Kawasaki Disease Without Fever: A Mild Disease?
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Abstract

Introduction: The spectrum of the clinical manifestations of Kawasaki disease (KD) is growing. In the classical and incomplete forms of the disease fever is present and KD without fever has been rarely described in the medical literature. Methods: We present three new cases and review the literature. Results: Although rare, KD can occasionally present without fever. A total of eleven cases of non-fever KD have been described. The majority of cases do not present major complications. Conclusion: Appropriate diagnosis and timely treatment are important to avoid complications in what could be considered a mild form of the disease.

Key words: Afebrile, Non-fever Kawasaki disease, incomplete Kawasaki Disease, coronary artery, atypical clinical manifestations

List of abbreviations: Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Intravenous immunoglobulins (IVIG), Kawasaki disease (KD)

Introduction

As knowledge of a specific disease grows, so does the spectrum of clinical presentations. Kawasaki disease (KD) could be considered a young disease, although the first descriptions date to the last century. According to the guidelines, fever is an essential manifestation to diagnose KD. In the absence of appropriate therapy, fever persists for a mean of 11 days, but it may continue for 3 to 4 weeks [1]. Incomplete KD refers to the clinical presentation of KD with fever and fewer than four principal findings [2]. The diagnosis of incomplete KD is difficult because many infectious and inflammatory conditions present with fever and one or more of the clinical findings of KD [2]. Non-fever KD poses an even greater challenge, as only a few cases have been recognized and no guidelines for the treatment of this presentation have been published so far.

In 2008, Saltigeral et al. described a patient
with clinical features of KD and without fever. After that description, several others corroborated this clinical observation [3]. We present three new cases of KD without fever from three different institutions, and compare these cases with the cases described in the literature [4-11].

Methods

Three cases of KD without fever are reported. A PubMed search was performed using the keywords Kawasaki disease, afebrile, feverless, fever, atypical manifestations and incomplete and atypical Kawasaki disease. We performed a cross-reference search through Scientific citations index of papers citing other reports. A qualitative analysis was performed, and the data are summarized, emphasizing clinical features and the type of treatment.

Case 1

A 5-year-old boy, who had been previously diagnosed with allergic rhinitis, presented with a three-day history of a maculopapular skin rash in his trunk and the extremities, and no fever or respiratory symptoms were presented. He had received antihistamines for the diagnosis of an allergic reaction without improvement. One day before admission bilateral conjunctival erythema and red fissuring of the lips were noted.

On physical examination the patient had bilateral conjunctival injection, strawberry tongue, dry fissured lips, inducive hands edema with mild palmar and plantar erythema, a generalized macular skin rash and desquamation of the perineal area. His vital signs were normal and an abdominal ultrasound was normal. Laboratory findings: Hb 13 g/dl, WBC 10860/mm3, platelets count 280,000/mm3. Blood and urine cultures were negative.

A diagnosis of incomplete KD was considered based on the findings observed upon physical examination. Intravenous immunoglobulins (IVIG) (2 g/kg), and acetylsalicylic acid (60mg/kg/day) were started in the fourth day. The patient´s clinical condition gradually improved over the following 36 hours with progressive regression of the clinical symptoms. On day 10 after diagnosis the patient developed a fine desquamation involving his fingers. Echocardiography performed on the day of admission and on follow-up showed no coronary arterial dilatation.

Case 2

A 5-year-old male presented with a 3-day history of a generalized, non-pruritic rash that resolved spontaneously without treatment. Twenty-four hours before admission the rash recurred with arthralgia, myalgia and edema in the hands and feet and painful left cervical adenopathy developed. Physical examination revealed a rash involving the face, conjunctival erythema, fissured lips and cervical adenopathy. The patient presented perineal erythema with pain and edema of the foreskin. Hepatomegaly, edema of the hands and feet and palmar-plantar erythema were evident.

Laboratory tests: Complete blood count and liver function tests were normal. Blood and urine cultures were negative. IVIG and aspirin were administered in the fourth day, resulting in the resolution of symptomatology. The patient didn’t present fever, until the day after IVIG administration the patient presented one peak of 38 C. Forty-eight hours after IVIG infusion he presented generalized desquamation. On admission and on follow-up the echocardiograms were normal.

