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Atypical Kawasaki Disease in A Two-Year-Old Girl With Initial Presentation of Acute Diarrhea

Penyakit Kawasaki Atipikal pada Seorang Anak Berusia 2 tahun dengan Gejala Awal Diare Akut

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Abstract

Kawasaki Disease is a spectrum of idiopathic, self-limited fever disease affecting children under 5 years old. This disorder can be challenging to be diagnosed by a pediatrician since there is no specific diagnostic laboratory test. One atypical Kawasaki Disease case presented with gastrointestinal symptoms, a two-year-old girl was hospitalized with fever, accompanied by non-hemorrhagic diarrhea three days before admission. Physical examination revealed unilateral cervical lymph enlargement and mild-moderate dehydration. Initial laboratory examination result showed thrombocytosis, leukocytosis (shift to the left), and normal routine fecal analysis. The patient was initially diagnosed with acute diarrhea with mild-moderate dehydration. She was treated with a rehydration regimen and antibiotic, but her fever persisted. On the third day of hospitalization, she fulfilled 3 of the classic Kawasaki Disease criteria (conjunctivitis, cracked lips with strawberry tongue, and lymphadenopathy). Further blood work resulted in increased C-reactive protein 43.35 mg/L and ESR 72 mm/hour, while chest X-ray and electrocardiograph were within normal limit. This patient was proceed to Hasan Sadikin General Hospital for further examination and therapy. Atypical Kawasaki Disease can be a puzzling diagnosis due to its uncommon presentations. Clinicians should importantly keep it in mind as a differential diagnosis in patients with prolonged fever.

***Keywords**: atypical Kawasaki disease; diarrhea; prolonged fever*

Abstrak

Penyakit Kawasaki adalah suatu penyakit idiopatik, *self-limited*, dengan gejala demam, biasanya menyerang anak usia kurang dari 5 tahun. Penyakit ini menjadi tantangan tersendiri bagi dokter anak untuk menegakkan diagnosisnya, karena tidak ada tes laboratorium yang spesifik. Dilaporkan sebuah kasus penyakit Kawasaki parsial dengan keluhan gejala gastrointestinal.

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Seorang anak perempuan berusia dua tahun, datang dengan keluhan demam, disertai diare tanpa disertai lendir dan darah. Pada pemeriksaan fisik ditemukan pembesaran kelenjar getah bening leher unilateral, dan dehidrasi ringan-sedang. Pemeriksaan laboratorium awal menunjukkan adanya trombositosis, leukositosis *(shift to the left*), hasil pemeriksaan feses dalam batas normal. Pasien didiagnosis awal sebagai diare akut dengan dehidrasi ringan-sedang. Pasien diberi terapi rehidrasi dan antibiotik, namun masih tetap demam. Pada perawatan hari ke-3, pasien memenuhi 3 kriteria klasik penyakit Kawasaki (konjungtivitis, bibir pecah-pecah disertai lidah stroberi, dan limfadenopati). Pemeriksaan lebih lanjut menunjukkan peningkatan C-reactive protein 43,35 mg/L, dan LED 72 mm/jam, sedangkan hasil pemeriksaan rontgen foto toraks dan elektrokardiografi dalam batas normal. Pasien kemudian dirujuk ke Rumah Sakit Hasan Sadikin untuk pemeriksaan dan terapi lebih lanjut. Penyakit Kawasaki atipikal, menjadi tantangan tersendiri dalam hal diagnosis karena gejala yang tidak khas. Klinisi harus tetap mempertimbangkan penyakit ini sebagai diagnosis banding pada pasien dengan gejala demam lama.

Kata kunci: diare; demam lama; penyakit Kawasaki atipikal

Introduction

Kawasaki disease (KD) is a systemic acute childhood vasculitis that may lead to coronary artery aneurysms in 25% of its untreated cases.[1,2] The disease was first discovered in Japan with annual incidence. In 2012, KD new cases in Japan was around 264.8 per 100,000 children less than five years of age. However, KD is now widely found globally.[1] Nakamura et al. reported that 1% of patients with a positive family history have a higher risk of developing a recurrent episode of coronary artery sequelae.[3,4] Within one year of the primary case, the sequelae rate in a sibling is 2.1%, 10-fold higher than the general Japanese population. In Japan, the United States, and the United Kingdom, KD cases happen more often during the early spring and winter seasons.[2,4,5] This disease affects more male than female by ≈1.5–1.7:1 in children less than 5-year-old with an approximate average age of 3 years. Asian children with Japanese ancestry blood history mostly at higher risk for KD compared to Caucasian.[1,5,6]

