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Unexplained Direct Hyperbilirubinemia and New-Onset Shock in a 17-Year-Old Male

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Case Report

A 17-year-old African American male with a past medical history of depression was transferred from an outside hospital with a 3-day history of nonbilious, nonbloody vomiting and new-onset erythematous blanching macular rash on the trunk, arms, and legs. In the emergency department, the patient was tachycardic (134 beats per minute), hypertensive (142/98 mm Hg), and febrile with a temperature of 38.5°C. Four hours later, he became hypotensive (90/60 mm Hg) and remained tachycardic. Due to concerns of septic shock, blood cultures were drawn, and the patient was started on empiric antibiotic treatment. After admission to the hospital, subsequent workup demonstrated hyponatremia (135 mMol/L), direct hyperbilirubinemia (6.18 mg/dL), low lactate dehydrogenase (111 units/L), polymorphic neutrophil dominant leukocytosis (12 800/mm^3), elevated C-reactive protein (99.3 mg/L), and sterile pyuria.

Hospital Course

The patient's direct hyperbilirubinemia continued to rise, peaking at 14.12 mg/dL 8 days after admission. However, γ-glutamyl transferase, lipase, amylase, and transaminases remained within normal limits. Alanine aminotransferase, at 51 Units/L, was at the high end of the normal range. Further laboratory investigations for causes of direct hyperbilirubinemia were all negative. An ultrasound showed an over distended gallbladder, but further imaging studies—including a computed tomography and magnetic resonance cholangiopancreatography—were negative for obstruction. An extensive infectious disease workup was negative, including, but not limited to, cytomegalovirus, Epstein-Barr virus, group A *Streptococcus*, human immunodeficiency virus, hepatitis panel, and blood and urine cultures.

During the patient's hospital admission, he remained hypotensive and tachycardic despite several fluid boluses. He also developed a S3 gallop, orthopnea, elevated brain natriuretic peptide (2749 pg/mL), and respiratory distress, suggesting heart failure. A chest X-ray demonstrated bilateral lower lobe pleural effusions, and a subsequent echocardiogram appreciated a mild decrease in left ventricular function, mild mitral and tricuspid valve regurgitation, and a small posterior pericardial effusion, while the coronary arteries did not demonstrate pathology such as dilatations or aneurysms. The patient was transferred to the pediatric intensive care unit due to concerns of new-onset heart failure and worsening leukocytosis.

In the pediatric intensive care unit, the patient's heart failure and respiratory distress stabilized. Further laboratory investigation revealed new-onset microcytic anemia, thrombocytosis, elevated ferritin, and low albumin, indicating significant systemic inflammation. At this time, the patient was diagnosed with incomplete Kawasaki disease (KD) due to his complete clinical picture satisfying the diagnostic criteria (Table 1).

The patient's hyperbilirubinemia was likely from acalculous cholecystitis due to systemic inflammation associated with KD and was treated with ursodiol. On diagnosis of incomplete KD, the patient received 2g/kg intravenous immunoglobulin (IVIG) and a moderate dose of 30 mg/kg/day divided every 6 hours (7.85 mg/kg once a day [QID]). Additionally, the patient continued to receive supportive treatment for shock.

Four days following treatment, the patient improved and was discharged from the hospital. At this time, he reported feeling back at his baseline. Physical examination still demonstrated scleral icterus, as his direct bilirubin remained elevated at 4.24 mg/dL but down trending. He

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Table 1. Diagnostic Criteria for Incomplete Kawasaki Disease[a].

Clinical Presentation		Our Patient
Clinical features (2 or 3)	Fever ≥5 days	X
	Peripheral extremity changes	X
	Polymorphous rash	X
	Conjunctival injection	
	Oral mucous membrane changes	
	Cervical lymphadenopathy	
Additional characteristics (1 or 2)	Elevated CRP or ESR	X
	Echocardiogram changes	X
Supplemental laboratory criteria (≥3)	Thrombocytosis after the seventh day of fever	X
	Albumin ≤3.0 g/dL	X
	Elevated ALT level	X
	WBC count ≥15 000/mm	X
	≥10 WBC/hpf on urinalysis	X

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ALT, alanine aminotransferase; WBC, white blood cell; hpf, high-power field; LAD, left anterior descending coronary artery; RCA, right coronary artery.
[a]The diagnostic criteria for incomplete Kawasaki disease, and the criteria that our patient satisfied. Echocardiograph changes are considered positive if *Z* scores of the LAD or RCA ≥2.5; or if a coronary artery aneurysm is observed; or 3 or more of the following are observed: decreased left ventricular function, mitral valve regurgitation, pericardial effusion, and *Z* scores between 2 and 2.5 in the LAD or RCA.[1]

was discharged on low-dose aspirin (5 mg/kg/day) and ursodiol 300 mg QID. At the scheduled follow-up 10 days after discharge, he continued to improve: he had minimal residual peeling of his palms and soles and his bilirubin normalized. Echocardiogram demonstrated grossly normal coronary arteries, and his previous abnormalities were no longer appreciated.

Final Diagnosis

The patient's final diagnosis was incomplete KD with atypical features and Kawasaki disease shock syndrome (KDSS).