Case 3

A four year-old male patient presented with a history of conjunctival injection, fissured lips and rhinorrhea. The patient was diagnosed as exanthema subitum and antihistamines and lubricant lotion were prescribed. On the fifth day, the patient presented strawberry tongue: a rash on the face, trunk and extremities and erythema in the genital and perianal regions. Fever was not reported. No Bacillus Calmette Guerin (BCG) erythema or adenopathies were found on physical examination. With three criteria of classic KD (conjunctival injection, alteration of mucous membranes and a polymorphous rash), the diagnosis of non-fever KD was made. The patient started treatment with IVIG (2 grsKg/day), aspirin (80mgrKg/day) and prednisone (0.5mgrsKgday) on the sixth day of illness. The liver tests, urine tests, c-reactive-protein (CRP) and pharyngeal exudates were normal. A complete blood count showed leukocytosis (12,300/mm3), a high erythrocyte sedimentation rate (ESR) (43 mm/h) and high antistreptolysins levels (397.7 IU (Normal <200 IU)).

Clinical improvement was observed 24 hours after treatment was started; and after 48 hours, the patient presented periungual desquamation of the lower extremities and his ESR
decreased to 10 mm/h. The patient was discharged without complications. Two weeks after, the patient presented periungual desquamation on the hands and his medications were stopped.

**Results**

Along with the three cases detailed here, a total of eleven cases of non-fever KD have been described (Table 1). Seven were in males (63.6%) and 4 in females (36.4%). Thrombocytosis was present in 3/10 patients (33%), and leukocytosis was present in 5/10 (40%). In total, 6/11 (54%) presented coronary artery alterations. Importantly, not all patients presented high CRP levels. All of the patients were younger than five years old. On admission all of the patients except two presented at least three of the principal clinical findings (9/11 (81%)). The majority of the patients met 4 of the principal clinical criteria (44%) and 33% had 5 of the clinical manifestations. Regarding classical signs, 8/11 presented conjunctivitis, 9/11 lips fissuring, 9/11 a rash, 9/11 periungual desquamation, 5/11 hands and feet edema, and 5/11 lymphadenopathy. One the patients showed erythema at the site of BCG.

**Table 1.** Demographic, clinical, echocardiographic and laboratory characteristics of reported cases of KD without fever.

