KAWASAKI DISEASE IN A YOUNG INFANT: DIAGNOSTIC CHALLENGES

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Abstract

Kawasaki disease (KD) is a multisystem vasculitis condition with a relatively unknown etiology. It has a high prevalence in children ages 6 months to 5 years, and patients often present with high fever, rash, cervical lymphadenopathy and mucocutaneous abnormalities. Visceral manifestations can be present, being coronary complications the most frequent. There is no diagnostic test for KD, its presentation can be complete or incomplete and, in some cases, it can be atypical. We report a case of a 3-month-old infant with 3-weeks of fever and aseptic meningitis. Infectious diseases were excluded and there was no response to antibiotics. Echocardiography was normal in the second week. Genetic test for CINCA syndrome was negative. In the third week, dilatation of coronary arteries determined Kawasaki disease's diagnosis. Prolonged fever, accompanied by nonspecific clinical symptoms were the only manifestations, becoming a challenging diagnosis. KD must be considered when prolonged fever is present, mainly in young children in whom the incomplete forms of the disease are more frequent.

Keywords: Kawasaki Disease; Vasculitis; Incomplete; Coronary Artery Aneurysms; CINCA Syndrome.

Introduction

Kawasaki disease (KD) is an acute, multisystem and self-limited vasculitis of unknown etiology that has a striking predilection for the coronary arteries of infants and young children[1]. Since its first description by Tomisaku Kawasaki in 1967, this enigmatic illness has surpassed acute rheumatic fever as the leading cause of acquired heart disease among children in developed countries[1,2].

Incomplete KD is more common in young infants than in older children, making accurate diagnosis especially important because of their higher risk for developing coronary abnormalities[6,7]. Coronary artery aneurysms occur in 20 to 25% of untreated children, predominantly in young children, with 80% of patients being younger than 5 years old[1].

Therapy with IVIG must be started within the first 10 days of illness because timely diagnosis and early treatment are two crucial points for KD's prognosis[6,8,10]. However, even when treated appropriately, 5% of children develop coronary artery dilatation and 1% develop giant aneurysms.

Case report

A previously healthy 3-month-old caucasian female infant, born to non-consanguineous parents, with an unremarkable past medical history, presented with a two-weeks high-grade (39ºC) continuous fever with diarrhea during the first three days. Before hospital admission, she was prescribed amoxicillin clavulanate for suspected urinary tract infection. Physical examination revealed a febrile (38,7ºC), but "non-ill appearance" child. Bilateral cervical and inguinal lymph nodes were enlarged (<1cm in diameter), accompanied by a subtle hepatomegaly. Cardiopulmonary examination was normal. There was no rash, conjunctival injection, changes in the lips or oral cavity or edema/erythema of the hands.

Laboratory findings showed normocytic anemia (haemoglobin – 8.7 g/dL), leukocytosis of 13,100/mm³ (44% neutrophils; 42.5% lymphocytes), thrombocytosis of 891,000 platelets/mm³, C-reactive protein of 11.39 mg/dL, erythrocyte sedimentation rate of 110mm/1st hr. Chest radiogra-

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phy was normal.

Examination of the cerebrospinal fluid (CSF) was compatible with meningitis - white blood cell count – 25/mm³ with polymorphonuclear predominance, protein – 70.1 mg/dL, glucose – 52 mg/dL, and intravenous ceftriaxone was started. Transfontanelar ultrassonography was normal. CSF Gram stain and culture were sterile and protein-chain reaction for herpes simplex 1 and 2 was negative. Additional analytic findings: hypoalbuminemia (2.6g/dL), hyperferritinemia (360ng/mL) and mild elevation of hepatic aminotransferases. Abdominal ultrassonography showed an heterogenous hepatomegaly.

Echocardiography excluded cardiac involvement and ophthalmologic evaluation was normal.

The patient remained febrile until day 20 of illness, with no response to antibiotics and persistently elevated acute phase reactants (Figure 1). Exhaustive laboratory searching for infectious and autoimmune diseases was negative (Table I). Considering the association of persistent high fever with aseptic meningitis, genetic test for *chronic neurologic cutaneous and articular* (CINCA) Syndrome was performed and it was negative.

On day 22 of illness she developed a maculopapular erythematous rash of the trunk, palms and soles followed by periungual desquamation of the fingers and toes. At that time echocardiography showed right and left coronary arteries dilatation (3,4 and 4,2 mm in diameter respectively – Figures 2 and 3). IVIG 2 g/kg and acetylsalicylic acid 100 mg/kg/day were started, with significant clinical and analytic improvement (Figure 1). On hospital day 39 of illness, the patient was discharged home on high-dose aspirin, which was reduced to 5mg/kg/day two weeks later. Follow-up echocardiography at week 4 of therapy showed persistent coronary arteries dilatation (4mm) which was subsequently improved at week 8. Aspirin was discontinued after complete resolution of coronary involvement, demonstrated by coronary angiocomputed tomography, at 4 months of treatment.

