, TSI and Urease test were carried out, with results of citrate (+), sulfide (+), indole (-), motility (+), ALK/A, gas (+), H2S (+) and urease test (-) (Figure 4). Bacterial identification and AST using BD Phoenix™ revealed *Salmonella sp.* bacteria, sensitive to antibiotics amoxicillin clavulanate, ampicillin sulbactam, aztreonam, cefotaxime, ceftazidime, cefoperazone sulbactam, fosfomycin, tigecycline, ceftriaxone, cefoxitin, imipeneme, piperacillin tazobactam, tetracycline and trimethoprime sulfamethoxazole.

The patient has had fluctuating fever with the highest temperature of 39.5^{0}C

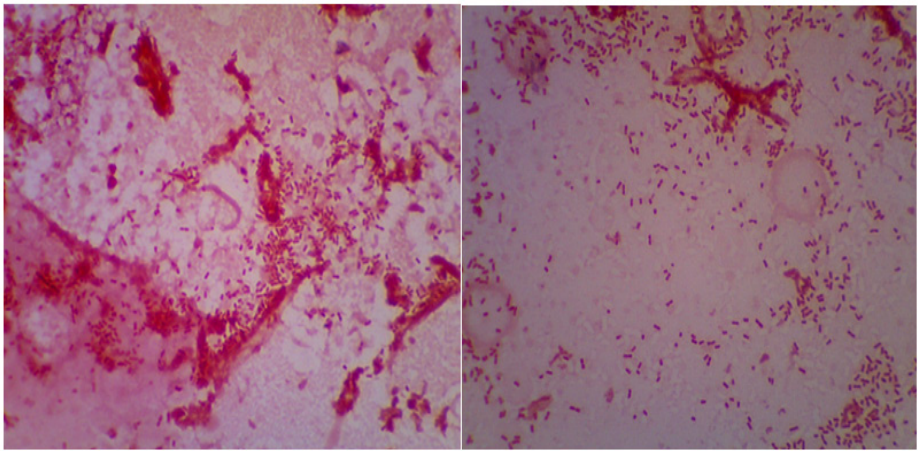

Figure 1. Direct gram stain from bactec, TTP 1x24 hours, gram negative rods in high power field

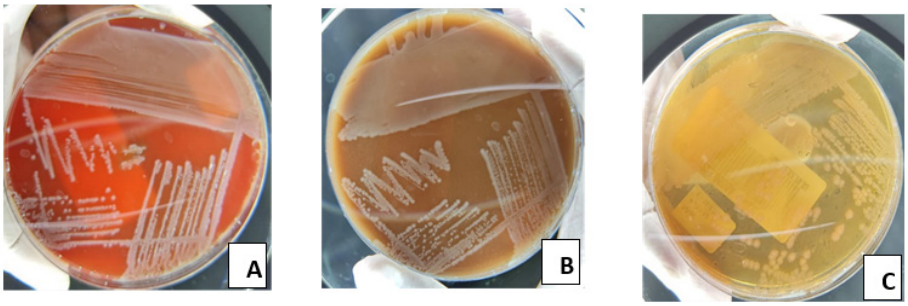

Figure 2. Colony growth in (A) blood agar, (B) chocolate agar , (C) maconkey agar after incubation 1x24 hours, at temperature 37^{0}C.

Figure 3. Colony growth in SS agar. Colonies appear colorless with black center on each colony, NLF, after incubation 1x24 hours, at temperature 37^{0}C