A "complete" KD diagnosis is made based on the findings of five-day-fever with other four of the five classic criteria, or fever and coronary artery aneurysms (CAA) plus three additional criteria.[4] However, due to its multiple organ involvements systemically, KD has high variability in symptoms and signs that makes it difficult to be diagnosed early in patients with non-typical presentation or uncommon manifestations.[6] In one-third of children diagnosed with this disease, other commonly identified infections such as viral illnesses, gastroenteritis, Group A streptococcal tonsillitis, and pneumonia are concurrently present.[5] Patients who do not present

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with principal clinical findings may be diagnosed as "incomplete" or "atypical" Kawasaki Disease. The "atypical" patients, especially those who present without eye or oral mucosal involvement presentation and whose age is less than six months, may face substantial delay in diagnosis and treatment.[1] All mortality in patients with KD is generally caused by its cardiac sequelae, which occurs 15 to 45 days after fever onset; the time which well-established coronary artery vasculitis, and a notable increase in blood hypercoagulability and platelet count concomitantly occur.[1,5] Nevertheless, in children and adults with coronary sequelae (particularly in patients with missed childhood "KD" diagnosis), myocardial infarction (MI) may cause sudden death later in the future, underscoring the importance of early diagnosis and prompt treatment.[1] The number of gastrointestinal presentation in KD is remarkably uncommon, and data are only available from single case reports and a few case series.[7]

In this paper, a case of an Indonesian child with a diagnosis of atypical KD who has a gastrointestinal presentation were reported and reviewed.

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A two-year-old girl was escorted by her parents to the Emergency Department with the chief complaint of abrupt continuous fever up to 40^{o} C accompanied by 4-5 episodes of copious, watery, non-hemorrhagic diarrhea, mild irritability, and reduce appetite since three days prior to admission. Physical examination revealed temperature 38.6^{o}C, 2 cm diameter right anterior cervical lymph enlargement, moderate dehydration, no audible cardiac murmur, no skin rashes. Initial laboratory examination result showed platelet count 592,000/µL, leucocyte count 16,000/µL with neutrophil 84%, lymphocyte count 13%, and erythrocyte sedimentation rate (ESR) 70mm/hour; routine fecal analysis and urinalysis were within normal limit.

The patient was initially diagnosed with acute diarrhea with moderate dehydration. Intravenous fluid rehydration regimen and Cefobactam antibiotic, as well as oral zinc therapy, were delivered promptly. Her diarrhea frequency improved on the second day of hospitalization, although she still experienced continuous fever (38.2^{o}C). On her third day of hospitalization (day-6 fever), she developed non-suppurative conjunctivitis with mild periorbital edema, cracked lips, and strawberry lips (Figure 1). Further blood work results indicated high acute phase reactant C-reactive protein (CRP) 43.35 mg/L and increased ESR 72 mm/hour. Chest X-ray and electrocardiograph (ECG) results were within the normal limit.

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The patient was referred to Dr. Hasan Sadikin General Teaching Hospital for further echocardiography examination and intravenous immunoglobulin (IVIG) administration. Dr.Hasan Sadikin General Teaching Hospital laboratory examination revealed hypoalbuminemia 2.8 gr/dl. Echocardiography examination showed normal coronary artery: left main coronary artery (LM) 2.6mm, left anterior descending (LAD) artery 2.2mm, left circumflex artery (LCx) 2.0mm, right coronary artery (RCA) 2.7mm, with mild posterior circumferential pericardial effusion with a size of 0.27-0.54 mm. She was treated with oral aspirin 4 x 250mg for five days, titrated (on her sixth day of disease) down to 1x 60mg on day 11 of the disease. Due to financial issues, her family refused IV-IG administration and laboratory work follow-up; and decided to be discharged from Dr.Hasan Sadikin General Teaching Hospital.

