Cholestatic Hepatitis as a Presentation of Atypical Kawasaki Disease: A Case Report

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ABSTRACT

Kawasaki Disease (KD) is an acute, multisystemic febrile vasculitis of unknown cause and is the leading cause of acquired pediatric heart disease in developed countries. It presents with a fever lasting more than five days, oral mucosa alterations, lymphadenopathy, rash, limb involvement, or conjunctival injection. Hepatic involvement can range from mild transaminase elevation to severe cholestatic hepatitis or gallbladder hydrops.

We present a case of a 5-year-old patient whose condition began with acute febrile cholestatic hepatitis of unknown origin. On the 14th day of illness, the patient developed non-purulent conjunctival injection, periungual desquamation, and thrombocytosis. Suspecting atypical KD, we performed an echocardiogram, revealing coronary involvement.

It is essential to consider the variability of symptoms in KD, as the prompt initiation of appropriate treatment reduces the occurrence and severity of associated complications.

Keywords: Kawasaki disease, lymph node mucocutaneous syndrome, cholestatic hepatitis, coronary

Hepatitis colestásica como forma de presentación de enfermedad de Kawasaki atípica: informe de un caso

RESUMEN

La enfermedad de Kawasaki (EK) es una vasculitis febril aguda, multisistémica de causa desconocida y la principal causa de cardiopatía adquirida pediátrica en países desarrollados. Cursa con fiebre mayor de cinco días, alteraciones en mucosa oral, linfadenopatías, *rash* (exantema), compromiso de miembros y/o inyección conjuntival. Puede haber compromiso hepático que puede abarcar desde un aumento leve de transaminasas hasta hepatitis colestásica grave o hidropesía (hidrops) vesicular, o ambas.

Se presenta a una paciente de 5 años cuyo cuadro comenzó con una hepatitis febril aguda colestásica, sin causa aparente. Al día 14 de evolución agregó inyección conjuntival no purulenta, descamación periungueal y trombocitosis. Ante la sospecha de EK atípica se realizó ecocardiograma que informó afección coronaria.

Resulta importante tener en cuenta la variabilidad de síntomas en la EK, ya que la rápida instauración del tratamiento adecuado disminuye la aparición y gravedad de las complicaciones asociadas.

Palabras clave: enfermedad de Kawasaki, síndrome mucocutáneo linfonodular, hepatitis colestásica, aneurisma coronario.

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INTRODUCTION

Kawasaki disease (KD) is an acute febrile, multisystemic vasculitis of unknown cause, predominantly affecting children under five years of age[1], first described in 1967 by T. Kawasaki[2]. It is the most common cause of acquired pediatric heart disease in developed countries[3].

The diagnosis is clinical, and the main criteria are fever lasting more than five days, changes in the oral mucosa, lymphadenopathy, skin rash, involvement of peripheral extremities, or conjunctival injection.

The main complications occur at the cardiac level. The most common is coronary artery dilation, which leads to aneurysm formation. Other complications include acute myocardial infarction and, less frequently, coronary fistulas[4,5].

Liver involvement may occur, ranging from a mild asymptomatic increase in liver enzymes to severe cholestatic hepatitis or hydrops of the gallbladder, which is a factor associated with a higher risk of resistance to intravenous immunoglobulin (IV)[6-8]. Cholestasis without ultrasound abnormalities in the gallbladder and intrahepatic bile ducts is uncommon[9].

We present a 5-year-old girl with atypical KD and coronary involvement, whose initial presentation was cholestatic hepatitis. The timeline of the clinical symptoms differs from that of other patients reported in the literature.

