

Otorrhea in Kawasaki disease diagnosis complicated by an EBV infection: coincidental disease or a true association

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Abstract. – The Authors report on two children affected by Kawasaki disease (KD). The diagnosis of KD was made after exclusion of conditions with similar presentation. At admission these children (cases 1 and 2) presented fever, purulent caseous pharyngotonsillitis, and cervical bilateral lymphadenopathy, as well as an erythematous non-vesicular rash over the face and trunk, and a mild bilateral non-exudative conjunctivitis in case 1. After respectively three and two days corticosteroid therapy was started without any significant improvement of the general condition and any diminutions of the fever. Two days later in case 1 the child presented a clear otorrhea, a cutaneous non vesicular rash, and soon after all the remaining signs of Kawasaki disease, in case 2 otorrhea was found after 4 days and then the other signs of the KD. These patients were treated with intravenous immunoglobulin (2 g/kg day), with an improvement of their general condition. To our knowledge we report the first cases of otorrhea in the setting of Kawasaki disease. We cannot exclude that the presence of Kawasaki disease in the context of otorrhea in children positive for Epstein-Barr virus (EBV) is merely coincidental. Besides, recent acquisitions show that KD is due to a new virus that could cross-react with the EBV.

The Authors conclude that the presence of EBV infection or similar condition in a febrile child may not exclude Kawasaki disease and a differential diagnosis has to be performed for a timely commencement of intravenous immunoglobulin therapy.

Key Words:

Kawasaki disease, EBV, Childhood, Otorrhea.

Introduction

Kawasaki disease is a leading cause of acquired heart disease among children in the United

States and other developed countries. Most children who contract this illness are less than two years old, and 80 percent of affected children are younger than five years of age. Kawasaki disease occurs in 19 out of every 100,000 children in the United States, and in England in 7-9 children; instead in Italy it is nearly 14 children every 100,000. It is most common among children of Japanese and Korean descent, but the illness can affect all ethnic groups¹⁻³. Described for the first time by Tomisaku Kawasaki in 1967, the disease is a generalized vasculitis of unknown aetiology, Kawasaki disease can cause coronary artery abnormalities, including coronary aneurysms. From 20 to 25 percent of untreated children develop coronary artery abnormalities, which may resolve or persist. These abnormalities are of particular concern because they can lead to thrombosis, evolve into segmental stenosis or, rarely, rupture. The principal cause of death from Kawasaki disease is myocardial infarction. The cause of the disease remains unknown, but epidemiologic investigations and the clinical presentation suggest a microbial agent⁴⁻⁶. Diagnostic criteria, including fever and other principal features, have been established (Table I). In the acute phase of the disease, treatment with acetylsalicylic acid and intravenously administered immunoglobulin is directed at reducing inflammation of the coronary arteries and myocardium. Early recognition and treatment of Kawasaki disease can reduce the development of potentially life-threatening coronary artery abnormalities.

Case 1

N.M., a 30 month-old girl was admitted to the Division of Pediatrics of the Hospital Civile of Ragusa (Ragusa, Italy), due to fever, purulent

Table I. Diagnostic criteria for Kawasaki disease and analysis of our patients (KD criteria presence of at least of five of the first six conditions).

	Case 1	Case 2
Bilateral (non purulent) conjunctivitis	+	-
Polymorphous rash	+	+
Fever for five days or more	+	+
Diffused redness of oral or pharyngeal mucosa	+	+
Changes in lips and mouth: reddened, dry, or cracked lips	+	-
Cervical lymphadenopathy: more than 15 mm in diameter, usually unilateral, single, not purulent, painful	+	+
Indurative edema of hands or feet	+	+
Desquamation of skin of hands, feet and groin (in convalescence)	+	+
Purular caseous pharyngotonsillitis (more common in EBV infection) (no diagnostic criteria of KD)	+	+
Clear Otorrhea (never reported in KD)	+	+

