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Coronary involvement in Mediterranean spotted fever

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SUMMARY

Mediterranean spotted fever (MSF) is a tick-borne acute febrile disease caused by *Rickettsia conorii* and characterized by fever, a maculo-papular rash and a black eschar at the site of the tick bite. We describe the case of a 3-year-old boy with MSF who developed a transient right coronary artery ectasia. The patient was brought to the hospital after four days of fever and mild myalgia of the legs. The suspicion of MSF arose due to the presence of a maculo-papular skin rash and treatment with oral clarithromycin was started. After four days fever persisted and the differential diagnosis of Kawasaki syndrome was considered. Echocardiography showed a dilated right coronary artery with hyperreflective walls. Treatment with intravenous immunoglobulin was initiated while clarithromycin was continued. After one day the fever disappeared. An immunofluorescent antibody test performed after four weeks confirmed a *R. conorii* infection. A follow-up echocardiography was normal six weeks and six months later. We suggest that ectasia of the coronary arteries may be a manifestation of rickettsial vasculitis. Prospective studies are needed to understand the frequency and the possible consequences of this phenomenon in the course of MSF.

KEY WORDS: Rickettsia, *Ehrlichia*, *Anaplasma*, Spotted fever, Boutonneuse fever, Coronary, Kawasaki syndrome

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INTRODUCTION

Mediterranean spotted fever (MSF) is caused by *Rickettsia conorii,* which is transmitted by the dog tick *Rhipicephalus sanguineus*. It is an acute infectious disease typically characterized by fever, skin rash, and a black eschar at the site of tick bite (Raoult and Roux, 1997). Every year, about 300 cases are notified (mainly from June through September) on the Italian island of Sicily (Cascio *et al.*, 2001, Cascio *et al.*, 1998). Sporadic cases have been diagnosed in travelers in other countries as well (Laurent *et al.*, 2009). We describe the case of a 3-year-old boy with MSF who developed a transient right coronary artery ectasia.

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CASE REPORT

In July 2010 a 3-year-old Italian boy who had previously been healthy was admitted to the pediatric emergency clinic of the "G. Di Cristina Children Hospital" with persistent high fever of 4 days duration. In addition, to occasional chills accompanying the fever and mild myalgia of the legs, there were no other complaints, specifically, no nausea, vomiting, or diarrhea, no coughing or dyspnea, and no headaches. Physical examination revealed a temperature of 40°C, a pulse of 104 beats per minute, and a blood pressure of

92/50 mmHg. The boy appeared quite sick. He presented a generalized maculo-papular rash consisting of sparse papules that affected also the palms and soles. Conjunctives and pharynx were hyperemic. The liver and spleen were palpable 2 cm under the costal margins. Rhonchi were heard on thoracic auscultation. He had a palpable lymphadenopathy in the neck. The rest of the physical examination was unremarkable.

Complete blood count and formula revealed a total leukocyte count of 14,780 cells per L with 71% neutrophils, 20.5% lymphocytes, and 3% monocytes, hemoglobin 11 g% and a platelet count of 303,000 per L. Blood biochemical tests showed the following abnormal results: C-reactive protein, 29.2 mg/l (normal value, <5 mg/l); fibrinogen, 444 mg/dl (normal value, 200-400 mg/dl); lactic dehydrogenase, 478 U/l (normal value, 100-240 U/l). Other biochemical studies including glucose, aspartate aminotransferase, alanine aminotransferase, glutamyl transpeptidase, total protein, albumin, cholesterol, blood urea nitrogen, creatine phosphokinase, creatinine, alkaline phosphatase and total bilirubin and coagulation profiles were all within normal limits.

The diagnosis of MSF was considered very likely and oral clarithromycin at 15 mg/kg/day was started. As fever persisted after 4 days, the presence of an infection other than MSF, as well as atypical Kawasaki syndrome (KS) were taken in consideration. For this reason blood cultures, serology for a number of viral and bacterial pathogens, chest X-ray, abdominal echography and echocardiography were performed.

Chest X-ray showed a honeycomb appearance of the right perihilar region and diffuse interstitial septal thickening. An abdomen ultrasound examination showed an enlarged homogeneous liver and an slightly enlarged spleen (longitudinal diameter, 86 mm [normal value for 2-4-year-old children, 64-85 mm]. Cardiac ultrasound showed a functionally and structurally normal heart. The right coronary artery had a diameter of 2.8 mm with hyper-reflective walls (Figure 1). The width of the left coronary artery was normal (diameter, 1.7 mm). The electrocardiogram showed no changes.

Considering the diagnosis of KS, treatment with 2 g/kg intravenous immunoglobulin and aspirin was initiated while clarithromycin was continued to cover for atypical and intracellular bacteria. Moreover, an infection with *R. conorii* continued to be regarded as a likely possibility. In the meantime, serological studies for HIV-1, HIV-2, HSV1 and HSV2, cytomegalovirus, parvovirus, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Brucella*, were negative. Tests for EBV capsid IgG and IgM antibodies were negative. IgM and IgG antibodies against *R. conorii* were both moderately positive (1:80 and 1:40, respectively) by indirect immunofluorescent antibody test (IFAT). Multiple blood cultures, a urine culture and a pharyngeal swab were negative for bacteria and fungi. After one day the fever had disappeared and the patient was alert and playful. Blood cultures were still negative. WBC, C-reactive protein (CRP) and fibrinogen values normalized. The patient was then discharged from the hospital in good clinical condition. Continued aspirin treatment was advised. Four weeks later, the patient was in excellent condition and IgM and IgG titers against *R. conorii* had risen to 1:320 and 1:640, respectively. The diagnosis of MSF was then considered proven. Cardiac ultrasonography six weeks after presentation was normal (left and right coronary artery diameter <2.0 mm) and aspirin was discontinued. At six-month follow-up no echocardiographic abnormalities were found.