CLINICAL CASE

A 5-year-old female patient previously healthy whose clinical picture had started three days before the initial consultation with fever and asthenia, followed by choluria, pale stools, and generalized jaundice. She went to the Emergency Department, where she was diagnosed with weakness, feverish, generalized jaundice, and hepatomegaly. Blood tests showed hyperbilirubinemia with a predominance of direct bilirubin (total bilirubin 23.49 mg/dL; direct bilirubin 19.86 mg/dL), elevated transaminases (ALT 150 U/L; AST 107 U/L), ALP 568 U/L, GGT 273 U/L, leukocytosis (23.2 thousand/mm^3), normocytic normochromic anemia without need for transfusion (hemoglobin 10.3 g/dL; MCV 79; MCH 27.1; MCHC 34.3), platelets 355,000/mm^3, and CRP 81 mg/L. We decided to hospitalize her with a diagnosis of acute hepatitis with cholestasis for further evaluation and treatment.

We ordered blood and urine cultures to rule out an infectious cause without microbiological results. Viral serologies (HIV, HAV, HBV, HCV, EBV, and Parvovirus B-19 were negative; CMV IgG was positive), and a Widal agglutination test to rule out salmonellosis was negative. Abdominal ultrasound and echocardiogram showed no pathological findings. Immunological lab results (IgG, IgA, IgM, C3, C4, ANA, ANCA, ASMA, anti-LKM, anti-transglutaminase, and anti-deamidated gliadin peptide) were normal.

She received empirical treatment for suspected cholecystitis with cefotaxime at 150 mg/kg/day for seven days.

Due to clinical and liver function improvement and a progressive decrease in acute-phase reactants, and without a definite etiologic diagnosis, she was discharged from the hospital with outpatient follow-up.

Fourteen days after the onset of symptoms, we evaluated the patient in a fair general condition, with the reappearance of fever. On physical examination, she presented with jaundice, conjunctival injection without discharge, hepatomegaly, and periungual desquamation on both hands. Blood tests revealed anemia (Hb 8.6 g/dL) and thrombocytosis (1,200,000 platelets/mm^3). Due to the suspicion of atypical Kawasaki disease, we decided to readmit the patient and performed a transthoracic echocardiogram (TTE), which showed dilation of the ostium and trunk of the left coronary artery (3.5 mm; Z +2-3), uniform dilation of the anterior descending artery, and mild mitral regurgitation (Fig. 1). She started intravenous immunoglobulin (IVIG) treatment at 2 g/kg along with acetylsalicylic acid (ASA) at 5 mg/kg/day. Because of persistent fever after 48 hours, we assumed refractoriness to treatment and started methylprednisolone 30 mg/kg pulses on three consecutive days, with a good response.

After thirteen days of hospitalization, with clinical and laboratory improvement (liver function tests and acute-phase reactants), hospital discharge was granted, continuing treatment with maintenance-dose methylprednisolone, ASA 5 mg/kg/day, and outpatient follow-ups with rheumatology and cardiology.

A follow-up transthoracic echocardiogram (TTE) showed a progressive decrease in the dilation of the left coronary artery, and normalization was achieved two months after the onset of the condition.

DISCUSSION

Kawasaki disease (KD) is an acute, self-limited systemic vasculitis of unknown etiology; the main theory suggests that a prior infection triggers the activation of the immune system in a genetically predisposed child.[5]

If no specific complementary tests are available, the diagnosis is clinical and based on core and associated criteria[1] (Table 1). KD requires the presence of fever lasting five or more days; when four or more of the five major characteristics are present, it is known as "complete or typical KD," while when two to four manifestations are present, it is called "incomplete or atypical KD." That includes cases with unusual symptoms, such as hemophagocytic secondary syndrome and nephritis, etc.[10]

Atypical or incomplete forms occur in nearly 20% of patients; they are more frequent in younger patients, although they can also appear in those older than five.[1] In these cases, laboratory tests and echocardiograms are recommended to ensure timely diagnosis and proper follow-up.[11] (Fig. 2).

In this case report, we present a patient with acute hepatitis.

