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ARDS in a patient with homozygous beta-thalassemia due to yersiniosis

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Abstract We report a case of *Yersinia enterocolitica* sepsis syndrome and the acute respiratory distress syndrome in a chronically transfused adolescent with beta-thalassemia. This manifestation of serious *Y. enterocolitica* infection has not previously been reported. Dyspnea, hypoxia, and fever were the principal features of the clinical presentation. The acute onset of respiratory symptoms occurred after appendectomy. Chest radiographs revealed frontal bilateral infiltrates and alveolar consolidation to three quadrants. *Y. enterocolitica* was identified from blood and intraoperative appendix cultures. Although there was no need for mechanical ventilation, a remarkable persistence of clinical and X-ray findings was noted. Ther-

apy with high levels of oxygen, and intravenous amikacin and piperacillin/tazobactam led to a favorable outcome.

Key words Beta-thalassemia · ARDS · Sepsis syndrome · *Yersinia enterocolitica*

Introduction

Patients with homozygous beta-thalassemia are at increased risk for serious *Yersinia enterocolitica* infections. The cause of this increased susceptibility is related to systemic iron overload and the use of iron chelators [1]. Extraintestinal sites of systemic *Yersinia* infection include lymphadenitis, arthritis, osteomyelitis, pneumonia, endocarditis, meningitis, and dermatitis [2]. There are also numerous reports of *Y. enterocolitica* sepsis in patients with iron overload [3], yet there is no report of a relationship between the acute respiratory distress syndrome (ARDS) and *Yersinia* sepsis in the current literature. A clinical situation mimicking ARDS due to yersiniosis has been described, but the strict definition of ARDS has not been respected [4]. We present a case

of *Yersinia* sepsis syndrome and ARDS in a female adolescent with homozygous beta-thalassemia.

Case report

A 15-year-old girl (weight 64 kg) with homozygous beta-thalassemia, had been on regular red cell transfusion therapy since infancy. Desferrioxamine chelation (50 mg/kg per day) had been used for 12 years. The serum ferritin level was stable at 800–1000 ng/ml (normal range 10–150 ng/ml), and she had not undergone splenectomy. Human immunodeficiency virus serology was negative.

One week after the last red blood cell transfusion she developed fever to 39°C for 3 days with nausea, vomiting, and non-bloody diarrhea. She had not yet received any antibiotics. Progressive pain in the right lower quadrant and signs of peritonitis necessitated laparotomy and appendectomy. Chest and abdominal radi-

Fig. 1 Chest radiograph on admission showing alveolar consolidation confined to three quadrants

Fig. 2 Normal chest radiograph was obtained on the 18th day after admission

ography performed in the immediate preoperative period was normal. White blood cell count was $15 \times 10^3/\text{mm}^3$ with 84% neutrophils before surgery. The patient was begun on intravenous amikacin (1 g/day) and piperacillin/tazobactam (9 g/day). Surgical abdominal exploration revealed an inflamed and enlarged appendix and mesenteric lymph nodes. Pathological study confirmed an acute purulent appendix. In the immediate postoperative period her temperature was raised (39°C). Dyspnea and hypoxia occurred 8 h after surgery. A chest radiograph was then taken, which revealed diffuse shadows in both lung fields. Persistence of high fever and increasing dyspnea with a high oxygen requirement precipitated a transfer to the intensive care unit of our hospital 4 h later.

On arrival, the physical examination was remarkable for a tachypneic (respiratory rate 60 breaths/min), tachycardic (heart rate 130 beats/min) young adult with severe respiratory distress. She was febrile to 39.5°C and the blood pressure was 130/

60 mmHg. Respiratory sounds were diminished and crackles were audible bilaterally during inspiration. Results of the heart examination were normal except for the tachycardia. The arterial blood pressure remained stable. The head, throat, and extremities were normal. No cutaneous lesions of lymphadenopathy were found. The abdomen was soft and the liver was unpalpable. An already known splenomegaly due to thalassemia was noted. Arterial blood gas analysis on 100% oxygen inspiration showed pH 7.45, partial pressure of oxygen PO_2 81 mmHg, partial pressure of carbon dioxide PCO_2 32 mmHg, bicarbonate HCO_3^- 21 mmol/l, and oxygen saturation 96.7%. Her white blood cell count was $14.5 \times 10^3/\text{mm}^3$ with 80% neutrophils and a marked shift to the left not accompanied by eosinophilia. Other blood count data were hemoglobin 9.3 g/dl, hematocrit 28%, and platelets $58 \times 10^3/\text{mm}^3$. C-reactive protein was 182 mg/l. Blood coagulation, liver and renal function, and blood sugar were normal. A chest radiograph on arrival showed remarkable deterioration since the first X-ray was taken at the first hospital in the early postoperative period. The radiograph revealed bilateral infiltrates and alveolar consolidation confined to three quadrants (Fig. 1). Cardiac echocardiography did not show any cardiac dysfunction (Ejection fraction = 75%, shortening fraction = 37.5%). From the above findings we made a diagnosis of ARDS developing in the sepsis syndrome.

