CASE REPORT

The diagnosis challenge of the incomplete Kawasaki disease

O desafio diagnóstico da doença de Kawasaki incompleta

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DOI: 10.5935/2238-3182.20150019

ABSTRACT

Objectives: Kawasaki disease is an acute self-limiting systemic vasculitis that affects medium and small caliber vessels, preferably the coronary arteries. Patients who do not present all the necessary criteria for diagnosis are classified as bearers of the incomplete form. This study describes a child with the incomplete form of Kawasaki disease emphasizing the clinical and laboratory aspects that may be of aid in the disease diagnosis. **Case description:** male patient, six years old, with fever, myalgia, and meningeal signs admitted to the hospital with a diagnosis of meningitis. He presented bilateral conjunctival hyperemia and conjunctival hemorrhage. The spinal tap showed pleocytosis and elevated proteinorachy. Started treatment for meningoencephalitis, with the disappearance of fever and meningeal signs. On the third day of hospitalization expressed heart failure, and the fever reemerged four days after persisting for seven days. The research of infection was negative. After fever defervescence, the echocardiogram revealed dilated coronary. The incomplete Kawasaki syndrome was diagnosed. On the same day, laminar desquamation was observed at fingertips. **Discussion:** the incomplete Kawasaki syndrome should be considered in every child with prolonged fever for more than five days without apparent focus, associated with some of the main typical manifestations. The late diagnosis represents higher risk for coronary artery disease.

Key words: Mucocutaneous Lymph Node Syndrome/diagnosis; Coronary Disease; Child.

RESUMO

Objetivo: *a doença de Kawasaki é uma vasculite sistêmica aguda autolimitada que acomete vasos de médio e pequeno calibres, preferencialmente as artérias coronárias. Os pacientes que não apresentam todos os critérios necessários para o diagnóstico são classificados como portadores da forma incompleta. Este trabalho descreve criança com a forma incompleta da doença de Kawasaki, ressaltando os aspectos clínicos e laboratoriais que possam ser de auxílio no diagnóstico da doença.* ***Descrição do caso:*** *paciente masculino, seis anos de idade, com febre, mialgia e sinais meníngeos admitido no hospital com diagnóstico de meningite. Apresentava hiperemia conjuntival bilateral e hemorragia conjuntival. A punção lombar evidenciou pleocitose e elevação da proteinorraquia. Iniciado tratamento para meningoencefalite, com desaparecimento da febre e dos sinais meníngeos. No terceiro dia de internação manifestou insuficiência cardíaca e quatro dias após a febre ressurgiu, persistindo por sete dias. A pesquisa de foco infeccioso era negativa. Após a defervescência da febre, o ecocardiograma revelou coronárias dilatadas. Diagnosticada a síndrome de Kawasaki incompleta. No mesmo dia, foi observada descamação laminar nas pontas dos dedos das mãos.* ***Discussão:*** *a síndrome de Kawasaki incompleta deve ser considerada em toda criança com febre prolongada por mais de cinco dias sem foco aparente, associado a algumas das principais manifestações típicas. O diagnóstico tardio representa alto risco de coronariopatias.*

Palavras-chave: *Síndrome de Linfonodos Mucocutâneos/diagnóstico; Doença das Coronárias; Criança.*

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Submitted: 2013/03/22
Approved: 2014/02/19

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INTRODUCTION

The Kawasaki disease is an acute self-limiting systemic vasculitis that affects medium and small caliber vessels, preferably coronary arteries. It is considered the leading cause of acquired heart disease in children in developed countries, affecting mainly those under five years of age.[1]

In the absence of a laboratory exam that can identify patients with the disease, clinical criteria for the diagnosis were proposed based on at least five days of fever and four or more of the five major clinical characteristics: edema and peeling of extremities, polymorphous exanthema; non-exudative bilateral conjunctivitis; lip dryness, enanthema in the oral mucosa; and cervical unilateral lymphadenomegaly.[2] Patients who do not present all the necessary criteria for diagnosis are classified as suffering from the incomplete form. In the past, the term atypical and incomplete Kawasaki were mixed up, however, currently, the term "incomplete" is preferred to "atypical" because patients with this form demonstrate the absence of clinical signs to meet the diagnostic criteria and do not display symptoms that can be classified as atypical.[2]

The concept of incomplete Kawasaki disease should be applied to patients with fever for five days or more associated with at least two of the clinical criteria used for the diagnosis of the disease if they have laboratory data consistent with systemic inflammatory disease and no other explanation for the clinical framework.[2] The incomplete form of Kawasaki disease affects mostly infants, less than six months old, and children over five years of age; a high risk of coronary artery disease is particularly observed in the youngest group.[2]

The incomplete Kawasaki diagnosis is considered of extreme importance because of the high risk of developing coronary artery abnormalities. This study describes the case of one child with the incomplete form of Kawasaki disease, emphasizing the clinical and laboratory aspects that may be of aid in the disease diagnosis. The project was approved by the Research Ethics Committee of the Hospital where the child received assistance.

