Clostridium baratii bacteremia associated with Kawasaki syndrome. First case report

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SUMMARY

We experienced a case of a 3-year-old boy who presented signs and symptoms of Kawasaki syndrome. Two blood culture sets were processed by the hospital microbiology laboratory using a standard blood culturing system. The anaerobic bottles gave a positive result at day 3 after inoculation. The biochemical profiles produced by the RapID ANA II System showed that the organism was *Clostridium baratii* with a probability of 99%. Our case highlights the importance of *C. baratii* as a potential human pathogen and reports the associations with manifestations, which, to our knowledge, have not been previously described concomitantly with a clostridial infection.

KEY WORDS: Kawasaki syndrome, *Clostridium baratii,* Bacteremia

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Kawasaki syndrome (KS) is an acute, self-limited systemic vasculitis of unknown aetiology that occurs in children. The diagnosis is confirmed by the presence of fever for at least 5 days and of four of the five criteria below, and by the lack of another known disease process to explain the illness:

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

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These features need not be present at one particular time and in fact, may evolve sequentially over a period of few days (Burns & Glode, 2004).
The importance of KS is due to the coronary artery aneurysms that develop in 20-25% of cases if the treatment is not given early in the course of the disease. Their development is clinically silent in most cases and may be recognized only years later at the time of sudden death or myocardial infarction (Burns *et al.*, 1996; Kato *et al.*, 1992).
The genus *Clostridium* is a phylogenetically heterogeneous group of anaerobic, endospore-forming, rodshaped bacteria; they are usually GRAM-positive, but some species may stain GRAM variable or GRAM-negative (Allen *et al.*, 2003; Jousimies-Somer *et al.*, 2002).
Clostridium strains are widely distributed in the environment and form part of the normal colonic microflora of humans and many animals (Allen *et al.*, 2003; Jousimies-Somer *et al.*, 2002). More than 150 species have been described to date, but most are believed to be harmless saprophytes (Allen *et al.*, 2003).

Some isolates of *C. baratii* produce type F botulin neurotoxin and *C. baratii* has been associated with rare cases of botulism both in adults and children. In most of these cases, the patients appeared to be colonized in the gastrointestinal tract with neurotoxic *C. baratii* rather than to have consumed food contaminated with neurotoxin (Barash *et al.*, 2005; Gupta *et al.*, 2005; Hall *et al.*, 1985; Harvey *et al.*, 2002; McCroskey *et al.*, 1991; Paisley *et al.*, 1995).

We describe here a case of bacteremia caused by *C. baratii* in a child with symptoms of KS. This report is the second of bacteremia caused by this microorganism (Woo *et al.*, 2005). To our knowledge, it is the first time that a clostridial infection has been associated with KS.

A 3-year-old Italian boy presented for evaluation of fever (t max 39°C), abdominal pain, vomiting and polymorphous erythematosus rash on the extension surfaces of the extremities of 3 days duration. Three weeks before he presented with irregular fever and micropapulous exanthema over the truncus for 3 days followed after two days by perianal hyperaemia, scrotal oedema and balanopreputial hyperaemia and swelling.

On admission, he was febrile (temperature, 38.0°C), the pulse rate was 112 min/h and the respiratory rate was 26 per min. Height and weight were appropriate for age (15.2 Kg (25°P), 107 cm (95°P)).

Physical examination disclosed quite good general conditions, fine desquamation on the palms and fingers especially in the periungual region; severe hyperaemia of perianal region with scaling areas; erythematosus pharynx, strawberry tongue, dry and fissured lips, angular cheilitis; left enlarged jugulodigastric nodes.

Laboratory examinations revealed a white blood cell count of 5000/µL with 54% neutrophils and 38% lymphocytes. A platelet count of 222000/µL, C-reactive protein concentration of 50 mg/l and an erythrocyte sedimentation rate of 27 mm/h. IgA 297 mg/dl (normal range 35-190 mg/dl). Within the normal range: Anti-Streptolysin O**,** IgM, IgG, BUN, glycemia, creatinine, bilirubin, transaminases, gamma-glutamyltransferase, CD3 T cells, CD4 T cells, CD8 T cells, CD19+ B cells, NK cells and CD4/CD8 rate. Specific IgM for EBV, CMV, Herpes simplex virus type 1 and type 2, Adenovirus, Parvovirus B19, Coxsackie viruses, Echovirus and C. *pneumoniae* were absent.

Microscopic examination of urine under high power (400x) showed 10 WBC per microscopic field and absence of bacteria.

Before the culture results were obtained, since a viral etiology was initially suspected, the patient was not given any antibiotic therapy. The patient's general condition improved within 36 h, he became afebrile after 3 days and all his symptoms disappeared within 8 days.

During the first days of hospitalization the diagnosis of KS was not considered and consequently intravenous immunoglobulin was not administered. On day 7 echocardiography was normal and did not show any coronary changes. Cultures of stool, urine and pharyngeal swab were negative.

About 10 ml of peripheral blood was collected from veins of forearms on day 1 and day 2 and used to inoculate blood culture for anaerobic and aerobic bacteria bottles.

Two blood culture sets were processed by the hospital microbiology laboratory using a standard blood culturing system (BACTEC 9120; Becton Dickinson). The anaerobic bottles gave a positive result at day 3 after inoculation.