Discussion

Kawasaki disease is an idiopathic vasculitis that becomes the most common etiology of acquired heart disease in childhood, especially in developed countries.[1,7]It mainly affects children under five years of age and has a boy to girl ratio of 1.5-1.7:1. Its diagnosis is based on the presence of fever (lasting more than five days) and of four of the five diagnostic criteria (oropharyngeal changes, bilateral bulbar conjunctival injection without exudate, rash, change of the extremities, cervical lymphadenopathy ≥1.5 cm diameter).[1,2,5] However, diagnosis can be made with incomplete features if fewer than 4 of the criteria mentioned before are present.[5]

In its classic form, Kawasaki disease is usually diagnosed by experienced clinicians with no significant challenges. However, it is not uncommon that KD patients come with subtle presentations that clinicians are not aware of, especially when they present as atypical KD. The terminology of ‘atypical Kawasaki Disease” initially pertained to the patients whose clinical presentations failed the classic Kawasaki Disease criteria but were found to have coronary artery abnormalities. However, many cases revealed cardiac abnormalities without meeting the strict classic KD criteria, and the "incomplete" case can progress in time into a "complete" case. Therefore, most clinicians nowadays use the atypical term to describe the patients who did not encompass the classic KD criteria but presented with compatible supportive examination findings after excluding any other underlying disease.[4,6, 8] With this approach, patients have a greater chance of promptly initiating therapy, hopefully reducing coronary artery complication rate.[8] Incomplete KD is commonly found in children aged less than two years old, and the affected children are at greater risk of developing coronary disease; although another study by Gorczyca

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et al. showed no significant difference in the age group between complete versus incomplete KD.[7, 9, 10]

Our patient experienced an abrupt onset of fever in the first three days of illness along with gastrointestinal symptoms: watery diarrhea and dehydration that initiated her admission to the hospital. Her fever remained constant throughout her stay in the hospital and was persistent towards antipyretic and antibiotic treatment. Only later in her third hospitalization day (day 6 of illness), she developed bilateral conjunctivitis, cracked lips, and strawberry tongue (Fig.1) in her acute phase. The hallmark of KD is the abrupt-onset and persistent fever. This fever is typically non-responsive to the antipyretic agent and tends to remain above 38.5°C during most of the acute phases of the illness (often exceeds 40°C), and sometimes preceded by symptoms of an upper respiratory or gastrointestinal illness.[5,7] Abdominal pain and vomiting are commonly reported, and approximately one-fourth of children with KD have profuse and watery diarrhea during the acute febrile period.[5,7,11] Baker and colleagues studied 198 patients' symptoms within ten days before their KD diagnosis and reported that half of their patients experienced irritability, vomiting (44%), decreased food intake (37%), diarrhea (26%), and abdominal pain (18%).[12] In the next three to four days, the patients will develop conjunctivitis, changes in the buccal and oral mucosa, cervical adenitis, a pleomorphic rash, erythema, and edema in the upper and lower extremities due to a systemic necrotizing vasculitis with fibrinoid necrosis of the medium-sized muscular arteries. Moreover, the coronary arteries are the predominant sites of this systemic vasculitis involvement, causing sequelae many years later.[5,6]

This patient also presented with unilateral localized right anterior cervical lymphadenopathy during her diarrhea episodes on her admission. Cervical lymphadenopathy in KD, usually unilateral or only affect one single node, is the least common manifestation occurring in 50% to 75% of patients that usually shrinks with or without specific therapy after 3 or 4 days.[5,13,14] However, in atypical cases, this lymphadenopathy may antecede other symptoms.[6] Other clinical findings relatively specific to KD but not listed in the classical diagnostic criteria are induration and erythema at the BCG immunization sites.[4,15] The presence of high and persistent fever, conjunctival injection, strawberry tongue, and cervical lymphadenopathy in our patient suggested the diagnosis of suspected Kawasaki disease with diarrhea presentation.