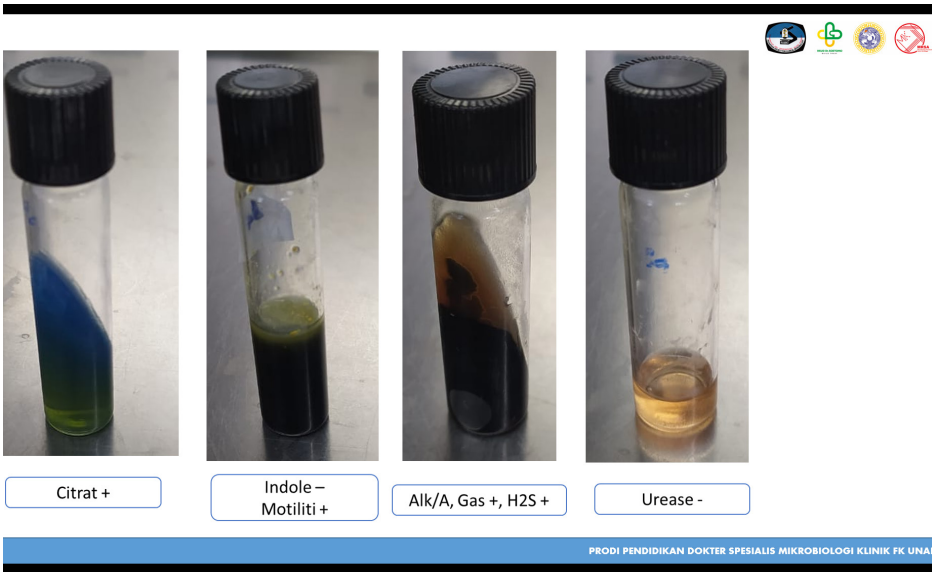

Figure 4. IMVIC test result

and diarrhea with mucus but without blood with a frequency of 4-10 times/day, during the period of hospitalization and through identification process. On the third day of hospitalization (24/12/21), Procalcitonin shows result of more than 100 ng/ml, so the empiric antibiotic regiment was replaced with cefoperazone sulbactam 3x300 mg and amikacin 1x125 mg. On the eighth day of treatment, the patient still had a fever accompanied by diarrhea. Procalcitonin reexamination on sixth day of hospitalization shows result 31.61 ng/ml. A stool culture was planned but the patient's family refused the test and requested the patient to be discharged from the hospital.

DISCUSSION

Kasabah-Merrit-Syndrome are associated with systemic hematologic dysregulation that increase the susceptibility and severity of infection. In this case report we reported 1.7-year-old girl receiving Kasabah-Merrit-Syndrome therapy and shows some symptoms of typhoid fever. The clinical manifestations of typhoid fever may vary, manifesting as ordinary fever to severe toxaemia with involvement of multiorgan systems.[19,23] After the ingestion of the pathogen, symptoms will usually appear between 5-21 days. The disease manifest as a low-grade fever in the first week and gradually increases and persists as high fever. Other systemic manifestations, such as headache, malaise, myalgia, and lethargy will follow after the manifestation of high fever. Constipation may be an early feature of typhoid fever. Other late gastrointestinal symptoms may include abdominal pain, nausea, vomiting, or diarrhea.[16,18,20,24] *S. paratyphi* is thought to cause milder symptoms than *S. typhi*, with clinical findings being predominantly gastrointestinal.[25] The symptoms of paratyphoid fever usually begin 6–30 days after exposure, followed by a gradual onset of a high fever occurs over several days. Headaches, loss of appetite, and weakness can also commonly occur, while skin rashes with rose-colored spots may manifests in some individuals, all of which, if untreated, could last several weeks.[21]

The etiology of the enteric fever in this patient has been confirmed by the single-phase blood culture, which included findings such as, gram negative rod colonies in gram stain after Bactec incubation of 1x24 hours, single colony growth on BA, Choc and Mac Agar, NLF, and colorless colonies with black centers on SS agar. Bacterial identification using BD Phoenix™ found *Salmonella Sp* bacteria and IMVIC test with results of citrate (+), Sulfide (+), Indole (-), Motility (+), ALK/A, Gas (+), H2S (+), Urease (-). These results are consistent with the characteristics of the *Salmonella serovar paratyphi B* bacteria.[20]

Salmonella is infected predominantly by ingestion. The number of ingested Salmonella organism corresponds to the risk factor of an infection, as well as, the length of incubation period, symptoms, and severity of the disease.[24,26] Gastric acidity is the first line of defence against any ingested organisms, and factors that reduces gastric acidity contributes to the survival of the organism. Neonates are particularly susceptible to symptomatic salmonellosis for this reason due to hypochlorhydria and rapid gastric emptying. Immunocompromised hosts with altered cellular and humoral immune defences are also susceptible to severe *Salmonella* infection.[20]