The isolates were GRAM-positive rods. Growth on 5% sheep blood agar (Becton Dickinson) revealed traslucid B-haemolytic smooth, circular, yellow-pigmented colonies, 1-2 mm in diameter, within 24 h of incubation.

The biochemical profiles produced by the RapID ANA II System (Remel, Inc., Lenexa, KS) showed that the organism was *C. baratii* with a probability of 99%. In particular, the isolates were alpha galactosidase positive, beta-galactosidase positive, arginine aminopeptidase positive, L-pyrrolidonyl peptidase positive and urease negative.

Antibiotic susceptibility testing of the isolates was carried out by the E-test (AB Biodisk, Solna, Sweden) according to the manufacturer's instructions. The isolate was found to be susceptible to ceftriaxone, ampicillin, piperacillin ciprofloxacin, chloramphenicol, and it was resistant to ceftazidime, gentamicin and tobramycin. The isolates of *C. baratii* were not analyzed for production of botulin neurotoxin or other clostridial toxins.

When *C. baratii* was identified (day 4 after hospitalization), the patient was afebrile, no antibiotic was added in therapy and blood cultures were repeated and no growth was observed. The search of *C. baratii* in stool samples in aerobic and anaerobi conditions was negative. Clinical

conditions improved further. Laboratory studies performed on the seventh day of therapy revealed a white blood cell count of 4900 mm^3 with 39% neutrophils, 53% lymphocytes and 4% monocytes, a C-reactive protein concentration of 4 mg/L and an erythrocyte sedimentation rate of 16 mm/h. Blood cultures were negative. Echocardiography was repeated after 3 weeks and after 3 months and did not show any changes.

Pathogenic *Clostridium* spp. may be involved in a wide variety of human infections or illnesses. Such conditions are usually endogenous (e.g., brain abscess, pneumonia, intrabdominal abscess, cholecystitis, bacteremia) and arise from the host's own microflora; other illnesses may be exogenous (e.g., food poisoning, pseudomembranous colitis, tetanus, botulism, myonecrosis) (Allen *et al.*, 2003).

Clostridium bacteraemia is uncommon, constituting 0.7-2.6% of all bacteraemic episodes in the studies that supplied this information (Benjamin *et al.*, 2006; Gorbach and Thadepalli, 1975; Grasberger *et al.*, 1984; Ingram & Cooper, 1989; Pietrafitta and Deckers, 1982; Tanabe *et al.*, 1989). The most common sources of *Clostridium* spp. in cultures of blood are the colon, the lung, tubo-ovarian or endometrium, the biliary tract and decubitus ulcer (Rechner *et al.*, 2001). In the paediatric series reported by Caya *et al.* the source of bacteremia was the gastrointestinal tract in the 81.4% of the cases, and a malignant neoplasia was present in 61% of the cases (Caya and Truant, 1999).

The clinical spectrum of clostridial bacteremia ranges from an asymptomatic patient having an incidental positive blood culture to a full-blown, life-threatening infection characterized, in its most devastating form, by fever, shock, massive intravascular haemolysis and death (Caya and Truant, 1999). The *Clostridium* species most identified in blood cultures are: *C. perfrigens*, *C. septicum*, *C. clostridioforme*, *C. tertium*, *C. difficile*, *C. sphenoides*, *C. Ramosum*, *C. butyricum* and *C. innocuum* (Allen *et al.*, 2003; Caya and Truant, 1999; Rechner *et al.*, 2001).

In literature there is only one paper in which a *C. baratii* bacteremia is reported, this case was considered by the authors not clinically relevant (Woo *et al.*, 2005).

Recently, another three *Clostridium* species never reported as cause of bacteremia have been described: *C. hathewayi* in a 27-year-old man with acute cholecystitis and hepatic abscess presenting with intermittent fever and abdominal pain (Elsayed, 2004) and in 39-year-old woman with acute appendicitis (Woo *et al.*, 2004); *C. intestinale* in a adolescent female with fever and abdominal pain (Elsayed and Zhang, 2005); and *C. symbiosum* in a 70-year-old man with metastatic colon cancer (Elsayed and Zhang, 2004).

The cause of KS remains unknown. The hypothesis that bacterial toxins acting as superantigens could trigger the cascade of events that lead to KS has been widely debated (Meissner and Leung, 2000). Most recently, a multicentre, prospective study detected no difference in the rates of isolation of superantigen-producing bacteria between patients with the syndrome and febrile controls (Leung *et al.*, 2002).

Generally, during KS laboratory findings are consistent with severe systemic inflammation even if laboratory data are not considered among the diagnostic criteria of KS.

The diagnosis in our case was confirmed by the presence of fever for 6 days, four of the five criteria required, and by the lack of another known disease process to explain the illness.

We cannot exclude either that our patient had two independent events (*C. Baratii* bacteremia and KS) without a cause and effect association, or that *C. baratii* may have triggered an abnormal immune response causing KS.

The clinical significance of clostridial bacteremia in some blood cultures continues to be a diagnostic challenge that is anything but easy to define, especially in view of the high rate of apparent contamination and clinically innocuous, transient bacteremia (Caya and Truant, 1999). However, the growth of *Clostridium* spp. in blood cultures should always be properly evaluated and never ignored (Benjamin *et al.*, 2006).

Our report highlights the importance of *C. baratii* as a potential human pathogen. Moreover, we report the associations with KS, which has not been previously described concomitantly with a clostridial infection.

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