Reumatismo, 2018; 70 (2): 115-116

Acute myocarditis as a revealing clue of complete Kawasaki disease

G. De Rosa[1], L. Andreozzi [2,3], M. Piastra [4], B. Castelli [2], D. Rigante[2]

[1]Section of Pediatric Cardiology, Fondazione Policlinico Universitario A. Gemelli, Università Cattolica Sacro Cuore, Rome, Italy; [2]Institute of Pediatrics, Fondazione Policlinico Universitario A. Gemelli, Università Cattolica Sacro Cuore, Rome, Italy; [3]Pediatric Unit, Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; [4]Pediatric Intensive Care Unit, Fondazione Policlinico Universitario A. Gemelli, Università Cattolica Sacro Cuore, Rome, Italy

To the Editor:

Fifty years have passed since 1967, when the first case series of Kawasaki disease (KD), a multisystem immune-mediated vasculitis of unknown origin affecting children less than 5 years of age, was described for the first time (1). Nowadays we know that KD is recognized as the most common cause of acquired heart disease among this age group in the developed world, though it occurs in both endemic and community-wide epidemics in children of all ethnicities (2). The disease starts as prolonged fever over 5 days, bulbar conjunctivitis, diffuse mucosal inflammation, nonsuppurative neck lymphadenopathy, polymorphous skin rashes, and indurative edema of the hands and feet, and requires treatment with intravenous immunoglobulin (IVIG) within the first 10 days after onset (3). When KD is left untreated, coronary artery abnormalities may develop in 25% of children after acute phase of the disease, whereas early intervention can reduce these complications to fewer than 5% (4).

Cardiovascular involvement in KD might also occur before the acute phase of KD, as shown by our case referred to a 5-year-old girl, transferred to our hospital by another hospital due to the suspicion of infectious mononucleosis, showing high fever, started 2 days before, cervical lymph node enlargement, neutrophil leukocytosis (50.200/mm^3, 96% neutrophils), increased markers of inflammation (C-reactive protein, CRP, 290 mg/L, n.v. <10, erythrocyte sedimentation rate 49 mm/h) and increased transaminases (GOT 139 IU/L, GPT 96 IU/L). Indeed, the girl was addressed directly to the Pediatric Intensive Care Unit (PICU) of our hospital, due to sudden onset of chest pain, tachycardia (150 beats/minute), galloping rhythm (with a third tone), tachypnea, and capillary refill time of 4" inside the ambulance. Serum creatine phosphokinase (CPK-MB) was 21.4 ng/ml (n.v. <7.0), cardiac troponin I (cTnI) 6.11 ng/ml (n.v. <0.040), and NT-proBNP 9150 pg/ml (n.v. <450). The electrocardiogram (ECG) showed sinus tachycardia and mild ST segment elevation in leads V4-V6. Chest X-ray film was normal. A first echocardiogram revealed 44% of ejection fraction with mild mitral insufficiency.

Following these first examinations, an initial diagnosis of acute myocarditis was made, and the patient was put on milrinone, levosimendan and dopamine, because of progressive hypotension, though she failed to improve. High fevers up to 40°C continued and general condition worsened 12 hours after the girl's entrance in the PICU. The day after, which was the 4th day of fever, other clinical signs were noted: diffuse maculopapular rash, bilateral conjunctivitis, strawberry tongue, and edema in the extremities, clearly suggesting the diagnosis of KD. KD was also confirmed by a new echocardiogram, revealing a hyper glossy right coronary artery (with a diameter of 2.6 mm), minimal pericardial effusion, and ejection fraction of 62%. All serologic and immunologic investigation was negative.