Medical support consisted of: (1) oxygenation [fractional inspired oxygen (FIO_2 100%)] and (2) intravenous amikacin (1 g/day) and piperacillin/tazobactam (9 g/day). There was no need for mechanical ventilation because an arterial oxygen saturation greater than 96% was achieved by supplemental oxygen, and arterial carbon dioxide tension PaCO_2 values were within the normal range. The reason for the choice of antibiotics was that the main target of therapy was gram-negative bacteria including *Y. enterocolitica*.

Bacterial cultures of two blood samples, received on hospital day 1, and serology revealed *Y. enterocolitica* serotype 0:3. The same microorganism was isolated from the intraoperative appendix culture. Amikacin and piperacillin/tazobactam were sensitive and the minimum inhibitory concentration (MIC) was <4 and <8 µg/ml, respectively. Other sensitive antibiotics were aztreonam (MIC < 8 µg/ml), cefoxitin (MIC < 4 µg/ml), ceftazidime (MIC < 4 µg/ml), ceftriaxone (MIC < 8 µg/ml), cefuroxime (MIC < 4 µg/ml), ciprofloxacin (MIC < 0.28 µg/ml), ofloxacin (MIC < 0.5 µg/ml), tobramycin (MIC < 2 µg/ml), gentamicin (MIC < 2 µg/ml), mezlocillin (MIC < 8 µg/ml), and trimethoprim-sulfamethoxazole (MIC < 1/19 µg/ml). The microorganism was found to be resistant to ampicillin (MIC > 16) and cefazolin (MIC > 16).

Progressive improvement of the clinical signs of ARDS and X-ray findings was noted after the 4th day of admission. Intermittent fever (up to 39°C) persisted for 10 days. Because of the persistence of high fever an ultrasonogram was performed which was negative for intraabdominal abscess. The patient was discharged from the intensive care unit after 10 days. A normal chest radiograph was obtained on the 18th hospital day (Fig. 2). She received a total of 3 weeks of intravenous antibiotics while chelation therapy was withheld.

Discussion

The patient described had the characteristics of a young adult with homozygous beta-thalassemia: chronically transfused, chelated with desferrioxamine, yet with iron overload. The initial clinical presentation was typi-

cal of a *Yersinia* infection in a patient with iron overload: invasive infection, fever, abdominal symptoms, and finally acute appendicitis with positive intraoperative appendix culture.

Infections due to *Y. enterocolitica* are usually associated with the gastrointestinal tract. Invasive and noninvasive endotoxin-producing strains of this gram-negative bacterium are the most commonly recognized bacterial cause of acute terminal ileitis. They also cause nonspecific abdominal pain or "pseudoappendicitis" and occasionally acute colitis or acute appendicitis. Severe *Y. enterocolitica* infections are described in patients with homozygous beta-thalassemia. Iron excess and iron chelator use are predisposing factors, as supported by clinical, animal, and in vitro data. To understand the pathogenesis of the infection one must remember that *Y. enterocolitica*, an extremely iron-siderophore – dependent microorganism, lacks siderophores yet has receptors for them. Desferrioxamine supplies the microorganism with iron in a form it can use (chelating agents bound to iron = exogenous siderophores) [1]. The source of *Y. enterocolitica* in this patient was not identified. It is known that the microorganism is transmitted to humans mainly from contaminated dairy products, meat, or water. It may also be transmitted human to human via blood transfusion from a bacteremic donor. This possibility cannot be excluded in our case, although the typical clinical presentation of a transfusion-induced infection in an iron-overloaded patient is severe septicemia within 24 h after infusion [5].