CASE REPORT

Male patient, six years of age, with fever and headache for two weeks, referred to the João Paulo II Children's Hospital (Hospital Foundation of Minas Gerais) with suspected meningitis. He had received a previous diagnosis of sinusitis, evolving with clinical worsening with the use of amoxicillin for seven days. The admission showed signs of meningeal irritation, bilateral conjunctival hyperemia with sub-conjunctival hemorrhage, and discreet lip dryness. The physical examination did not show exanthema, cervical lymphadenomegaly, or alterations in the oral cavity.

A lumbar puncture performed on admission showed discrete pleocytosis and elevated proteinorrhachia (Table 1). Other laboratory tests showed elevated C-reactive protein and thrombocytopenia (Table 1). Polymerase chain reaction (PCR) for the simplex herpes virus type-1 and 2 and bacteria culture were requested in the liquor; the treatment for meningoencephalitis was immediately initiated with ceftriaxone and acyclovir.

Table 1 - Laboratory data during the patient's hospitalization

	1st DIH	3rd DIH	5th DIH	7th DIH	9th DIH
Hemoglobin/Hematocrit (g/dL/%)	11.7/33.4	9.6/29	10/30	10.2/32	9.2/28
Global white blood cells/mm³	4200	6500	7800	12700	12500
White cell count (%)	0/73	0/79	7/62	2/2/2/73	0/70
Platelets/µL	89000	156000	232000	440000	741000
C-reactive protein (mg/dl)	170	178	223	131	84
Albumin (g/dl)		1.6			
AST/ALT (U/L)	19/23	23/27		33/31	55/62
Liquor fluid	18 (90% poly-morphonuclear) cells; 60 mg/dl glucose; 85 mg/dl proteins; Gram stain and culture of liquor: negative	18 cells (68% of lymphocytes); 87 mg/dl glucose; 70 mg/dl protein			

DIH: day of hospitalization.

After the medication initiation, the patient remained afebrile already on the second day of treatment, with the improvement of neurological symptoms and spontaneous resolution of conjunctival and labial alterations. On the third day of hospitalization, he evolved into cardiogenic shock with increased cardiac area and pulmonary congestion. He was transferred to the intensive care unit where he received diuretics and amines until resolution of the clinical picture. At that time, a skull tomography, without alterations, and a new lumbar puncture, was performed, which showed persistent pleocytosis and hyper-proteinorrhachia (Table 1). The herpes-simplex virus and examinations of Gram and culture research in the liquor turned out negative.

The possibility of aseptic meningitis secondary to an infectious systemic involvement framework was raised after the heart and neurological involvement and negative results for viral and bacterial liquor research were known. From there, chances of infection by the dengue virus were raised considering the high endemicity of this disease in the region, in addition to leptospirosis and Rocky Mountain spotted fever; serologic tests for the diagnosis of these diseases were requested. While waiting for the test results, the therapy with ampicillin and chloramphenicol to cover the possibilities of leptospira and Rickettsia rickettsii was initiated. The epidemiological data of the patient reported previous contact with rats or ticks.

He was discharged from the intensive care unit on the seventh day of hospitalization when he spiked a fever. He evolved from that day on, with clinical stability and fever maintenance, which persisted for seven days; the research on febrile focuses was negative. The laboratory tests performed during the febrile period revealed the resolution of the thrombocytopenia previously observed, with a tendency to thrombocytosis, discrete anemia, and persistent leukocytosis with the emergence of immature forms. The C-reactive protein showed persistently high values since his admission (Table 1). The serological tests proved negative for the diagnosis of dengue fever, Rocky Mountain spotted fever, and leptospirosis.

On the ninth day of hospitalization, an echocardiogram was conducted as propaedeutics of heart failure, which had already been requested for four days. The echocardiogram revealed normal-looking chambers; coronaries in normal positions with ostia dilatation, and proximal portions (right coronary: 0.4 cm; left coronary: 0.6 cm). Given the observed alterations, the child was evaluated by the Pediatric Cardiology team, which considered the coronary dilation significant and suggestive of Kawasaki disease. Based on the clinical alterations shown during the patient's evolution, associated with the maintenance of elevated inflammatory proteins in the blood, emergence of thrombocytosis, and observation of coronary disease, the diagnosis of incomplete Kawasaki disease was reached and the antiplatelet therapy with acetylsalicylic acid was started. Treatment with immune globulin was not chosen because the patient was afebrile. On the same day, laminar desquamation on fingers and toes tips was observed.

DISCUSSION

The diagnosis of incomplete Kawasaki disease is challenging because the typical disease-related criteria are flawed in the recognition of the clinical picture, and there is a possibility that the manifestations that may occur at different times.[3, 4, 5] The incomplete clinical picture has been described as an important factor related to the late diagnosis of the disease due to the difficulty in the diagnostic definition in the absence of clinical criteria. In this case, in addition to the fever that persisted for seven days, only conjunctival hyperemia and lip fissures qualified among the classic signs of the disease. However, other not well-described alterations were also observed such myocarditis, aseptic meningitis, and conjunctival hemorrhage, which when linked to the laboratory data were critical for the final diagnosis.