caseous pharyngotonsillitis, mild bilateral non-exudative conjunctivitis and cervical bilateral lymphadenopathy. Fever, unresponsive to paracetamol, had started 3 days before hospitalization. There was no history suggestive of specific focus of infection, diarrhea, headache, convulsion, altered sensorium, arthralgia, chest pain, palpitations or syncopal attacks or drug intake. At the time of hospitalization the child's weight was g 16,500 (10th-25th percentile), height 93 cm (50th percentile) and head circumference 53 cm (50th percentile). Physical examination revealed a moderately ill-looking child, with a temperature of 39.3°C, pulse 119 b/m, and blood pressure 99/63 mmHg. Routine laboratory findings, including total serum protein and albumin, gamma-GT, CPK, coagulation studies (prothrombin time, activated partial thromboplastin time, fibrinogen concentration, antithrombin III, Factor V, fibrinogen/fibrin degradation products), immunoglobulins, anti-streptolysin O titer, and RF were all within the normal values. Anti-nucleus antibodies (ANA), anti-mitochondrial antibodies (AMA), anti-smooth-muscular antibodies (ASMA), Widal-Wright, Weil-Felix, TORCH, anti-Leishmania, and anti-Mycoplasma were negative. Other investigations revealed total WBC count of 18,660/mm³ with 88% neutrophils, elevated ESR (88 mm at the end of 1 h) and raised serum C-reactive protein (74 mg/l), and normal platelet count (260,000/mm³). Throat swab culture was negative. Electrocardiogram and echo-cardiocolor doppler were normal. VCA-EBV: Ig G 20 and Ig M 31 UL/ml. EBNA IgG 54 UL/ml; IgM 28 UL/ml (normal value < 20 uL/ml). The diagnosis of EBV was made and treatment with corticoids

at a dosage of 0.5 mg/kg/die in two oral administrations, for two days was started, without any improvement of her general condition and with the persistence of the fever.

Two and half days later, the child presented clear otorrhea, swollen palms of the hands and soles of the feet with a purple-red color, swollen tongue with a white coating and large red bumps, red, dry and cracked lips, an erythematous non-vesicular rash over the face and trunk, and the following day the skin on the child's hands and feet began to peel off in large pieces.

In view of these clinical and laboratory data, 3-4 days after the admission a diagnosis of Kawasaki disease was suspected and treatment with intravenous immunoglobulins (2 g/kg/die for one day) and high dose aspirin (100 mg/kg/die) was started; with a rapid normalization of the temperature and of her general condition. The inflammatory signs of both mucosae and skin disappeared a few days after treatment. Absence of conjunctival vessel dilatation and iridocyclitis was confirmed by slit lamp examination. All the clinical signs manifesting in our patients are shown in Table I.

Fourteen days after admission, the laboratory test showed WBC 8340 mm³, RBC 4,865,000 mm³, Hb 14.5; PLT 554,000 mm³; with N 46.2%, L 40.8%, M 6.7%, E 2.8%. Erythrocyte sedimentation rate (ESR) was 37 mm/h, IK 27 mm/h, C-reactive protein 25 mg/l. At one month the control ECG and echocardiocolor Doppler were still normal and treatment with aspirin was continued at a dosage of 5 mg/kg.

Clinical and echocardiographic evaluations carried out up to 6 months were still normal.

Case 2

M.F, a 4 year-old girl was admitted to the Division of Pediatrics of the Hospital Vittorio Emanuele (Catania, Italy), due to fever, pharyngotonsillitis, and cervical bilateral lymphadenopathy. Fever, unresponsive to paracetamol, had started 2 days before hospitalization. There was no history suggestive of specific focus of infection, diarrhea, headache, convulsion, altered sensorium, arthralgia, chest pain, palpitations or syncopal attacks or drug intake. At the time of hospitalization the child's weight was 19,500 (25th percentile), height 103 cm (50th percentile) and head circumference 55 cm (50th percentile). Physical examination revealed a moderately ill-looking child, with a temperature of 39.5°C, pulse 134 b/m, and blood pressure 109/77 mmHg. Routine laboratory findings, including total serum protein and albumin, gamma-GT, CPK, coagulation studies (prothrombin time, activated partial thromboplastin time, fibrinogen concentration, antithrombin III, factor V, fibrinogen/fibrin degradation products), immunoglobulins, anti-streptolysin O titer, and RF were all within the normal values. Anti-nucleus antibodies (ANA), anti-mitochondrial antibodies (AMA), anti-smooth-muscular antibodies (ASMA), Widal-Wright, Weil-Felix, TORCH, anti-Leishmania, and anti-Mycoplasma were negative. Other investigations revealed total WBC count of 22,660/mm³ with 78% neutrophils, elevated ESR (104 mm at the end of 1 h) and raised serum C-reactive protein (96 mg/l), and normal platelet count (326,000/mm³). Throat swab culture was negative. Electrocardiogram and echocardiocolor doppler were normal. VCA-EBV: Ig G 14 and Ig M 34. EBNA Ig G 39; Ig M 32 (normal value < 20 uL/ml). The diagnosis of EBV was made and treatment with corticosteroids at a dosage of 0.5 mg/kg/die in two oral administrations, for two days was started, without any improvement of her general condition and with the persistence of the fever. Four days later, the child presented clear otorrhea, swollen palms of the hands and soles of the feet with a purple-red color, red, dry and cracked lips, an erythematous non-vesicular rash over the face and trunk, and the following day the skin on the child's hands and feet began to peel off in large pieces.