The diagnosis of sepsis syndrome was established in our case by the following findings: (1) signs of systemic response to infection including tachypnea, tachycardia, hyperthermia and leukocytosis, (2) severe hypoxemia [arterial oxygen tension (PaO_2)/ $\text{FIO}_2 < 100$ mmHg] without preexisting pulmonary or cardiovascular disease, and (3) positive blood cultures. The term septic shock did not characterize the condition of the patient according to the definition suggested by Bone and colleagues [6]. The diagnosis of ARDS was based on the following criteria: (1) acute onset of respiratory symptoms, (2) frontal chest radiography with bilateral infiltrates, and (3) exclusion of left heart disease and congestive heart failure. The lung injury score obtained for the patient was 7 (alveolar consolidation confined to three quadrants and $\text{PaO}_2/\text{FIO}_2 < 100$ mmHg), which also confirmed severe lung injury [7]. The possibility of bilateral hematogenous *Yersinia* pneumonia after systemic spread from the bowel due to surgery has to be mentioned here; however, the acute onset of clinical presentation, the radiographic findings of widespread airspace consolidation, and the fact that repeated cultures of bronchial secretions were negative, make this diagnosis of secondary importance [8].

In fact, gram-negative sepsis is strongly associated with the development of ARDS. Endotoxemia causes

lung dysfunction through a variety of mechanisms [9]. Many studies indicate that sepsis is the most frequent event precipitating the development of ARDS. Pfenniger et al. [10] found that in children aged 2 weeks to 15 years, intraabdominal infection and/or sepsis are the most common causes. On the other hand, among patients with gram-negative bacteremia or sepsis the frequency of ARDS has been reported to vary from 18 to 38% [9]. It is interesting that, although many cases of septicemia due to *Y. enterocolitica* have been described, there is no reference to ARDS related to *Yersinia* sepsis in the current literature.

Referring to the patient's treatment, antimicrobial therapy consisted of a combination of an aminoglycoside and an ureidopenicillin/ β -lactamase inhibitor which were found sensitive in the microorganism isolated from blood and intraoperative appendix cultures. The dosage of intravenous amikacin administered was 15 mg/kg per day, which is suggested as effective treatment for *Y. enterocolitica* septicemia unless adaption to the patient's renal function is necessary [3]. Amikacin blood levels were measured during treatment and were found to be within therapeutic limits. The combination of an aminoglycoside and a third-generation cephalosporin or a fluoroquinolone is also suggested by many to be effective in *Yersinia* sepsis. In particular, fluoroquinolones are suggested to be a suitable treatment for *Y. enterocolitica* septicemia because most of the available parameters (in vitro activity, pharmacological properties, therapeutic effect in animal models, and clinical results) are favorable [3]. Persistence of clinical signs of ARDS and X-ray findings was noted. This is probably due to the increased susceptibility to *Yersinia* infections of these patients and is also confirmed by reports of acute septicemia, intraabdominal abscess, intestinal perforation, or gangrene and peritonitis following *Yersinia* infection of the gastrointestinal tract even under antiyersinial therapy [2]. However, we cannot know whether changing the treatment to other sensitive antibiotics (combination of a fluoroquinolone and a third generation cephalosporin or an aminoglycoside) would have shortened the response to therapy in our case [3]. Nevertheless, authors agree that early and accurate diagnosis and specific therapy are required in such patients. When *Yersinia* enterocolitis or mesenteric adenitis are suspected, an ultrasound examination has to be performed. Initial treatment includes antiyersinial therapy and temporarily stopping chelation [1]. Surgery may lead to hematogenous contamination and enhance sepsis [11]. This probably explains the rapid postoperative development of the sepsis syndrome in our patient. Recognition of *Yersinia* infection does not always forestall laparotomy; such patients may have conditions with true surgical consequences of infection accompanying adenitis, as was described in our case.

The absence of cardiovascular instability (hypotension) and the noninvolvement of an extrapulmonary or

gan system were, beyond the intensive care treatment, important factors for the good outcome [12]. The patient's immunological condition is also critical for the prognosis of *Yersinia* sepsis in patients with beta-thalassemia. Our patient was not immunologically compromised by splenectomy, which is consistent with improved conditions for survival [13].

A rare case of ARDS following *Yersinia enterocolitica* sepsis in a young adult with beta-thalassemia has

been described. Although there was no need for mechanical ventilation, a remarkable persistence of clinical and X-ray findings despite antiyersinial therapy was noted. This is related to the increased virulence of this microorganism due to iron burden and use of iron chelators. Treatment in the intensive care unit with oxygen and intravenous antibiotics allowed a favorable outcome.

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