The incidence of coronary aneurysms increases by about three times when the diagnosis is late, and treatment is started after the 10th day of illness.[6] Other studies published in Japan show that approximately 15 to 20% of cases of coronary heart disease occur in children who present less than four diagnostic criteria.[5]

The differential diagnosis of the Kawasaki disease is vast and includes other diseases, which also manifest clinical pictures of exanthema, lymphadenopathy, and alterations in the oral cavity and ocular conjunctiva such as rubella, adenovirus, mononucleosis, scarlet fever, and leptospirosis.[2] In addition, some studies show that previous infectious frameworks could act triggering vasculitis mediated by immune complexes, which in predisposed individuals would result in the disease emergence. Such claim is based on the temporal correlation between the two enti-

ties: the endemic nature of Kawasaki disease and increased risk of disease in household contacts. Studies show that 33% of patients with Kawasaki disease had concomitant infections at the beginning of the clinical picture as was observed in this patient.[3,4]

Myocarditis in Kawasaki disease is present in at least 50% of cases and results from the infiltration of inflammatory cells in the myocardial interstitium. Heart failure is a rare clinical presentation.[4] Cardiogenic shock has been described in some cases of the disease, being compatible with a reduction in the left ventricular contractility that may be observed in the acute phase.[5] In a study conducted in California, 13 patients expressed cardiogenic shock.[3] In the late stage, most commonly after the 10th day of evolution, coronary aneurysms are observed, which is a highly suggestive abnormality of this disease when identified in children.[2] The literature shows that coronary disease in childhood has also been observed in patients with juvenile idiopathic arthritis, lupus, and polyarteritis nodosum. However, in these cases, other signs that are suggestive of chronic inflammatory disease are commonly registered.[2]

Renal, gastrointestinal, neurological, and ocular and lung involvements have been described in the Kawasaki disease and may be present in the incomplete form.[2] Although these do not match the characteristic findings for the confirmation of disease, they are important symptoms on the suspicion of the incomplete disease because they can favor the diagnostic hypothesis.

The nervous system is rarely involved, but reports of neurologic manifestations are increasing in the literature.[5] Its involvement is generally related to the severe form of the disease. Aseptic meningitis occurs in up to one-third of cases, and may explain the extreme irritability in children. Some authors state that meningitis appears to be more common than believed because spinal puncture is rarely performed.[2, 5,7]

Conjunctival hyperemia has been associated with previous uveitis in 83% of patients examined in the first week of illness and is among the typical manifestations of Kawasaki disease. Other ophthalmologic alterations can occur in acute and subacute phases of the disease suggesting that the ophthalmologic examination can aid when suspecting the disease. Among them, the conjunctival hemorrhage has been described as an important finding as well as point keratitis, optic neuritis, amaurosis, and papilledema; these findings are not described among ocular alterations that are characteristics of the typical disease.[2,7]

The laboratory findings in the typical Kawasaki disease have also been found in the incomplete form. The main alterations are described as thrombocytosis (more evident after the second week of illness), elevation in the C-reactive protein and erythrocyte sedimentation rate (ESR), anemia, leukocytosis with immature forms, and hypoalbuminemia are common findings in both forms of disease.[2,5] This data is of great assistance in the diagnosis of the incomplete form because they can be observed despite the absence of clinical criteria.[5] The increase in inflammatory markers such as C-reactive protein and ESR is observed in most cases of Kawasaki disease, and their normalization occurs only after six to 10 weeks from the onset of symptoms.[5]

These findings are important in the differential diagnosis in clinical pictures with prolonged fever because the elevation of inflammatory proteins is not present in infections by viral agents. Anemia has been described as a bad prognosis factor and is related to coronary heart disease, hearing loss, and cognitive sequelae.[2,3,4,7] Leukocytosis is a typical finding in the acute phase of disease, with predominance of mature and immature granulocytes and registered in approximately 50% of patients.[5,8] Thrombocytosis is a typical finding in the disease after the first week of evolution, however, thrombocytopenia, although uncommon, has been considered by some authors in the acute phase of the disease and associated with high risk for coronary aneurysm.[5] Patients with hypoalbuminemia tend to have the more severe and prolonged acute disease.[8]

CONCLUSION

The diagnosis of Kawasaki disease in its incomplete form constitutes a challenge for physicians because of the difficulties encountered due to the absence of characteristics of the typical disease, from which, the diagnosis is established. Thus, the knowledge about more rare manifestations and laboratory alterations is important because they can assist in the formulation of a diagnostic hypothesis. The difficulty in the diagnosis of incomplete Kawasaki disease was evident in the approached clinical case and serves to alert about the need for high levels of suspicion of the disease in patients with fever for more than five days without an apparent focus. The late diagnosis reveals a high risk of unfavorable disease evolution because it is associated with a significant incidence of coronary artery diseases and cardiac sequelae.

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