In view of these clinical and laboratory data, 5 days after admission (over 7 days and half of continuous fever) a diagnosis of Kawasaki disease was suspected and treatment with intravenous immunoglobulin (2 g/kg/die for one day)

and high dose aspirin (100 mg/kg/die) was started; with a rapid normalization of the temperature and of her general condition. The inflammatory signs of both mucosae and skin disappeared a few days after treatment.

Absence of conjunctival vessel dilatation and iridocyclitis was confirmed by slit lamp examination.

All the clinical signs manifesting in our patients are shown in Table I.

Two weeks later, the laboratory test showed WBC 6400 mm³, RBC 4,730,000 mm³, Hb 13,5; PLT 496,000 mm³; C-reactive protein 35 mg/l. At one month the control ECG and echocardiocolor Doppler were still normal and treatment with aspirin was continued at a dosage of 5 mg/kg.

Clinical and echocardiographic evaluations carried out up to 6 months and were still normal.

Discussion

Kawasaki disease is an acute systemic febrile illness of unknown aetiology, affecting children younger than five years of age. Diagnosis of KD is based on the clinical criteria shown in Table I; five of the six criteria are considered essential for diagnosis^{1,3,5-9,10-13}. These features need not be present at one particular time and, in fact, may evolve sequentially over a period of a few days. The patient had high levels of acute phase reactants, and subsequently went on to develop thrombocytosis during convalescence, which are known to occur in KD. The clinical symptoms are variable and all the system and organs can be involved. Our group report on two children, who presented fever and thrombocytopenia associated with scrotal swelling at the onset of the illness, showing that the presence of hydrocele in a febrile child with thrombocytopenia may represent an early clinical sign of Kawasaki disease¹².

Zulian et al¹⁴ in a study in 2003 described ten children (4.6%) among a cohort of 219 with KD that had their onset with severe abdominal complaints. Incomplete KD presentation at the time of acute abdomen was present in nine of the 10 patients. Acute abdominal pain and distension, vomiting, hepatomegaly, and jaundice were the most common symptoms at onset. All patients completely recovered, but 50% developed coronary aneurysms despite early intravenous gammaglobulin treatment.

Some Authors⁹⁻¹⁸ have reported gastrointestinal symptoms that appear within 4 weeks after the occurrence of major clinical symptoms of KD.

Diagnosing classical KD is difficult enough. Recognizing cases that do not fully meet the syndrome diagnostic criteria offers an even greater challenge. Nevertheless, it is important to be aware of this entity, since waiting too long could lead to irreversible complications such as coronary artery aneurysms and/or other cardiac involvements.

In "incomplete" or "atypical" forms all the essential manifestations are not present. To help clinicians to reach a diagnosis, Japanese and North American groups have evolved diagnostic criteria^{10,11,19}. Some experts consider any four of the six clinical criteria sufficient for the diagnosis of KD while others recognize the presence of three criteria to be sufficient for the diagnosis of KD, with echocardiography or angiography that reveals coronary artery changes due to arteritis. As coronary lesions are often present by day 9 or 10 of illness, attempts have been made to find out if any of the laboratory criteria could help in diagnosing atypical or incomplete forms of KD¹⁰⁻¹². Levy et al¹⁵ found that thrombocytosis was consistently present in atypical forms with peak thrombocytosis occurring at 13.5 ± 5.9 days of illness and concluded that the presence of thrombocytosis should be considered compatible with the diagnosis of KD.