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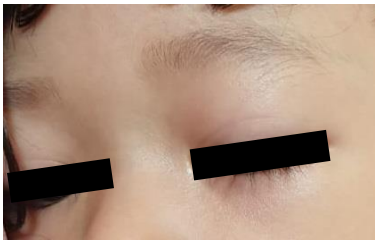
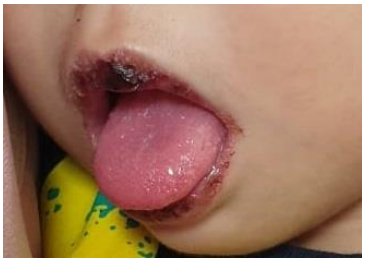
The most common classic manifestations are non-suppurative bulbar conjunctivitis bilateral, cervical lymphadenopathy >1.5 cm, a polymorphous rash with no vesicles or crusts found, changes of lips or oral mucosa (such as red, cracked lips, "strawberry" tongue, or diffuse erythema of oropharynx), as well as changes of extremities (seen as erythema and edema of palms and soles in the initial stage, and manifest as peeling of skin from fingertips in convalescent stage).[1,4,6, 16] These manifestations may change in a fluctuant mode and present in no particular pattern in the first 7 to 10 days of the disease course.[5,12] Other common clinical signs in KD include pneumonitis, aseptic meningitis, arthritis, uveitis, otitis, mastitis, dysuria, and gastroenteritis. Clinicians may mistakenly attribute fever and pyuria findings in an infant or young child to a urinary tract infection; and the subsequent evolution of red eyes, rash, and red lips in patients to an antibiotic reaction.[1,8]

(a)

(b)



(c)



(d)

Figure 1 (a) Physical findings on the 6th day of fever. (b) Bilateral non-suppurated bulbar conjunctivitis. (c) Minor bilateral palpebral edema. (d) Cracked lips and strawberry tongue.

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Our patient experienced mild irritability that might be a part of her KD manifestation other than a clinical symptom of dehydration. In some literature, children with prolonged fever, irritability, and laboratory finding of cerebrospinal fluid's culture-negative pleocytosis suggestive of aseptic meningitis (or if antibiotics have been given, partially treated meningitis) may lead clinicians to overlook the diagnosis of KD.[1,4,8] Although in our case, we decided not to test her cerebrospinal fluid due to financial issues to prioritize other more important supportive examinations.

Clinically, the patient only fulfills 3 out of the 5 classic symptoms required for a complete Kawasaki Disease. However, once we suspect our patient for Kawasaki Disease, we immediately transferred her to a higher health system to receive further examination and therapy to comply with the investigation and evaluation algorithm for incomplete KD-suspected patients by Baumer[17](Please see Fig.2).

Initial laboratory work in our hospital indicated the patient to have an infection shown by leukocytosis with a "shift to the left" and high ESR counts, so she was treated with the antibiotic. However, suspicion was raised due to her elevated platelet count. Only when her following classic KD signs developed, the ESR and CRP counts were promptly checked, and the results supported her diagnosis as suspected Kawasaki Disease. Until recently, no specific diagnostic tests are available for KD,[5,14] but at the beginning of the disease, clinicians may find indicators of ongoing inflammation such as leukocytosis with a "shift to the left" trend of white blood cell (WBC) differential count, [4,5,11] as well as elevated C-reactive protein (CRP) and ESR count.[4,10,15] (Table 1). However, there are no differences between complete and atypical KD in laboratory investigation results statistically.[10,14]