The patient in this case report is being treated with immunosuppressant drugs such as methylprednisolone and the cytotoxic drug-vincristine as treatment for KMS. This may cause the suppression of the cell-mediated immune system caused by corticosteroids, while vincristine causes opsonization by complement which then inhibits dendritic cells' stimulation of T cell proliferation and decreases the inflammatory response. This suppression may render the immune response inadequate to combat the infection, causing the individual to have greater risk to contract the disease.[20,27–29] The treatment given is based on the 2013 expert consensus guidelines issued by The Journal of Pediatrics, which suggested steroid and vincristine combined therapy as first-line treatment, with steroid monotherapy advised if vincristine is not easily accessible.[30] Other case reports also found promising results using sirolimus for vincristine-resistant and refractory KMS that showed alleviated tumor size, improved platelet count, and normalized hematologic parameters.[31,32] Aspirin and ticlodipine were also found helpful in some studies, as those medications inhibit platelet aggregation. However, aspirin use in children has the potential to cause Reye syndrome, so it should be used with caution.[33–36] Treatment for typhoid fever is challenging as new *Salmonella* strains are resistant to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol, all of which are previously first-line antibiotics for the disease.[26,37] Newer recommendations include broad-spectrum cephalosporins, azithromycin, or fluoroquinolones as drugs of choice for empirical treatment before obtaining results from susceptibility testing.[38] The use of a single antibiotic regimen is preferred to combination therapy, as both show similar efficacy. There is no consensus regarding the duration of third-generation cephalosporin treatment for children with typhoid fever, although a regimen of 10-14 days is usually recommended.[20] The use of fluoroquinolones in the United States is not approved by the FDA for patients under 18 years of age, unless the benefits outweigh the risks, due to risk of cartilage toxicity on children.[20,24]

This patient was treated with ampicillin, an antibiotic derived from penicillin, as the empiric antibiotic therapy. Penicillin is effective against many gram-positive and gram-negative bacteria. However, *Salmonella* has shown widespread resistance to ampicillin in the last two decades.[39] After new clinical findings and the infection marker of procalcitonin reaching more than 100 ng/ml, a combination therapy of amikacin and cefoperazone sulbactam was then initiated. A case report by Rai et al. also utilized intravenous ampicillin and gentamicin on a 26-day-old male baby with sepsis caused by Salmonella paratyphi B. The condition improved after stopping gentamicin and starting cefotaxime on the third day after submission. They found that the baby stopped being febrile, maintained a normal SpO2 level, and was able to breastfeed normally after the continuous administration of intravenous antibiotics for 14 days.[40] The availability of drugs and drug sensitivity testing on bacterial cultures determined the treatment options.

This case report has several limitations as the source of this infection is not been explored. Considering the timeline of previous hospitalization and the incubation period of *Salmonella paratyphi* ranging around 6-30 days, it is difficult to determine whether the source of exposure was nosocomial or community-acquired from the patient's home. There was also no history regarding the patient exposure risk to foodborne disease such as consumption of market snacks with questionable hygiene, ingestion of untreated water, or exposure during preparation of pre-cooked food. To look for other sources of infection require further tests, including faeces culture examinations on the patient's family members as well as the microbiological examination of the hospital pantries responsible for serving patient's food. Furthermore, the patient was discharged before more test could be done due to the patient family's insistence, for unknown reasons, and there is no new information or patient visits after the discharge.

CONCLUSION

Salmonella paratyphi B (Paratyphoid B) is a rare infection. The symptoms are typically mild, and children are chronic carriers in most endemic countries. Those with impaired immunity may show a more severe manifestation of the disease. This report shows the presence of *S. paratyphi* B as a cause of sepsis in immunocompromised patient with KMS at RSUD dr. Soetomo Surabaya Hospital, Indonesia, which differs the epidemiological findings of predominantly S. *paratyphi* A as the main cause of paratyphoid fever in Asia. This highlights the importance of surveillance as to identify changes in the epidemiology of enteric fever, which in part with the introduction of new typhoid conjugate vaccines, may contribute to the dominance of paratyphoid fever as a more significant cause of enteric fever. Beside that, rapid identification of bacterial infection and antimicrobial suceptibilty testing is crucial for effective treatment.

DISCLOSURE

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: Suharyadi Sasmanto, Eddy Bagus Wasito; data collection: Suharyadi Sasmanto; analysis and interpretation of results: Suharyadi Sasmanto, Eddy Bagus Wasito; draft manuscript preparation: Suharyadi Sasmanto, Eddy Bagus Wasito. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of Interest

The authors have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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