To improve the clinical diagnostic standard and explore the mechanism of multiple clinical manifestations of EBV infection by studying the primary symptom and related disease spectrum in EBV infected children, Li et al¹³ retrospectively reviewed 190 EBV infected children whose serum EBV-VCA-IgM was positive as detected by enzyme-linked immunosorbent assay (ELISA). The primary symptoms of EBV infection were different: the most common primary symptom was fever (66.8%), followed by cough (14.2%), skin eruption (7.9%), lymphadenopathy (5.3%), eyelid edema (3.2%), pharyngalgia (1.6%), cardiac arrhythmia (1.6%), convulsion (1.6%), arthralgia (1.0%), and gross hematuria (0.5%). Most systems and organs were involved in the disease, including liver, spleen, lymph nodes, kidney, heart, lung, bone marrow, and brain, which made the disease spectrum diverse. The most common disease caused by EBV infection was respiratory tract infection (40.5%), followed by infectious mononucleosis (17.9%), Kawasaki disease (6.3%), idiopathic thrombocytopenic purpura (5.8%), viral myocarditis (2.6%), viral encephalitis (2.6%), hemophagocytic syndrome (1.6%), rheumatoid arthritis (1.0%), and acute lymphadenitis (1.0%).

Culora and Moore¹⁶ tried to establish whether infection with EBV contributed to the development of coronary artery lesions in a six-year-old child with an aneurysm and stenoses of the coronary arteries and suspected Kawasaki disease. Postmortem paraffin wax sections of the coronary artery and myocardium were examined by *in situ* hybridisation for expression of EBER-1 (EBV-encoded RNA-1). Positive controls consisted of an EBV positive case of Hodgkin's disease and a case of post-transplantation lymphoma. No EBER-1 positive cells were identified in either myocardium or walls of the coronary artery. These Authors concluded that although EBV has been implicated in the etiology of Kawasaki disease and development of coronary artery lesions, in this patient this process was not confirmed.

Kanegane et al¹⁷ described a two-year-old boy, who exhibited not only clinical manifestations which suggested a recurrence of KD but also evidence of a primary infection by EBV including tonsillitis, splenomegaly and atypical lymphocytosis in the peripheral blood. An inverted CD4/CD8 ratio in lymphocyte subsets suggested the presence of infectious mononucleosis (IM). EBV titers (viral capsid antigen-immunoglobulin G 1:20; Epstein-Barr virus-associated nuclear antigen < 1:10) showed an acute EBV infection and the presence of the EBV genome in the blood was determined by the polymerase chain reaction technique. In Japan, the peak incidence of KD and IM is in children under 4 years of age. From the investigation of EBV titers, it has been reported that some patients with KD develop an associated, unusual primary EBV infection. KD concurrent with a primary EBV infection as in this case, suggests the possibility of an etiologic agent related to KD rather than to the EBV infection itself. Perhaps, KD is usually not pathogenically associated with EBV infection, or with similar herpesviridae: in fact, Marquette et al¹⁸ reported the prevalence of EBV capsid antibody in KD patients, and found no significant difference from that of controls, and the antibody response in those infected with EBV was the same as that in other children similarly infected. No EBV was isolated from acute-phase patients. All patients with capsid antibody at the onset of KD also had Epstein-Barr nuclear antigen antibody: 36 patients developed antibodies within 3 months after onset of KS; in 10, EBV infection could have been coincidental with the disease. Cytomegalovirus (CMV) was isolated from 9 pa-

tients with KD and 10 controls. A similar number of controls and patients had antibodies to human herpesvirus 6 (HHV6). None of the herpes viruses (EBV, CMV, HHV6, varicella-zoster virus, or herpes simplex virus) plays a unique or dominant role in the etiology or pathogenesis of KD in Hawaii.

Otorrhea is not a clear sign of KD, to our knowledge this is the first report of this unusual association. We do not know if otorrhea is secondary of the EBV coinfection or clearly a coincidental association. Probably KD is preceded by a new virus that can cross-react with EBV. Recently, Rowley et al²⁰ hypothesized that the infectious etiologic agent of KD may be a "new" RNA virus. In conclusion, to prevent complications, the physician has to start therapy much earlier. Hence, it is imperative that KD be diagnosed early and treatment be initiated promptly.

Conclusions

Unless a high index of suspicion is maintained, patients with KD will continue to escape our attention. We now know KD better, and our ability to diagnose and treat KD has greatly improved in recent years. We have identified treatments that reduce the damage to the heart and have devised ways of closely monitoring cardiac status after the disease, but new ongoing research is needed to learn more about the causes of this illness and how to prevent it.

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