Another face of Kawasaki disease

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SUMMARY: Aldemir-Kocabaş B, Karbuz A, Karadeniz C, Çiftçi Ö, Özdemir H, Bolkent MG, Uçar T, Tutar E, Atalay S, Fitöz S, Çiftçi E, İnce E. Another face of Kawasaki disease. Turk J Pediatr 2014; 57: 392-398.

We aimed both to define the characteristics of patients with Kawasaki Disease (KD), and to highlight infrequent and unusual findings of the disease by presenting selected cases. We retrospectively evaluated 35 patients diagnosed with KD in our clinic between January 1994 and January 2013. The male to female ratio was 1.33 and the median age at admission was 22 months (1.5-132 months). Fourteen patients (40%) had coronary artery lesions (CAL). Twenty-five cases (72%) had complete and 10 cases (28%) had incomplete KD; the incidence of CAL in these groups was 36% and 50%, respectively. Two patients had giant coronary aneurysms. Six cases received a second dose of intravenous immunoglobulin, and one patient received pulse methylprednisolone. Seven cases had unusual and/or infrequent presentation patterns and/or follow-up. Physicians should be aware of all symptoms and laboratory findings of KD in order to avoid any delays in diagnosis and decrease the risk of life-threatening complications.

Key words: coronary artery aneurysm, infrequent symptoms, Kawasaki disease, unusual findings.

Kawasaki disease (KD) is a vasculitic disease that can affect almost all of the systems in the body. Coronary artery aneurysms are the most important and life-threatening complication of KD. For the diagnosis of KD, there should exist at least four of five principal clinical criteria with prolonged (≥5 days) high fever. However, patients can be diagnosed with "incomplete KD" in the presence of two or three principal symptoms accompanied by high fever. Additionally, a number of clinical and laboratory findings have been described to support the diagnosis of KD. Incomplete KD is more prevalent in young infants, and some authors suggest that it is associated with increased incidence of coronary artery lesions (CAL)[1-7]. Because all patients do not present with the full set of principal criteria and delays in the diagnosis of KD can lead to CAL, clinicians should also be aware of unusual clinical and laboratory findings of KD. In this paper, we aim both to define the characteristics of patients diagnosed with KD in our hospital, and to highlight some infrequent findings of the disease by presenting selected cases.

Material and Methods

We retrospectively evaluated the medical records of cases diagnosed with KD and hospitalized in our clinic between January 1994 and January 2013. Clinical and laboratory data of all cases were analyzed using patient files and medical records. The diagnosis of Kawasaki Disease was based on the cases' clinical features. Patients with prolonged fever and two or three clinical signs of KD were considered to have incomplete presentations. We also selected for reporting seven cases having unusual clinical features or progress, in order to highlight some infrequent presentations of KD.

Results

A total of 35 patients (20 male, 15 female) diagnosed with KD were enrolled in this study. The male to female ratio was 1.33, and the median age at admission was 22 months (1.5-

132 months). After being classified according to the clinical findings, 25 cases (72%) had complete and 10 cases (28%) had incomplete KD. Among them, a total of 14 patients (40%) had coronary artery involvement; incidence of CAL in the two groups was 36% and 50%, respectively (Table I). Thirty patients received treatment consisting of a high dose of intravenous immunoglobulin (IVIG) (2 g/kg/day, over 12 hours), together with a high dose of acetylsalicylic acid (ASA) (80-100 mg/kg/day). However, four patients received only IVIG (due to elevated serum transaminases in two patients, gastrointestinal bleeding in one patient and thrombocytopenia in one patient). Two patients did not receive IVIG due to an anaphylactic reaction at the beginning of infusion in one case and late admission after fever resolved in the other. Unresponsiveness was defined as the persistence of fever and other symptoms during the first 48 hours of treatment. Thus, a second dose of IVIG was required in six patients during follow-up. CAL had developed in four of these cases, two of them having giant coronary aneurysms. While 12 patients with mild-to-moderate coronary abnormalities received an antiplatelet agent such as low-dose ASA (3-5 mg/kg/day), two cases also received warfarin due to giant coronary aneurysms. Pulse methylprednisolone (PMP) was given in addition to IVIG treatments in one of these cases (Case 5).