Discussion

Although KD primarily affects young children

					IVIG ↓	Discharge ↓				
Day of illness	**D11**	**D14**	**D17**	**D20**	**D22**	**D28**	**D34**	**D49**	**D83**	**Units**
Hemoglobin	8.7	8.7	8.0	7.9	8.9	9.4	10	11.2	10.8	**g/dL**
White blood cell	9,300	11,900	12,400	6,700	10,900	12,700	8,200	8,900	7,400	**X10³/µl**
Platelets	891	987	891	891	891	891	588	413	421	**X10³/µl**
C-reactive protein	11.39	11.24	10.84	6	6.7	2.55	2.37	1.51	0.53	**mg/dL**
Erythrocyte sedimentation rate	110	100	80	80	122	110	79	–	23	**mm/1st h**

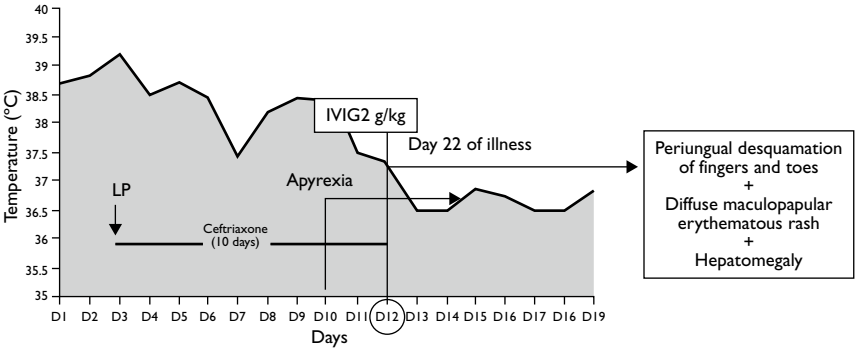

Figure 1. Clinical and laboratory evolution during hospitalization and after discharge
Legend: LP – lumbar punction; IVIG – Intravenous Immunoglobulin

Table I. First laboratory searching for infectious and autoimmune diseases

Infectious Etiology	
Antistreptolysin O test (ASO); anti-Dnase B	Normal; <200 U/ml
Venereal Disease Research Laboratory (VDRL)	Negative
PCR for *Enterovirus* and *Adenovirus* (stool) and *Human Herpesvirus type 6* (blood)	Negative
Serologic evaluation for *Cytomegalovirus, Epstein-Barr* virus, *Parvovirus, Adenovirus, Respiratory syncytial virus* (RSV), *Influenza and Parainfluenza* virus, *Rickettsias, Mycoplasma pn, Chlamydia pn, Human immunodeficiency virus* (HIV) 1 and 2, *Hepatitis B virus* (HBV), *Hepatitis C virus* (HCV), *Toxoplasma gondii, Brucella* and *Leishmania*	Negative
Tuberculin test	Anergic
Cultures from blood (2), stool (3), sputum and urine	Sterile
Immunologic Evaluation	
Antinuclear, anti-DNAds, anti-sm, anti-RNP and anti-smoth muscle antibodies	Negative

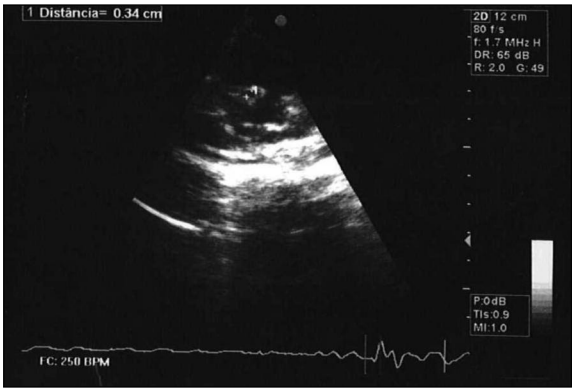

Figure 2. Echocardiography image showing right coronary artery dilatation (3.4mm in diameter)