Treatment with IVIG (2 grams/kg of body weight/dose) was started, leading to sharp improvement of clinical, laboratory and cardiac signs after only 24 hours. Body temperature and heart rate turned to normal; cTnI reduced to 1270 ng/mL at the end of IVIG infusion. Aspirin (30 mg/kg/day in four doses) was started the fol-

Corresponding author:
Donato Rigante
Institute of Pediatrics,
Fondazione Policlinico
Universitario A. Gemelli
Università Cattolica Sacro Cuore
Largo A. Gemelli, 8
00168 Rome, Italy
E-mail: drigante@gmail.com

lowing day, when the girl was transferred in our Department, where she stayed for 1 week, and CRP and transaminases became normal, consenting to switch aspirin to antiplatelet dosage. However, aspirin was changed with dipyridamole (6 mg/kg/day in three doses) due to epistaxis and ultrasound signs of mild liver steatosis. On day 10 since disease onset a new echocardiogram revealed a normal aspect of all coronary arteries, ejection fraction of 73%, minimal mitral insufficiency and minimal pericardial effusion. Also ECG became normal, as well as CPK-MB, cTnI and NT-proBNP. All infectious investigations remained negative. KD subacute and convalescence periods were symptomless, although sporadic arthralgias and thrombocytosis (lasting two weeks) combined with skin peeling in the hands were noted. Laboratory abnormalities subsided and, after 1 year of follow-up, the girl remains free from any cardiac sequelae.

The incidence of KD is increasing worldwide, but our knowledge of the infectious agent(s) involved in its onset is far from being decoded (5). KD diagnosis still depends on the temporal sequence of clinical signs, none of which is by itself pathognomonic, combined with fever: severe systemic inflammation can cause cardiovascular involvement, particularly coronary artery abnormalities, but also other heart-related symptoms or signs (6, 7). In recent years, it has been reported that some KD patients might present hemodynamic instability during the acute phase of the illness with severe shock symptoms, named *KD shock syndrome*, frequently misdiagnosed as a mere septic shock and often receiving a delayed treatment (8). In a histopathological evaluation of patients who died during the acute phase of KD all patients showed inflammatory cell infiltration in the myocardium: myocarditis might develop even earlier than KD coronary vasculitis, leading to severe hemodynamic instability, though it is seldom recognized as part of the KD clinical spectrum. KD myocarditis is rarely observed at the onset of KD, as it usually peaks by disease day 10 and then disappears gradually after day 20, being distributed unevenly in the myocardium of patients, ranging from only the epicardial layer of the base to the entire heart (9).

Our case indicates that myocarditis can start in the very early phase of KD with a severely compromised general status, before other classic KD signs have appeared or have been recognized. In addition, this case teaches that, if myocarditis is symptomatic, KD can be complicated by cardiogenic shock and that IVIG might completely reverse the pathologic myocardial picture. Finally, in general terms, failure of myocarditis in a child to improve clinically despite treatment should prompt a thorough search for an unrecognized coincident etiology explaining myocardial involvement, such as KD.

REFERENCES

1. Falcini F, Capannini S, Rigante D. Kawasaki syndrome: an intriguing disease with numerous unsolved dilemmas. Pediatr Rheumatol Online J. 2011; 9: 17.
2. De Rosa G, Pardeo M, Rigante D. Current recommendations for the pharmacologic therapy in Kawasaki syndrome and management of its cardiovascular complications. Eur Rev Med Pharmacol Sci. 2007; 11: 301-8.
3. Rigante D. Autoinflammatory syndromes behind the scenes of recurrent fevers in children. Med Sci Monit. 2009; 15: RA179-87.
4. Rigante D, Andreozzi L, Fastiggi M, et al. Critical overview of the risk scoring systems to predict non-responsiveness to intravenous immunoglobulin in Kawasaki syndrome. Int J Mol Sci. 2016; 17: 278.
5. Esposito S, Rigante D, Principi N. The role of infection in Kawasaki syndrome. J. Infect. 2013; 67: 1-10.
6. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation. 2017; 135: e927-99.
7. Rigante D, Valentini P, Rizzo D, et al. Responsiveness to intravenous immunoglobulins and occurrence of coronary artery abnormalities in a single-center cohort of Italian patients with Kawasaki syndrome. Rheumatol Int. 2010; 30: 841-6.
8. Zhang MM, Shi L, Li XH, et al. Clinical analysis of Kawasaki disease shock syndrome. Chin Med J (Engl). 2017; 130: 2891-2.
9. Harada M, Yokouchi Y, Oharaseki T, et al. Histopathological characteristics of myocarditis in acute-phase Kawasaki disease. Histopathology. 2012; 61: 1156-67.