During the illness, we suspected this condition due to the presence of febrile syndrome associated with conjunctival injection, periungual desquamation

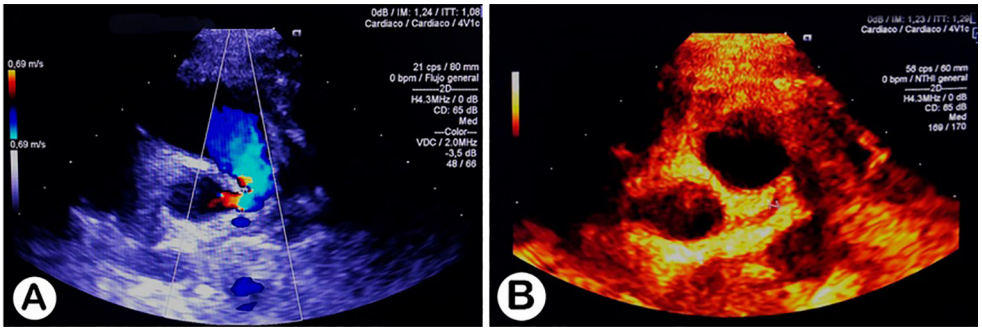

Figure 1. Transthoracic echocardiogram: dilation of the ostium of the left coronary artery and trunk with a diameter of 3.5 mm (Z-score +2.3). Left anterior descending artery with a diameter of 2 mm (Z 0.6). Right coronary artery with a diameter of 2 mm (Z 0.6).

Table 1. Diagnostic criteria for Kawasaki disease[1]

CRITERION	DESCRIPTIÓN
Mandatory criterion	
Fever	Duration ≥ 5 days (including cases where the fever subsided before the fifth day due to therapy response))
Main criteria	
Oral mucosa alterations	Erythema of the lips, strawberry tongue, diffuse congestion of the oral and pharyngeal mucosa
Lympadenopathy	Acute non-suppurative cervical lymphadenopathy (at least 1 lymph node > 1.5 cm in diameter)
Rash	Polymorphous skin rash, morbilliform or scarlatiniform
Peripheral extremity involvement	Redness of the palms and soles, indurated edema (initial stage): membranous peeling of the fingertips (subacute stage))
Ocular involvement	Bilateral conjunctival injection without exudate

Complete KD: fever + four principal criteria.

Incomplete KD: suspected KD that does not meet at least four of the principal criteria.

(two out of the four main KD criteria proposed by the American Heart Association [AHA]), and elevated acute-phase reactants, especially a thrombocytosis greater than 1,000,000 platelets/mm^3. Therefore, we performed a transthoracic echocardiogram (TTE), which revealed coronary involvement, confirming the diagnostic suspicion. Based on the clinical findings and the previously mentioned disease timeline, she was assumed to be in the subacute phase of the disease, with fever reappearing on day 14 from symptom onset.

Literature reports cases of KD where the presenting symptom was cholestatic jaundice and, as complications, gallbladder hydrops and coronary involvement. In those cases, after assuming the diagnostic suspicion and establishing treatment with intravenous immunoglobulin, there was clinical improvement, followed by resolution of the condition.[12–15]

The literature reports cases of KD where the initial presentation was cholestatic jaundice, and complications included gallbladder hydrops and coronary involvement. In these cases, after assuming the diagnostic suspicion and initiating intravenous immunoglobulin treatment, there was a clinical improvement, followed by resolution of the condition.[12–15]

Although the patient initially presented with a cholestatic laboratory pattern, abdominal ultrasounds showed no hepatobiliary involvement. During the illness, the laboratory results spontaneously improved, even before the administration of intravenous immunoglobulin, which distinguishes our patient