<table>
<thead>
<tr>
<th>Case (Author)</th>
<th>Age</th>
<th>Gender</th>
<th>Fever</th>
<th>Clinical manifestation</th>
<th>Abdominal ultrasound</th>
<th>Echo</th>
<th>CRP</th>
<th>ESR</th>
<th>LT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saltigeral-Simental 2008</td>
<td>3 yo</td>
<td>F</td>
<td>No</td>
<td>Fissured lips, rash, hands and feet edema, finger desquamation</td>
<td>NR</td>
<td>CE</td>
<td>NR</td>
<td>13 mm/hr</td>
<td>Normal</td>
</tr>
<tr>
<td>Caudevilla La Fuente 2012</td>
<td>3 yo</td>
<td>M</td>
<td>Two days</td>
<td>Rash, dry lips, conjunctivitis, cervical lymphadenopathy, finger desquamation</td>
<td>Normal</td>
<td>A LCA</td>
<td>7.09 mg/dL</td>
<td>103 mm/hr</td>
<td>Normal</td>
</tr>
<tr>
<td>Kato 2012</td>
<td>2 yo</td>
<td>M</td>
<td>No</td>
<td>Conjunctivitis, desquamation</td>
<td>NR</td>
<td>CE, pericardial effusion</td>
<td>4.1 mg/l</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hinze 2009</td>
<td>3 mo</td>
<td>M</td>
<td>No</td>
<td>Erythematous rash, conjunctivitis, erythematous lips, lymphadenopathy</td>
<td>NR</td>
<td>Proximal right, distal left anterior descending and circumflex aneurysms</td>
<td>158 mg/l</td>
<td>40 mm/h</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Ulloa-Gutierrez 2012</td>
<td>5 yo</td>
<td>F</td>
<td>No</td>
<td>Rash, cervical lymphadenopathy, conjunctivitis, erythematous and edematous palms and soles, strawberry tongue, desquamation</td>
<td>NR</td>
<td>Normal</td>
<td>102 mg/l</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Di Cara 2012</td>
<td>9 mo</td>
<td>F</td>
<td>No</td>
<td>Rash, fissured lips, conjunctivitis, cervical lymphadenopathy</td>
<td>NR</td>
<td>Mild pericardial effusion, brightness proximal LADCA</td>
<td>1.5 mg/l</td>
<td>35 mm/h</td>
<td>Normal</td>
</tr>
<tr>
<td>Kekindemirci 2013</td>
<td>17 mo</td>
<td>M</td>
<td>No</td>
<td>Swollen hands with desquamation of the fingertips, Redness eyes and cracks above the lips</td>
<td>Normal</td>
<td>Normal</td>
<td>54 mg/L</td>
<td>75 mm/hr</td>
<td>Normal</td>
</tr>
<tr>
<td>Lee 2015</td>
<td>7 mo</td>
<td>M</td>
<td>No</td>
<td>Rash, BCGitis Desquamation of the fingertips</td>
<td>NR</td>
<td>Left coronary artery dilated</td>
<td>NR</td>
<td>ALT 110 U/L</td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>5 yo</td>
<td>M</td>
<td>No</td>
<td>Rash, conjunctivitis, fissured lips, erythema planomplar, perineal desquamation,</td>
<td>NR</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Case 2</td>
<td>5 yo</td>
<td>M</td>
<td>One day</td>
<td>Rash, cervical lymphadenopathy, palmoplantar erythema, feet edema, erythematous and fissured lips,</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>NR</td>
<td>Normal</td>
</tr>
<tr>
<td>Case 3</td>
<td>4 yo</td>
<td>M</td>
<td>No</td>
<td>Conjunctivitis, Fissured lips, strawberry tongue, rash, erythema genital and perineal finger desquamation.</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>High</td>
<td>Normal</td>
</tr>
</tbody>
</table>

CBC: complete blood count, LT liver tests, CRP-c-reactive protein, UT urine test, ESR- erythrosedimentation rate.
F: female; M: male; yo: years old, mo: months old
RCA: Right coronary artery; LCA Left coronary artery; LADCA Left anterior descending coronary artery A: aneurysm; E: ectasia
vaccination, and four patients presented perineal erythema with desquamation. The reports are from different parts of the world; Japan, Korea, Turkey, Spain, Italy, Costa Rica, USA and Mexico.

**Discussion**

Over the years, the spectrum of signs and symptoms of KD has expanded, ranging from patients having a paucity of clinical manifestations (so called incomplete KD) to the development of vasculitis in other territories or even hemophagocytic syndrome and shock [4]. Incomplete cases have been described, and in these cases laboratory and echocardiographic findings are helpful. Uncertainties arise in diagnosis when not all of the classical signs are present and the physician faces an incomplete presentation of the disease. KD patients with fever as the sole manifestation have been described. Thapa et al. reported a 7-month-old male who presented fever and an echocardiogram revealed an aneurysm of the proximal left anterior descending coronary artery [12]. Fever subsided with IVIG and desquamation of the finger and toes were noticed. Yilmazer et al. present a similar patient, with fever and echocardiography revealed saccular aneurysm at left main coronary artery. Periungual desquamation of the fingertips emerged 1 day after IVIG therapy [13]. Interestingly, 9 of 11 patients with KD without fever presented this clinical finding, many of them after IVIG. Periungual desquamation could be an important clue to retrospectively support the diagnosis of KD.