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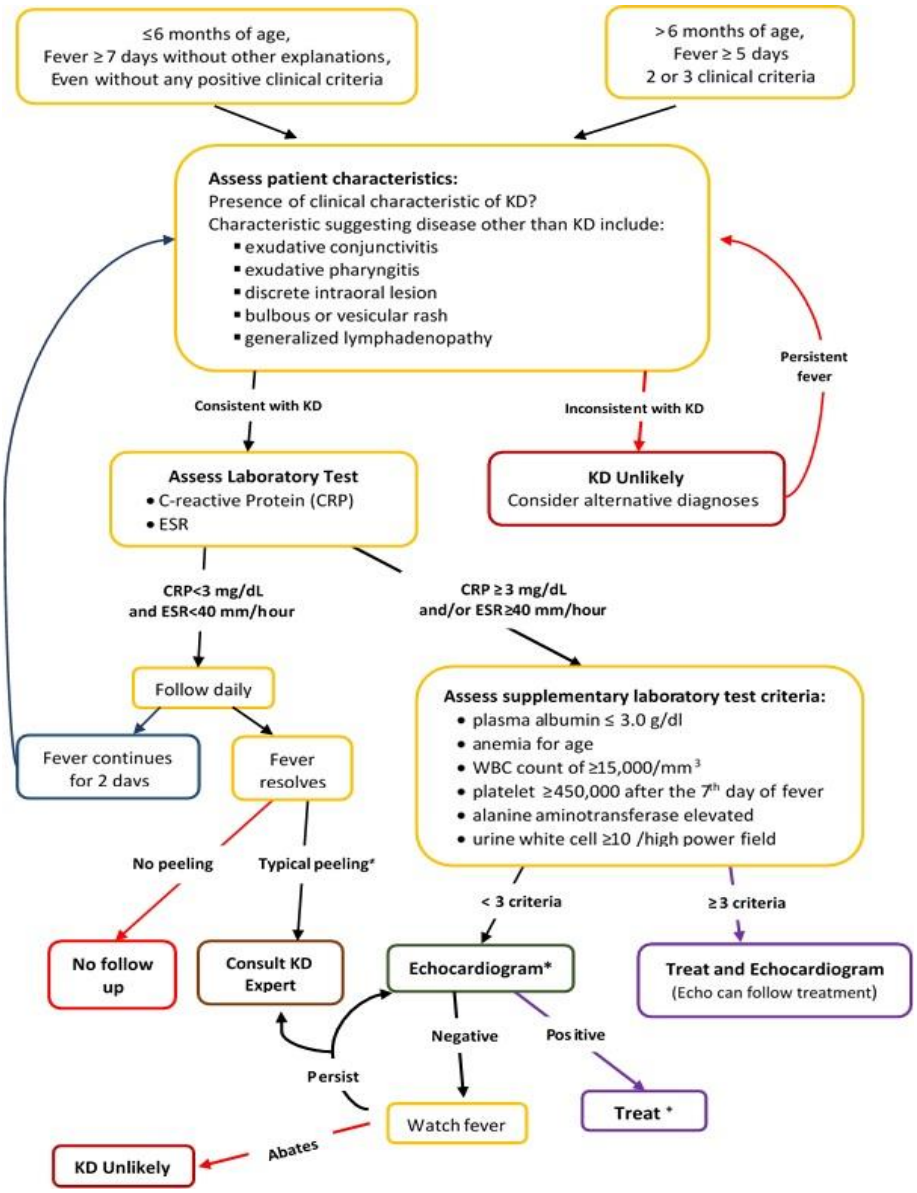

Figure 2. Kawasaki Disease Diagnosis Algorithm. Kawasaki Disease patients' investigation and evaluation flowchart. *****Echocardiogram positive if any of criteria are fulfilled: (1) left anterior descending (LAD) or right coronary artery (RCA) Z-score of 2.5 or more; (2) positive coronary arteries aneurysms criteria from Japanese Ministry of Health; (3) three or more presence of suggestive features [decreasing left ventricular function, perivascular brightness, pericardial effusion, mitral regurgitation, lack of tapering, or z scores in LAD or RCA of 2–2.5. [+]If the echo result is positive, start treatment within ten days of fever onset and beyond ten days for patients with clinical and laboratory signs of an existing infection. [≠]Classic peelings start under the fingers' nail bed and toes. A pediatric KD expert should always be consulted when fever persists or anytime needed. Alanine transaminase [ALT], C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], white blood cells [WBC]. Modified from: Baumer HJ [17]

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Table 1 Initial investigations for suspected Kawasaki Disease.

Initial Investigation for suspected Kawasaki Disease
• Full Blood count and film • Erythrocyte Sedimentation Rate (ESR) • C Reactive Protein (CRP) • Blood cultures • ASOT & anti DNase B • Nose and throat swab, stool sample for culture (superantigen toxin typing if *Staphylococcus aureus* and/or *β hemolytic streptococci* detected) • Renal and liver function test • Coagulation screen • Autoantibody profile (antinuclear antibodies; extractable nuclear antibodies; rheumatoid factor; antineutrophil cytoplasmic antibodies) • Serology (IgG and IgM) for mycoplasma pneumonia, enterovirus, adenovirus, measles, parvovirus, Epstein-Barr virus, cytomegalovirus. • Urine microscopy and culture • Dip test of urine and culture • Electrocardiogram and Echocardiogram • Consider serology for rickettsia and leptospirosis if history suggestive • Consider Chest X-Ray

Modified from: Brogan PA [4]