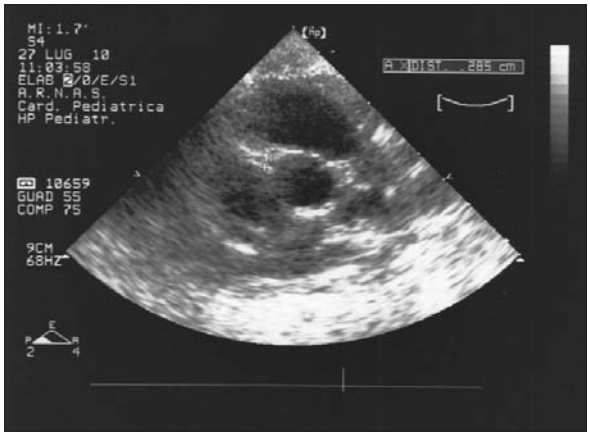

FIGURE 1 - *Echocardiogram showing dilated right coronary artery with hyperreflective walls.*

DISCUSSION

Typical clinical features of MSF include fever, myalgia, headache, generalized maculo-papular

rash and an inoculation eschar ('tache noire') at the site of the tick bite (Raoult and Roux, 1997). The black eschar is found in about 70% of cases; cervical adenopathy is often present when the "tache noire" is present on the scalp or in the neck. The rash may be only represented by sparse maculo-papular elements in about 7% of cases and sometimes by petechiae. Conjunctival hyperemia is present in about 6% of cases (Cascio *et al.*, 1998).

The major target of pathogenic *Rickettsiae* is the endothelium lining the small and medium-sized blood vessels. Accordingly, invasion and injury to endothelial cells, altered vascular permeability, platelet and hemostatic/fibrinolytic system changes, production of acute phase response proteins, activation of innate and acquired immune system, all leading to vascular inflammation/dysfunction, collectively termed 'rickettsial vasculitis', is reflected in the clinical features of all rickettsial diseases, especially in severe and complicated cases (Amaro *et al.*, 2003, Paddock *et al.*, 1999, Sahni and Rydkina, 2009). Furthermore, rickettsial species have been isolated from myocardial tissue or from the endothelium of coronary arteries and myocardial vessels in severe cases of rickettsial disease (DiNubile, 1996, Nilsson *et al.*, 1999, Walker *et al.*, 1989). A case similar to ours was described in 3-year-old girl with murine typhus (van Doorn *et al.*, 2006). In that study, as in our case, the temporary widening of the coronary artery was possibly considered a manifestation of systemic rickettsial vasculitis.

Rickettsiae have been initially implicated and subsequently dismissed as possible causes of KS (Burns and Glode, 2004, Kafetzis *et al.*, 2001, Rathore *et al.*, 1993, van Doorn *et al.*, 2006). However, the aspecific and partially overlapping symptomatology of rickettsioses and KS makes differential diagnosis difficult (Jenkins *et al.*, 1997, van Doorn *et al.*, 2006). We found only two reports in the international literature of KS occurring concomitantly with a rickettsial disease. These cases involved a 4-year-old girl with Rocky Mountain spotted fever (Bal and Kairys, 2009) and a 22-month-old girl with an *Anaplasma* sp infection (Chochlakis *et al.*, 2009). However, it cannot be excluded that the inflammatory response to rickettsial infections can occasionally trigger the cascade of events that eventually leads to KS.

KS is an acute, self-limited systemic vasculitis of unknown aetiology that occurs in children. The diagnosis is confirmed by the lack of another known disease process to explain the illness and by the presence of fever for at least five days and by the presence of four of the following five criteria:

1) bilateral conjunctival injection;
2) changes of the mucous membranes of the upper respiratory tract: injected pharynx; injected, fissured lips; strawberry tongue;
3) polymorphous rash;
4) changes of the extremities: peripheral oedema, peripheral erythema, periungual desquamation;
5) cervical adenopathy (Burns and Glode, 2004).

A threatening feature of KS is coronary artery aneurysms that develop in 20-25% of cases, which can subsequently (years later) cause sudden death or myocardial infarction (Burns *et al.*, 1996, Kato *et al.*, 1992).

Our patient suffered (apart from persistent high fever), from bilateral conjunctival injection, rash and cervical adenopathy - three of the required four criteria. However, it is known that the clinical symptoms of KS can develop sequentially during the course of the disease (Burns and Glode, 2004). Because our patient's dilated right coronary artery was attributed to KS, immunoglobulins were administered. However, it is more likely that coronary ectasia was the result of the rickettsial vasculitis. Echocardiographic screening could be offered to patients with MSF for research purposes until its clinical relevance is confirmed. This may lead to the detection of more cases of coronary ectasia than presently appreciated. Similarly, retinal vasculitis was found in a high proportion of MSF patients, even in the absence of ocular symptoms (Khairallah *et al.*, 2004).

CONCLUSIONS

MSF should be included in the differential diagnosis of KS in countries where MSF is endemic and in other countries when the patient has recently returned from an endemic area. *R. conorii* infection can cause coronary arteries ectasia and this fact, together with the aspecific and partially overlapping symptomatology of KS and MSF may complicate differential diagnosis.

Prospective studies are necessary to understand the frequency and the possible consequences of coronary artery ectasia in the course of MSF.

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