Among all of the KD patients, seven cases had unusual and/or infrequent presentation patterns and/or follow-up. The clinical features, principal and supportive symptoms, and findings for KD in these seven patients are documented in Tables I, II and III. Additional, more detailed information about the clinical characteristics and progress of these cases is given in the discussion section.

In summary, Case 1 presented with lymphopenia (830/mm^3), thrombocytopenia (62.000/mm^3) and eosinophilia (%14), while Case 2 had only thrombocytopenia (97.000/mm^3) at admission as an infrequent hematological finding. Rarely associated neurological symptoms and findings occurred in Case 2 (stiff neck and aseptic meningitides) and Case 3 (left-sided peripheral facial nerve palsy). Cases 4 and 5 had unusual gastrointestinal manifestations; Case 4 had a history of hospitalization in the pediatric surgery clinic because of paralytic ileus, and we had been consulted due to ongoing fever and rash before his operation. Subsequently, he was diagnosed with typical KD. Case 5 had undergone appendectomy at an outpatient clinic and was referred to us because of high-grade fever lasting for 25 days and elevated acute phase reactants (APR); he was diagnosed with typical KD complicated by multiple giant coronary aneurysms (a giant saccular aneurysm 9 mm in diameter and a fusiform aneurysm 5 mm in diameter on the right coronary artery; a giant saccular aneurysm 9 mm in diameter on the left ascending coronary artery; and a saccular aneurysm 7 mm in diameter on the circumflex artery). He received two doses of IVIG and one dose of PMP treatment. He had also had hypertension at admission, a very unusual finding in KD, which responded dramatically to the IVIG treatment. The last two infant patients (Case 6 and Case 7) were diagnosed with atypical KD, with the only symptoms being high-grade fever and elevated APR. Thus, it was our experience that CAL can be identified in an earlier phase of the disease, before other symptoms and findings appear, especially in young infants.

Discussion

Kawasaki Disease has been defined as the second most common vasculitis of children and the leading cause of acquired heart disease in developed countries[2, 8]. In addition to increased physician awareness all over the world, a real increase in the incidence of the disease has been shown in recent studies[1, 4, 5, 7]. In a previous study conducted in our clinic, we found that only 3 of 24 patients were diagnosed between 1994 and 2002, and the remaining 21 between 2003 and 2009[9]. Similarly, we have in the current study seen that 11 of 35 patients were diagnosed in the last three years (2009-2012). Even more strikingly, we have shown that patients with atypical symptoms and incomplete presentations could be diagnosed with KD in the more recent years. All of the 10 patients in the study with incomplete KD were diagnosed after 2003.

Young infants more frequently present with incomplete clinical criteria and also have the highest rate of CAL. Children over the age of 8 also have a higher rate of CAL[2, 5, 7]. Although it was reported in previous studies

Table I. Comparison of Characteristic Features Between Patients with Complete and Incomplete Kawasaki Disease

	Complete	Incomplete	Total
Sex			
Male	17	3	20
Female	8	7	15
Age			
<1 year (n)	3	3	6
>5 years (n)	6	2	8
Duration of fever (days)*	6 (2-25)	7 (2-19)	-
CAL n (%)	9 (36)	5 (50)	14 (40)

*Median (minimum-maximum); *CAL* Coronary artery lesion

that about 6.7-17.9% of cases had incomplete presentation[10, 11], the incidence of incomplete KD cases has reached levels up to 56.6% during the last decade[7]. In our study, 28% of the patients had incomplete KD. In addition, coronary artery involvement was observed more frequently in this group (50%). This relatively high rate of CAL in both the incomplete and complete KD cases is probably due to the study being conducted in a leading research hospital and consisting of selected cases. The majority of the patients with incomplete presentation were referred to our clinic with a diagnosis of fever of unknown origin and had a prolonged duration of fever. Thus, the incidence of CAL was found to be slightly higher (40%) than in other recent studies[7, 10, 11].