During the acute stage of illness, leukocytosis with predominant immature and mature granulocytes is classically found.[1,18] Children with KD have more common positive neutrophils' toxic granulation laboratory result compared to those with other febrile diseases. However, clinicians should keep in mind that sometimes significant neutropenia can be detected in the early stage, and this should be referred as a marker for other specific serious disease.[5] Although thrombocytosis is another typical feature of KD laboratory workup in most cases it usually does not appear until the second week, reaches its highest level in the third week (mean ≈700,000 per mm^3), and returns to its normal level by four to six weeks after onset of illness.[1,5] Other literature stated that in the most severe KD cases, secondary thrombocytes might escalate to 1,000,000/mm^3, a phenomenon called "reactive thrombocytosis".[1,18] No evidence shows that this phenomenon may lead to immediate thrombosis. Thus, experts recommend that treatment should only be given to KD patients who have other risk factors for thrombosis.[19] Normochromic and normocytic anemia is commonly discovered during KD laboratory workup, but it resolves along with the subsidence of KD's inflammation process. Forty to sixty percent of KD patients have

mild to moderate elevations of serum transaminases or gamma-glutamyl transpeptidase, and only 10 % of KD patients have mild hyperbilirubinemia.[1,18]

Clinicians should consider other illnesses if the suspected patient's ESR, CRP, and platelet count are within normal range after the 7th day of illness since Kawasaki disease diagnosis is least likely.[1] Persistent increasing ESR level after the fever recedes is a KD laboratory hallmark and may help doctors discerning KD from other infectious illnesses.[11] Elevated CRP (≥30 mg/l) and/or ESR (≥40 mm/hour) plus several other auxiliary laboratory tests (full blood count, ALT, plasma albumin, urinary white cell count) and echocardiogram results can provide information for doctors to make a clinical decision whether to treat KD patients with IVIG.[17] It is also important to remember that an increase in ESR count without any increase in CRP value may happen due to immunoglobulin therapy. Thus, ESR monitoring is not recommended for patients on the IVIG regiment.[18] Other blood chemistry parameters changes commonly found in KD are low serum protein and albumin, low serum sodium, elevated liver enzymes (ALT), and abnormal lipid profile (can be aggravated by IVIG treatment).[1,15] Our patient's lab result from Dr. Hasan Sadikin Teaching Hospital showed mild hypoalbuminemia (2.8 g/dl). She also experienced mild periorbital edema that might be a consequence of her hypoalbuminemia state (Fig.1c). Hypoalbuminemia and noncardiogenic edema in KD patient result from vascular leakage accumulation due to increased microvascular permeability and the role of vascular endothelial growth factor.[6] Moreover, hypoalbuminemia in KD is typical and associated with a more serious and more prolonged acute phase of the illness.[1,18]

Common ECG findings in KD patients (almost always reversible) are tachycardia, flattened T waves, decreased QRS voltages, and prolonged rate corrected QT intervals.[11,15] Arrhythmias, including heart block, may also occur. Electrocardiography may also show signs of MI due to coronary thrombosis in untreated large coronary artery aneurysms.[1,15] After transferred to Dr. Hasan Sadikin Hospital, our patient's ECG result was within the normal limit.

However, echocardiography (ECHO) is a more valid and sensitive supplementary examination to assess coronary artery aneurysms in the illness's acute and subacute stages.[2,11] Clinicians may reveal mitral regurgitation, decreased left ventricular function, and pericardial effusion from KD patients' ECHO results.[15] Moreover, ECHO can diagnose coronary aneurysms, which generally develop within two weeks of Kawasaki disease's onset. Coronary changes (z-score ≥ 2.5) can be seen in these KD patients, most commonly occurring in the LAD or RAC. The development of coronary aneurysms raises clinical suspicion for the diagnosis of KD.[16,18] In

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classic KD, an ECHO should be performed in the hospital at the time of diagnosis, followed by a repeat ECHO within two weeks. Doctors should also perform further ECHOs to assess illness improvement or progression at around 6–8 weeks.[11,16,18] Echocardiography follow-ups are also more frequently done in high-risk children with prolonged fever, pericardial effusion, coronary artery abnormalities, ventricle dysfunction, or valve regurgitation.[16,18] Echocardiography in our patient was done on her seventh day of fever (hospitalization day 4) in the transfer hospital. Our patient's echocardiography result showed mild posterior circumferential pericardial effusion with 0.27–0.54 mm size. Echocardiographic and cardiac angiographic data showed that around 20–40% of untreated KD patients develop coronary artery abnormalities. Approximately half of these lesions receded within five years, and in most patients with mild CAA (3–4 mm), regression occurs within two years.[4]

Occasionally, clinicians need to depict the coronary arteries' anatomy to investigate the extent of the vessel involvement in KD, making the additional imaging with a CT angiogram (CTA) or cardiac MRI as crucial examination in this step. However, a study suggested that in monitoring coronary aneurysms and their progression, CTA was equally invasive as an angiogram.[16] Common cardiac complications in Kawasaki disease are cardiac failures, cardiac tamponade, pericarditis, myocarditis, and coronary arterial abnormalities.[4,18] During the acute phase of Kawasaki disease, the universal findings of myocarditis and frequent diminished left ventricular function and contractility records should rise he clinicians' concern about KD's long-term effects on myocardial function.[11] Our patient was planned to received IVIG and aspirin as prompt management for incomplete Kawasaki Disease to prevent further risk.