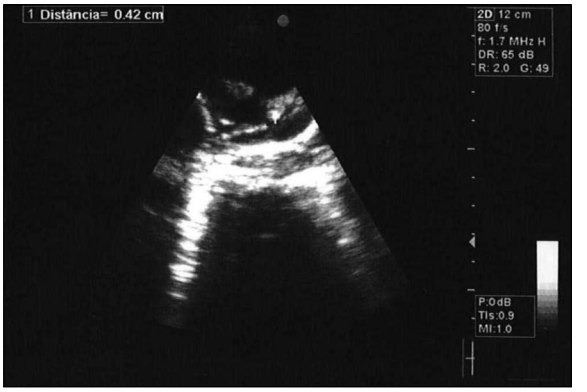

Figure 3. Echocardiography image showing main left coronary artery dilatation (4.2mm in diameter)

(peak incidence - 2 years), it is uncommon in children younger than 6 months-old and quite more under 3 months-old, accounting for only 1.6% of all patients with KD[11-13].

Patients who do not fulfil classic criteria for KD's diagnosis, besides the presence of five or more days of fever, should be referred as "incomplete" KD rather than the past designation of "atypical" KD, which should be reserved for patients who have unusual manifestations[3]. KD under 6 months-old is more likely to be incomplete and associated with coronary artery aneurysms[1,5,12]. Remains unclear whether young infants have a greater propensity to develop coronary artery aneurysms or if this complication results from delayed diagnosis in incomplete KD. Sometimes the presence of coronary artery aneurysms may be the only definite means to diagnose incomplete KD[7]. On the other hand, diagnosis may be delayed because signs and symptoms are not present simultaneously, but appear sequentially, as it was seen in our patient[5,14].

In fact, our patient had incomplete KD. Besides the 3-weeks long fever, she only had two diagnostic criteria: the diffuse maculopapular erythematous rash and the periungual desquamation of fingers and toes, and those only appeared on the third week of the disease. She had cervical lymphadenopathies, but they were bilateral and had less than 1.5cm in diameter. Other signs and symptoms occasionally associated with KD include diarrhea and hepatitis[1], which were present in this infant but also common in other clinical situations.

No specific laboratory test exists for KD but universal findings include leukocytosis, thrombocytosis and elevated acute phase reactants (erythrocyte sedimentation rate and C-reactive protein), which were present in our patient (Figure 1). Mild-to-moderate normochromic anemia and hypoalbuminemia were also present and it is often related to a more severe and prolonged inflammatory disease. During the subacute stage, platelet count elevation is the outstanding marker, and in the convalescent stage platelets levels and other mar-

kers begin to return to values within the reference range, requiring 6-8 weeks to normalize, as it was seen in our patient (Figure 1)[9].

In the reported child, the presence of a "non-toxic look" helped in the suspicion of KD. However, in a 3 month-old child disease's clinical patterns are not specific and it was mandatory to exclude infectious diseases.

Fever, rash, lymphadenopathy and hepatomegaly are common features in many childhood illnesses[1]. If those who have KD undergo lumbar puncture, approximately 50% have evidence of aseptic meningitis[1,2]. Differential diagnosis with CINCA syndrome should be kept in mind when an infant, in the first months of life, presents with fever, rash, lymphadenopathy, hepatomegaly, aseptic meningitis and high acute phase reactants[1] . CINCA syndrome, also known as neonatal onset multisystem inflammatory disease, is one of the CIAS1 syndromes characterized by fever and a persisting urticarial rash, often present at birth or in the first few months of life, accompanied by arthropathy with overgrowth (in about half), chronic meningitis with neutrophilic pleocytosis and, later on, cerebral atrophy, sensorineural deafness with developmental delay and growth delay[15]. Another differential diagnosis to be considered is systemic-onset juvenile idiopatic arthritis if arthritis was present[1]. However, her age (this autoimmune disease is rare before six months-old, with a median age of onset of 5 years old) make this hypothesis less probable.

The association of some infectious diseases with KD is well recognised, but rarely documented. Treatment with antibiotics doesn't change the disease's course, and fever persists unless IVIG is given, in responsive patients, as it was seen in our patient[14]. Considering delayed diagnosis and treatment in this child, it was expected a worse outcome then the observed, because 20% to 25% of untreated children develop coronary artery aneurysms[2,8].

Conclusion

KD should be considered in any infant or child, mainly if younger than 6 months-old, with persistent and unexplained fever and laboratory evidence of systemic inflammation, even without more clinical criteria suggestive of the disease, because early recognition and treatment may prevent development of coronary artery dilatation and aneurysm formation. On the other hand, this case report showed that it's important to perform serial cardiac evaluations because complications can develop only some weeks later. The clinical challenge lies in distinguishing cases of KD that do not fully meet the diagnostic criteria from those that strongly resemble a variety of common childhood disorders.

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