Hematological abnormalities such as leukocytosis, thrombocytosis, and anemia are well-known laboratory findings for KD patients[1, 2]. On the other hand, thrombocytopenia, eosinophilia, neutropenia and hemophagocytic syndrome have been reported infrequently in association with KD [12-18]. Thrombocytopenia is more commonly reported in girls and younger patients. It has also been suggested that patients with low platelet counts at presentation have increased risk for CAL[12, 13]. Two cases in our study (Case 1 and Case 2) were diagnosed with thrombocytopenia. Moreover, one of them (Case 1) also had lymphopenia and eosinophilia at presentation. Lymphopenia is quite a rare finding in KD; it has been described in an adult patient in the literature[19], but has rarely been reported in childhood. Despite these very unusual laboratory findings, no coronary involvement was detected in these patients.

The neurological complications of KD have been well described, but apart from extreme irritability, they are quite rare[1, 2]. Irritability was

Table II. Distribution of the Principal Symptoms of Kawasaki Disease in Seven Patients with Infrequent and/or Unusual Symptoms and Findings

Case	Sex	Age (months)	Duration of fever (days)	Changes in lips and oral cavity	Conjunctival injection	Lymphadenopathy	Rash	Changes in the hands and feet
1	M	108	5	+	+	+	+	+
2	M	84	7	+	+	+	+	+
3*	F	10	25	+	-	-	+	+
4	M	36	3	+	+	+	+	+
5	M	96	25	+	+	+	+	+
6*	M	2.5	8	-	-	-	-	-
7*	F	1.5	2	-	-	-	-	-

*Patients with atypical Kawasaki Disease; *F* Female, *M* Male

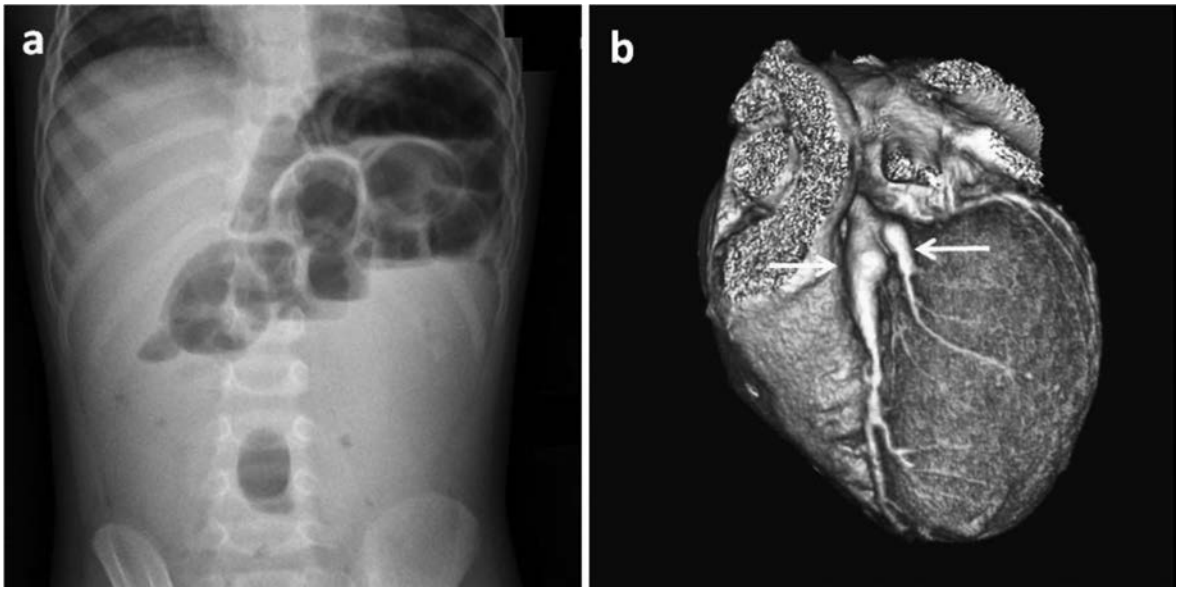

Fig. 1 (a) Abdominal X-ray of Case 4 reveals multiple air-fluid levels in small bowel loops. (**b)** Volume-rendered three-dimensional computerized tomography image of Case 5 shows aneurysmal dilatations of left anterior descending coronary artery and diagonal branches *(arrows)*.

present in 97% of our patients at admission, and all of these instances resolved soon after IVIG treatment. A stiff neck, aseptic meningitis and transient sensorineural hearing loss have also been described as neurological manifestations of KD[1, 2]. Case 2 presented with fever, a stiff neck and thrombocytopenia; further diagnostic procedures revealed aseptic meningitis. Cerebrospinal fluid analysis was normal. He had no coronary artery involvement, and all his symptoms and findings returned to normal within 12 hours after IVIG treatment.