The main objective of Kawasaki disease management strategy is to avoid long-term sequelae. The clinical error of inadequately managing a child with KD has a severe repercussion that, within reason and after cautious evaluation, the failure on unnecessary or premature therapy is preferable to missing or delaying therapy for a child whose KD diagnosis is vague. American Academy of Pediatrics and AHA recommend that aspirin and IVIG should be administered during the first ten days of the illness to those children diagnosed with Kawasaki.[1,15] Clinicians need to keep in mind that aspirin's administration as a single treatment for KD has not been subjected to randomized controlled clinical trials. Aspirin is administered in two different dosages. In the acute phase of the illness, it is given at relatively high "anti-inflammatory" doses (30–100 mg/kg/day)[4,17] till the time of defervescence and in "antiplatelet" dosages (2-5 mg/kg/ once daily) for at least 6-8 weeks,[9,11,19] or dependent on findings on echocardiography.[4] In the UK practices,

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pediatricians prescribe aspirin dose as 30 mg/kg/day during the acute phase of the illness for more tolerance of the gastrointestinal and other side effects.[4] In children with cardiac complications, particularly for children with small to medium aneurysms (<8 mm), low-dose aspirin (3–5 mg/kg daily) has been the pillar of KD therapy. Any other treatment administered beyond the first dose of IVIG and aspirin should be considered experimental.[2]

Experts recommend a long-term aspirin regiment for KD patients with persisting aneurysms on ECHO at 2–5 mg/kg/day. Pediatricians should consider another antiplatelet agent, such as dipyridamole, in the case of aspirin sensitivity in patients who have a particular risk of developing thromboses.[5] Due to ibuprofen's antagonizing action on the low-dose aspirin antiplatelet effects that causes children with KD to require more thrombosis protection, the AHA firmly against ibuprofen prescription for those children.[1] Pediatrician should discontinue aspirin after the patient's laboratory workup results return to normal (usually within two months of disease onset) if no coronary abnormalities are discovered during echocardiogram assessments and follow-ups.[5,11] Experts, through aspirin-binding studies, have warned that hypoalbuminemia in KD pediatric patients will make these patients more susceptible to toxic levels of free salicylate level, despite its "*within the therapeutic range*" measured values.[5,11] Our patient was put on an acute phase aspirin regimen with a range of 30–100 mg/kg/day (bodyweight 10kg) in divided doses 4 x 250mg orally for 5 days (day 6 to 10 of disease) as anti-inflammatory agent. On the 11th day of disease, her aspirin dosage was titrated down to 1 x 60 mg orally as antiplatelet.

The Kawasaki disease patients' coronary artery aneurysm (CAA) prevalence is positively affected by total IVIG dose but unaffected by aspirin dose administration.[4] About twenty to forty percent of these pediatric patients treated with aspirin alone will develop CAA. Study shows that CAA occurrence declines to 9% at 30 days and 4% at 60 days after the illness's onset when the combination regiment of aspirin plus high dose IVIG is administered as a single infusion.[4] Another study supports that the coronary artery abnormalities among pediatric patients with normal ECHO at the study initiation were significantly lower in those who received IVIG and aspirin combined than those who only received aspirin (3% vs 15%) in the seven weeks after treatment.[11] Recent studies have warranted and extended the evidence supporting IVIG's use as the mains therapy for Kawasaki syndrome.[2] The IVIG therapy should be started as soon as possible within the first ten days of the fever onset or when the KD diagnosis is established.[1,11] However, in KD patients exhibiting ongoing systemic inflammation (manifested by elevation of ESR ≥40 mm/hour or CRP ≥3.0 mg/dL) or whose diagnosis was missed earlier, IVIG should also