Discussion

Kawasaki disease is an acute febrile systemic vasculitis, typically found in young children, and is the leading cause of acquired heart disease in pediatric patients in developed countries.[1,2] The etiology of KD is unknown as there has yet to be a single unifying pathognomonic clinical or laboratory finding for the disease, and as such, we depend on the diagnostic clinical criteria for the diagnosis.[1] The diagnostic criteria are fever persisting at least 5 days and 4 of the following:

1. Changes in the extremities: erythema and edema of the hands and feet or membranous desquamation of the fingertips
2. Polymorphous exanthema of the skin
3. Bilateral, painless bulbar conjunctival injection without exudate
4. Changes in the lips and oral cavity: erythema and cracking of lips, strawberry tongue, or diffuse injection of the oral and pharyngeal mucosa
5. Cervical lymphadenopathy, usually unilateral

If there are fewer than 4 symptoms, the patient can still be diagnosed with KD if supplemental laboratory criteria are present or if coronary artery disease is detected by echocardiogram.

Up to half of the patients with KD may present without meeting all the diagnostic criteria; these cases, termed "incomplete" or "atypical" KD, carry the same risk of coronary artery disease as the complete form.[3] Historically, incomplete KD and atypical KD were used interchangeably. However, they are now considered 2 separate entities.[4] Patients with incomplete KD meet certain diagnostic criteria outlined in Table 1, whereas atypical KD present with findings rarely associated with the disease.[4] Atypical features may include neuronal deficits and hepatosplenomegally.[4] Our patient met the criteria for diagnosis on incomplete KD (Table 1), while also presenting with atypical features. He was older than the typical KD patient and developed severe, isolated direct hyperbilirubinemia with hemodynamic instability and new-onset heart failure. This clinical picture originally resembled that of septic shock, which was initially thought to be secondary to cholangitis or another infectious etiology but was ultimately found to be KDSS.

Kawasaki disease shock syndrome is a rare phenomenon in KD patients with an incidence of <10% of patients with KD.[5] In a 2009 article, Kanegaye et al defined KDSS as systolic hypotension (≤90 mm Hg in

individuals older than 10 years), a ≥20% decrease in blood pressure, or clinical signs of poor perfusion such as elevated lactate dehydrogenase.[5] Our patient met all of these criteria. Interestingly, KDSS may be more common in patients with incomplete KD compared with KD.[6] Similar to KD, the mechanism of KDSS is not well understood. However, a recently published retrospective study in China found that patients diagnosed with KDSS had significantly higher levels of cytokines, including interleukin-6, interleukin-10, tumor necrosis factor-α, and interferon-γ, suggesting that cytokines play a crucial role in the development of shock.[6] The increase in cytokines likely contributes to the decreased peripheral vascular resistance seen in KDSS.[1] Additionally, KDSS patients typically have cardiac dysfunction in the form of decreased ejection fraction and cardiac dyskinesia,[7] augmenting the SS.

In a study comparing KD with and without shock, KDSS patients were found to be diagnosed at an older age (mean age = 17.78 vs 23.2 months).[8] Patients with KDSS are more likely to present with atypical features that could lead to delayed diagnosis.[7] At 17 years old, our patient was much older than the typical age of presentation. He also had atypical features of KD, resulting in delayed treatment and an extended hospital stay. Our patient's clinical presentation was especially challenging, as he developed diagnostic features slowly throughout his hospital course. Eventually, however, his clinical picture met the criteria for incomplete KD (Table 1) with atypical features.

Furthermore, KDSS is a challenging diagnosis because of its resemblance to toxic shock syndrome (TSS). TSS is a toxin-mediated disease and can be misdiagnosed as KD due to similar clinical features of rash and fever. Compared with TSS patients, KDSS patients typically present younger (mean age = 36.8 vs 113.3 months), have significantly lower hemoglobin concentrations, and elevated platelet levels.[9] These identifying features were found to be statistically significant differentiators between KDSS and TSS; however, white blood cell count, liver function, and inflammatory protein levels were not statistically significant differentiators.[9]

Treatment of KD, including incomplete KD and atypical KD, consists of high-dose (2 g/kg) IVIG and moderate- (30-50 mg/kg/day) or high-dose (80-100 mg/kg/day) aspirin.[1] Other symptomatic features should be treated as appropriate, such as fluid resuscitation and vasopressors in KDSS. Our patient was given this regimen and responded well with complete clinical recovery. As seen in this patient's presentation, patients with both incomplete and atypical KD often receive IVIG later in their clinical presentation compared with patients with complete KD. This leads to a higher prevalence of coronary artery lesions and longer hospital stays.[10] To reduce morbidity and mortality, it is paramount that clinicians recognize the incomplete KD criteria and atypical features of KD and include it in the differential diagnosis of patients outside of the typical age range.[11]

Conclusion

The presented case is unique and teaches clinicians several important lessons. First, KD should remain on the differential diagnosis in older patient populations who present with unexplained fevers and other nonspecific clinical manifestations. This patient presented at 17 years old, whereas the mean age of diagnosis in the United States is around 3 years old.[11] He met the diagnostic criteria for incomplete KD (Table 1) while also presenting with atypical features, namely, KDSS and jaundice. KDSS, defined as hypotension and shock requiring fluid resuscitation and vasoactive agents, is a rare association of KD but needs to be recognized early. Naturally, delayed diagnosis prevents pertinent treatment. This delay can have dire consequences such as increasing the likelihood of coronary artery lesions, a common cause of morbidity in KD patients. Cytokine biomarkers might begin to play a pivotal rule in the early detection and diagnosis of the disease. We urge clinicians to diligently watch for signs and symptoms of incomplete or atypical KD with KDSS in patients with unexplained fever, hemodynamic instability, elevated inflammatory markers, and no identifiable infectious source.

Author Contributions

MH: contributed to conception and design; contributed to acquisition; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

LH: contributed to conception and design; contributed to acquisition; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

JYA: contributed to conception and design; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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Ethical Approval and Informed Consent

Per the Wayne State University guidelines, guardian and patient gave verbal assent for patient information to be included in this case report. Written consent was not required by institution guidelines.

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