It has been reported that facial nerve palsy in these patients may be associated with more severe clinical progress and a higher incidence of coronary aneurysms[20, 21]. Case 3 was referred to our clinic with complaints of fever lasting for 25 days, left-sided facial nerve palsy, irritability and erythema at the site of a Bacille Calmette-Guérin (BCG) scar, in addition to all the principal criteria of KD. Echocardiography revealed a saccular aneurysm on the right coronary artery; all symptoms were resolved after a single dose of IVIG and high-dose ASA treatment. Facial nerve palsy is quite a rare finding in patients with KD, although the exact incidence of this association is not known. Poon et al.[20] reported that coronary artery aneurysms occurred in more than half of the patients with facial nerve palsy. Facial nerve palsy is more often seen in females (1.4:1) and generally exhibits left-sided involvement. It is likely that both ischemic vasculitis of the arteries supplying the facial nerve and immunologic mechanisms contribute to the facial nerve dysfunction[20-22].

Diarrhea, vomiting and abdominal pain are most common gastrointestinal symptoms in KD and occur in approximately one-third of patients. KD may also cause gallbladder hydrops, hepatic enlargement and dysfunction, and jaundice[1, 2]. Furthermore, because KD is a vasculitic disease and can affect any organ system in the body, patients can present with acute surgical abdomen due to ischemia, necrosis and stenosis of the mesenteric arteries. Ileus can occur as a result of intestinal vasculitis and associated bowel obstruction related to ischemic strictures. Mesenteric artery vasculitis with bowel ischemia and associated dysfunction of the myenteric plexus can sometimes lead to a pseudo-obstruction[23, 24]. Case 4 was admitted to pediatric surgery clinic with complaints of fever and abdominal pain lasting for six days and one day, respectively. He also had abdominal distension and bilious vomiting. Abdominal x-ray revealed multiple air-fluid levels in the small bowel loops; the patient's clinical picture was consistent with ileus (Fig. 1a). While the patient was observed at the pediatric

Table III. Distribution of Infrequent and/or Unusual Symptoms and Findings of Kawasaki Disease in Seven Patients

Case	Hgb (g/dL)	WBC ($x10^3/mm^3$)	PLT ($x10^3/mm^3$)	Elevated APR	Elevated transaminases	Hyponatremia	Hypoalbuminemia	Sterile pyuria	CAL	Irritability	Uncommon findings	Treatment	CAL at the last visit
1	11.8	4.3	62	+	Mild	+	Mild	+	-	+	Lymphopenia Thrombocytopenia Eosinophilia	IVIG + ASA	-
2	9.6	4.2	97	+	Moderate	-	-	-	-	+	Stiff neck Aseptic meningitis Thrombocytopenia	IVIG	-
3*	6.6	13	118	+	Mild	-	-	+	+	+	Facial nerve palsy	IVIG + ASA	-
4	11.1	11.1	409	+	-	+	+	+	+	+	Ileus	IVIG + ASA	-
5	10.7	9.1	698	+	-	-	Mild	+	+£	+	Appendectomy Hypertension	IVIG (X2) + ASA + PMP	+£
6*	10.1	17.8	454	+	-	-	Moderate	-	+	+	None	IVIG + ASA	+
7*	9.3	13.3	338	+	-	-	Moderate	+	+	+	None	IVIG (X2) + ASA	+

Patients with atypical Kawasaki Disease (*) and giant aneurysm (£); Hgb Hemoglobin, WBC White blood cell, PLT Platelet, APR Acute phase reactants, CAL Coronary artery lesion, IVIG intravenous immunoglobulin, ASA acetyl salicylic acid, PMP pulse methylprednisolone

surgery clinic, we were consulted because of ongoing fever accompanied by skin rashes. He was diagnosed with complete KD and ileus. Intussusception was excluded with abdominal ultrasound. Echocardiography revealed mild dilatation in the left (2.3 mm in diameter) and right (2.5 mm in diameter) coronary arteries. All his symptoms and laboratory findings were resolved within 48 hours after a single dose of IVIG and high-dose ASA treatment.