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be administered after the tenth day of illness.[1] Subsequent studies have shown that IVIG therapy is most significantly beneficial if administered in the early illness course. An epidemiological survey of more than 5000 patients in Japan treated with 2 g/kg IVIG proved that cardiac complications at one month after the beginning of disease were fewer in the group treated before day 6 of illness than another group treated later.[2]

Due to its possible mechanisms of action such as augmentation of regulatory T-cell activity, modulation of cytokine production, suppression of antibody synthesis, neutralization of toxins or other pathogenic agents, and provision of anti-idiotypic antibodies, the experts concluded that IVIG appeared to have a generalized anti-inflammatory effect.[1,20] The theories behind that mechanism of actions include the macrophages' Fc-II and Fc-III receptors cross-linking, endothelial cells and natural killer cells interaction blockage, selective induction of interleukin-1-receptor antagonist, interleukin-8 binding to complement fragments, induction of immune inhibitory receptors, and provision of specific antibody to the causative agent or a toxin. In-vitro study findings show that IVIG exerts blocking effects on endothelial-cell proliferation and synthesis process of adhesion molecules, cytokines, and chemokines.[2,20] Experts recommend that IVIG 2 g/kg be administered together with acetylsalicylic acid as a single infusion over 10 to 12 hours.[1,11,19]

Less severe adverse reactions related to the IVIG regiment, including fever, chills, and hypotension, are variously linked with the specific product infused. Due to the immunogenicity reduction of the passive antibodies in IVIG preparation which are "vaccine-related", clinicians should defer injections of live virus vaccines (mumps, measles, varicella and rubella) at least 11 months after IVIG administration.[2,11] In all USA health care system, high-dose IVIG usage is considered cost-effective. In contrast, some health centers in Japan only indicate IVIG therapy for children with a predicted high risk for CAA development.[11] Similar treatment limitation happens in Indonesia; the high cost of IVIG treatment in Indonesia makes it difficult for most patients without proper health insurance coverage to afford it. Thus, our patient did not receive IVIG treatment due to this financial issue.

Eosinophil count is one of the essential parameters of Kawasaki disease's IVIG treatment failure. Eosinophil count alteration after IVIG treatment was positively relevant with interleukin (IL)-5 levels change and inversely correlated with treatment failure. Eosinophils and IL-5 levels increments after the IVIG regiment were inversely correlated with coronary artery lesion formation.[20] Ten to fifteen percent of KD patients treated with high-dose aspirin plus 2 g/kg IVIG

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will have a recrudescent or persistent fever.[11,20] If the fever is persistent, studies have provided other successfully tested treatment options in small case series, including pulsed intravenous methylprednisolone (30 mg/kg for three days), plasmapheresis, cyclosporin, cyclophosphamide plus prednisone, and monoclonal antibodies to TNF for clinicians as alternatives.[2,20] Since our patient's parents decided to discontinue hospitalization; the Dr. Hasan Sadikin Hospital staffs had to discharge her and educate on KD complication and the importance of follow up.

The first year recurrence rate for Kawasaki Disease is around 2%.[16] There are uncertain significances of these clinical findings in patients with no coronary aneurysms in KD acute phase such as coronary and peripheral arteries vasodilatory capacity impairment up to 15 years after the illness; higher blood pressure (both diastolic and systolic) and blood triglyceride concentrations, as well as increased adiposity, compared to control group up to 11 years after the onset of illness, and the myocardial fibrosis findings on endomyocardial biopsy up to 11 years after disease. Therefore, due to the unclear description of the illness potential sequelae without coronary aneurysms, identifying the proper and adequate follow-ups for these KD patients is still considered arduous.[2] Experts recommend that clinicians should acquire the initial echocardiogram when suspecting a diagnosis of KD and repeat the echocardiography at two weeks and six weeks following the disease for every KD patient. Clinicians should also conduct clinical re-examinations during the first two months of the illness to detect the presence of cardiac abnormalities such as valvular insufficiency, myocarditis, dysrhythmias, or congestive heart failure.[5] Partial Kawasaki Disease should importantly keep it in mind as a differential diagnosis in prolonged fever patients. Careful diagnosis and prompt KD management are crucial to prevent further morbidity and mortality.

Conclusion

Atypical Kawasaki Disease can be a puzzling diagnosis due to its uncommon presentations. Clinicians should importantly keep it in mind as a differential diagnosis in patients with prolonged fever.

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