Incomplete KD appears to be more common in infants than in older children [2]. Non-fever KD appears to be more common in toddlers (7/11). When the disease is diagnosed promptly, timely treatment can be given. Although fever is a constant clinical criterion according to today’s guidelines, cases of KD without fever have been described and fever may not be the predominant manifestation, as in the case reported by Caudevilla Lafuente [9]. Lin et al. report a 5-year-old boy who presented an incomplete form of KD with three days of fever, abdominal pain, bilateral conjunctivitis, fissured lips and strawberry tongue. Initially the fever subsided after three days and the diagnosis of KD was excluded according to the diagnostic guidelines and a normal echocardiogram, although the abdominal pain persisted. Twelve days later the echocardiography showed bilateral giant coronary aneurysms [14]. IVIG administration resolved the abdominal pain. Peeling of the fingers was found during the outpatient visit on day 22 of the illness [14]. More recently, Lee et al. presented a 7-month old boy with afebrile KD, who didn’t fulfilled the diagnostic criteria but developed a progressive coronary artery lesion. An important diagnostic clue in the patient was the presence of BCGitis [10].

Perineal erythema is considered to be a very specific manifestation of KD and all three patients described presented this clinical manifestation. Recurrent toxin-mediated perineal erythema is a cutaneous disease mediated by superantigens made by group A beta hemolytic streptococcus (GAHS) [15]. Saltigeral-Simental et al. hypothesized that recurrent-toxin-mediated perineal erythema could be a form of KD without fever [3]. Some cases of KD have been associated with the presence of GAHS like our third case [16]. Although antiestreptolysins were elevated, we diagnosed the patient as KD based on the presence of conjunctival erythema, the characteristic fissured lips and a non-scarlatiniform rash. None of the cases reported by Patrizi presented echocardiographic alterations, reinforcing that this form of KD might be milder [15].

Laboratory findings are sometimes useful to diagnose incomplete KD. Thrombocytosis and leukocytosis were present in 33% and 44% of the patients. Liver function test were not useful in non-fever KD as only two patients presented alterations. In the American Heart Association guidelines fever is necessary for the diagnosis of KD, however in the Japanese Criteria fever is one of the principal symptoms but the diagnosis can be made without its presence [17, 18]. Fever is a worrying sign for both parents and physicians. If fever is absent, the diagnosis could be misled to allergy or an alternative diagnosis or medical attention may not be sought. IVIG resistance have focused on the persistence of fever, but in a recent paper Fukuda et al. examined the relationship between persistent non-fever symptoms and coronary artery abnormalities in KD [19]. These authors conclude that persistent non-fever symptoms after IVIG may suggest latent inflammation which may increase the risk of coronary artery abnormalities. They consider that defervescence alone is not sufficient to define the responsiveness of KD patients to IVIG, a concept that highlight the importance of the other clinical signs [19].

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Di Cara et al reported echocardiographic alterations in a child with cow’s milk allergy [7]. They described a 9 month-old female who presented several features of KD including skin rash, conjunctivitis, fissured lips and cervical adenopathy, but no fever. The ESR and CRP levels were elevated with hypoalbuminemia and an echocardiogram presented pericardial effusion and perivascular brightness of the proximal left descending coronary artery. The authors commented that because of the absence of fever, the diagnosis of KD was excluded, and that during the two weeks of the infant’s admission, she never presented fever. We considered this case to be non-fever KD.

The treatment of these patients has been diverse. IVIG was administered in all but two cases. One out of 11 had a severe disease. Hinze et al. described a 3-month-old infant who developed aneurysms and required treatment with two doses of IVIG, aspirin and Coumadin [5]. Serial echocardiograms demonstrated normalization of his left coronary system and a decrease in the size of his right coronary system after more than two years of follow-up on low-dose aspirin.

Many other forms of vasculitis (Henoch-Schoenlein Purpura, Takayasu arteritis etc) and autoimmune diseases like lupus can be intensively active with ongoing inflammation and fever frequently is absent. The absence of fever in the patients described with Non-fever KD could be due to a dampened inflammatory host response resulting in mild vasculitis. Treatment guidelines have not been described for this group of patients. We believe that KD without fever, although in the mild spectrum of the disease, should be recognized, as treatment is required to avoid complications.

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