

## Community-Acquired Meningitis and Sepsis Caused by *Chryseobacterium meningosepticum* in a Patient Diagnosed with Thalassemia Major

Nisel Ozkalay,<sup>1\*</sup> Murat Anil,<sup>2</sup> Neval Agus,<sup>1</sup> Mehmet Helvaci,<sup>2</sup> and Seral Sirti<sup>2</sup>

Department of Microbiology<sup>1</sup> and Department of Pediatrics,<sup>2</sup> Tepecik Educational and Research Hospital, Izmir, Turkey

Received 20 March 2006/Returned for modification 28 April 2006/Accepted 18 May 2006

***Chryseobacterium meningosepticum* is a rare pathogen in cases of bacterial meningitis in adults and adolescents. We report on the case history of a 17-year-old boy with thalassemia major and meningitis and sepsis caused by *C. meningosepticum* in splenectomized. The patient received vancomycin therapy for 21 days and was discharged in a state of complete recovery.**

### CASE REPORT

A 17-year-old boy was diagnosed with thalassemia major (TM) at the age of 12 months. His  $\beta$ -thalassemia mutation was IVS-I-110 (G→A), homozygous state. He was treated with regular blood transfusions at 3- to 4-week intervals to maintain pretransfusion hemoglobin levels above 9.5 g/dl. Desferrioxamine treatment was started when the boy was 3 years of age. Because of an increasing requirement for packed red cells, he was splenectomized in 2000. Despite receiving desferrioxamine therapy, he was heavily iron loaded, so an orally active chelator, deferiprone (L<sub>1</sub>,1,2-dimethyl-3-hydroxypyridin-4-one), was added 6 months before the condition described here occurred. The latest serum ferritin level was 2,750 ng/dl. The patient did not have heart failure, diabetes mellitus, or cirrhosis of liver. There was no previous history of significant infection.

On 20 September 2005, the patient was admitted with fever, headache, and progressive disturbances of consciousness that had lasted for 2 days. On admission, physical examination revealed a pale and toxic appearance. He had positive signs of meningeal irritation. His body temperature was 39.2°C, his heart rate was 124 beats/min, his respiratory rate was 20/min, his blood pressure was 105/50 mm Hg, his body weight was 41 kg, and his body height was 155 cm. Hepatomegaly and a scar from the splenectomy were noted. Blood and cerebrospinal fluid (CSF) samples were taken and sent to the laboratory for culture and biochemical analyses. Results of the laboratory testing showed a white blood cell (WBC) count of  $9 \times 10^3/\mu\text{l}$  (90% neutrophils), a hemoglobin concentration of 6.1 g/dl, a hematocrit of 18.2%, a platelet count of  $258 \times 10^3/\mu\text{l}$ , an urea concentration of 30 mg/dl, a creatinine concentration of 1.2 mg/dl, a glucose concentration of 108 mg/dl, an aspartate aminotransferase concentration of 100 U/liter, an alanine aminotransferase concentration of 102 U/liter, a sodium level of 38 meq/liter, a potassium level of 4.0 meq/liter, an erythrocyte sedimentation rate of 150 mm/h, and a C-reactive protein concentration of 4.0 mg/dl. Study of the CSF revealed the