Case 5 had been operated on for appendicitis in another clinic and was referred to our clinic because of ongoing abdominal pain, fever and elevated APR. His complaints had started before the operation and been ongoing for 25 days. He also had elevated blood pressure and erythema at the site of a BCG scar. The patient had all the principal symptoms of KD; appendicitis is thought to be a rare complication of the disease[1, 23]. Echocardiography revealed multiple giant aneurysms (the largest was 8.7 mm in diameter) on the left coronary, right coronary and circumflex arteries. A three-dimensional computerized tomography image of the aneurysms is shown in Fig. 1b. These findings being consistent with complete KD, he received IVIG, high-dose ASA and heparin (subsequently switched to warfarin). At admission, another very unusual finding for this patient was elevated blood pressure (150/100 mmHg). Doppler ultrasounds of the renal arteries and abdominal aorta, as well as cardiac index values, were normal. Although irritability, abdominal pain and all principal findings of KD were resolved soon after IVIG treatment, hypertension continued for 24 hours. Because of an increase in the size of the CAL and a subfebrile fever on the third day after IVIG treatment, he was given a second dose of IVIG (2 g/kg, over 12 hours). Then, in consequence of lasting fever and elevated APR, a single dose (60 mg/kg/day) of PMP was given. After PMP, the fever departed and APR decreased. The patient did not experience any clinical signs or symptoms of myocardial ischemia while under anticoagulant treatment for six months. Hypertension associated with KD was an unusual finding for us, and we attributed it to a vasculitic process in the arterial system of the patient. To our knowledge, systemic hypertension has not been reported in acute KD despite the fact that systemic arterial hemodynamic alterations have been

documented previously[25, 26]. These alterations may lead to the development of abnormal arterial stiffness and compliance[25-27].

During the evaluation of children, especially those with intractable fever and elevated APR, KD must be kept in mind. In patients who do not fulfill the criteria, diagnosis of KD can be made based on echocardiographic findings of coronary artery abnormalities. A repeat echocardiogram is recommended in these patients even if the initial examination is normal[1, 5, 7]. Case 6 presented with only a high-grade fever, irritability and increased APR. All other laboratory tests, including lumbar puncture, were normal, and cultures remained sterile. While he was receiving treatment for fever of unknown origin, echocardiography on the 8th day of hospital admission revealed a fusiform and a saccular aneurysm on the left coronary artery (4.4 and 3.4 mm in diameter, respectively). He received IVIG and ASA treatment, since this was a case of KD presenting with only fever, increased APR and CAL. Another striking clinical course was observed in Case 7, a 1.5 month-old infant. She had a high-grade fever of only two days' duration, irritability, and increased APR. Physical examination revealed pharyngeal hyperemia and mild (1.5 cm) splenomegaly. Her hemoglobin level was 6.7 mg/dl, and cerebrospinal fluid analysis was negative. Laboratory tests for anemia etiology were unremarkable. She underwent echocardiographic examination due to suspicion of KD with an atypical course; this revealed enlargement of the right coronary artery (2.7 mm in diameter) and a saccular aneurysm on the left coronary artery (3.5 mm in diameter). A second dose of IVIG was administered due to subfebrile fever that continued for 48 hours after the first IVIG dose. Her fever decreased dramatically during infusion of the second dose of IVIG.

In conclusion, KD is a self-limiting vasculitis; diagnostic and therapeutic delays can cause life-threatening complications such as CAL. Although there are well-described principal criteria for KD, patients with "incomplete" or "atypical" symptoms can exhibit a variety of presentation patterns. Diagnosing this condition is of critical importance because of the increased risk of CAL in these patients. For that reason, KD must be at the top of the list for differential diagnosis in an infant with fever of unknown origin. Thus, physicians should be aware of all symptoms and laboratory findings of this systemic vasculitic disease in order to avoid any delays in diagnosis and decrease the risk of life-threatening complications.

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