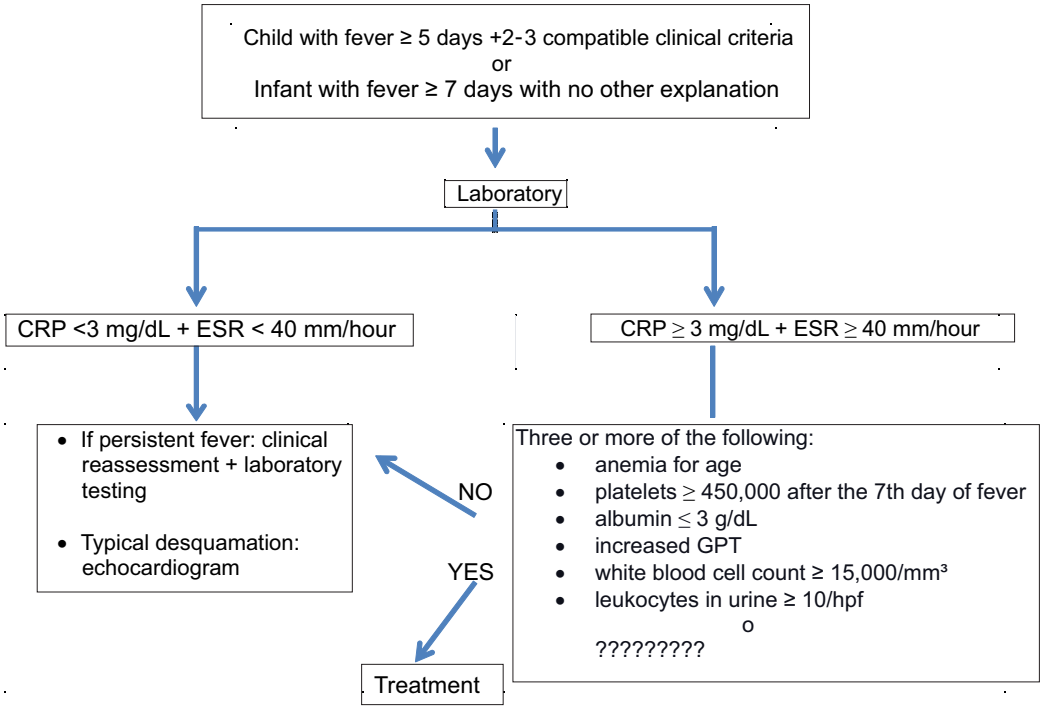

Figure 2. Algorithm for the evaluation of a patient with suspected incomplete KD[1]

from the cases recorded in the literature, where such improvement appeared after the administration of intravenous immunoglobulin.[15]

The prognosis of KD mainly depends on the presence and severity of coronary involvement, which can range from mild and transient dilations to giant aneurysms.[1] Coronary artery lesions occur in 25% of untreated KD patients and can also appear in 3-5% of patients who received intravenous immunoglobulin.

Intravenous immunoglobulin (IVIG) treatment administered within the first ten days of disease onset reduces the prevalence of coronary artery lesions to < 5%.[4] After the acute phase, the treatment must be carried out with patients with persistent fever and elevated acute-phase reactants or with those found to have coronary abnormalities.[10]

Those patients with KD who persist with fever 48 hours after the first dose of IVIG - or do not show a decrease in PCR higher than 50%- are considered resistant and should receive a second dose. If this fails, refractoriness is assumed, and other therapeutic options should be considered, along with consultation with an expert team.[10] These patients are thought to present a "hyperinflammatory phenotype," which would be associated with a higher risk of coronary involvement and other complications. Several factors are associated with such resistance, including abnormalities in liver function tests and abdominal involvement (pain, distension, diarrhea, bloody stools, etc.),[16] as evidenced in the case presented.

The diagnosis of atypical KD is a challenge for pediatricians, given the variety of clinical presentations, which can lead to delayed diagnosis, thereby increasing the risk of complications.[11] Based on this case, we suggest considering KD as a differential etiological diagnosis for febrile cholestatic acute hepatitis after discarding the more common causes of the condition since the rapid initiation of appropriate treatment will reduce the occurrence and severity of associated complications. It is important to remember that some symptoms -- such as unexplained fever, laboratory abnormalities like hypoalbuminemia or hyponatremia, or sustained sinus tachycardia that does not correlate with the fever-- increase the sensitivity for diagnosis.

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