following results: a WBC count of  $5,200/\text{mm}^3$ , a glucose concentration of 20 mg/dl, a protein concentration of 92 mg/dl, and a chloride level of 124 meq/liter; the CSF was negative by Gram staining. All of the remaining biochemical laboratory tests were unremarkable. A chest radiograph and computed tomography of the brain were normal. Empirical therapy with intravenous vancomycin at 60 mg/kg of body weight/day (maximum dose, 2 g/day) was initiated. The CSF specimen was cultured on 5% sheep blood, eosin-methylene blue, and chocolate agars at 35°C in 5 to 10% CO<sub>2</sub> for 24 to 48 h. Blood was collected when the patient was in the febrile period and placed in three bottles for culture, with each bottle containing 10 ml of the patient's blood. The blood cultures were incubated in a BACTEC 9120 instrument (Becton Dickinson and Company, Sparks, MD). Bacterial growth was detected within 48 h. The smooth and large colonies grew on all agars after 24 h. Additional conventional biochemical tests, including oxidase, catalase, indole, and urea reaction tests, and the API 20NE identification system (bioMérieux, Marcy l'Etoile, France) were used to determine the identities of these colonies. The organism was a nonmotile, oxidase-, catalase-, and indole-positive gram-negative bacillus that produced a pale yellow pigment on 5% sheep blood agar. In the API 20NE system the isolate gave biotype number 2476304 with a probability of 99.9%, which was interpreted as an "excellent identification." All tests showed that *Chryseobacterium meningosepticum* was present in the CSF and blood cultures. Antibiotic susceptibility testing was performed by the Etest (AB BIODISK, Solna, Sweden) (12). The susceptibility of the isolate to antimicrobial agents was determined by applying the Clinical and Laboratory Standards Institute susceptibility criteria used for *Pseudomonas aeruginosa* and *Staphylococcus* spp. (5). The isolate was susceptible to the following antibiotics; ciprofloxacin (MIC, 0.5  $\mu\text{g}/\text{ml}$ ), levofloxacin (MIC, 0.5  $\mu\text{g}/\text{ml}$ ), trimethoprim-sulfamethoxazole (MIC, 40  $\mu\text{g}/\text{ml}$ ), and vancomycin (MIC, 4  $\mu\text{g}/\text{ml}$ ). It was resistant or intermediate to the other antibiotics tested: ceftazidime (MIC,  $\geq 64$   $\mu\text{g}/\text{ml}$  [resistant]), ceftriaxone (MIC,  $\geq 64$   $\mu\text{g}/\text{ml}$  [resistant]), aztreonam (MIC,  $\geq 64$   $\mu\text{g}/\text{ml}$  [resistant]), cefepime (MIC,  $\geq 64$   $\mu\text{g}/\text{ml}$  [resistant]), amikacin (MIC,  $\geq 64$   $\mu\text{g}/\text{ml}$  [resistant]), gentamicin (MIC,  $\geq 16$   $\mu\text{g}/\text{ml}$  [resistant]), imipenem (MIC,  $\geq 16$   $\mu\text{g}/\text{ml}$  [resistant]), meropenem (MIC,  $\geq 16$   $\mu\text{g}/\text{ml}$  [resistant]), piperacillin (MIC, 32  $\mu\text{g}/\text{ml}$  [in-

\* Corresponding author. Mailing address: Department of Microbiology, Tepecik Educational and Research Hospital, Izmir, Turkey. Phone: 90 232 4696969. Fax: 90 232 4330756. E-mail: niseloz@yahoo.com.

intermediate]), and piperacillin-tazobactam (MIC, 32 µg/ml [intermediate]). The isolate had an inducible chromosomal beta-lactamase. A routine repeat lumbar puncture was performed within 48 h of the initiation of appropriate antibiotic therapy. Analysis of the CSF showed a decreased leukocyte count (200/mm<sup>3</sup>), a decreased glucose concentration (50 mg/dl), and a decreased protein concentration (49 mg/dl); and a follow-up culture was negative. The patient received a 21-day course of intravenous vancomycin therapy and was then discharged in a state of complete recovery.

*Chryseobacterium meningosepticum* was first reported by King in 1959. While he was studying unclassified bacteria associated with meningitis in infants, he named the organism that he recovered *Flavobacterium* ("the yellow bacillus") *meningosepticum* ("associated with meningitis and sepsis"). In 1994, it was reclassified in the genus *Chryseobacterium* and was named *Chryseobacterium meningosepticum* (7, 17, 21). It is a nonfermentative; nonmotile; slender; slightly curved; and catalase-, oxidase-, and indole-positive saprophytic gram-negative bacillus. *Chryseobacterium meningosepticum* causes disease predominantly in premature newborns and infants. Meningitis and bacteremia are the most common clinical presentations. However, *C. meningosepticum* remains a rare pathogen in cases of bacterial meningitis in adults and adolescents (1, 23). In this study, we report on a case of community-acquired *C. meningosepticum* meningitis and sepsis in an adult splenectomized TM patient. To our knowledge, this is the first report of primary *C. meningosepticum* meningitis in a splenectomized TM patient.

Most TM patients can now survive beyond three decades of life with regular blood transfusions and iron chelation therapy. Serious infection is the second most common cause of death in TM patients (15). Three major risk factors for bacterial infection have been identified in TM patients: intravascular catheterization, high serum ferritin levels ( $\geq 2,000$  ng/ml), and splenectomy (19). Splenectomized TM patients are vulnerable to overwhelming infections because of both splenectomy and iron overload (10, 20). Studies on the immune status of transfusion-dependent TM patients have been performed. Various forms of immunological defects were described: reversed CD4/CD8 ratio, decreased mitogen responsiveness, defective neutrophil chemotaxis, and depressed natural killer cell function (8, 14). These patients are at risk of infections with both gram-positive and gram-negative encapsulated organisms (10, 11). However, primary meningitis caused by *C. meningosepticum* is a very unusual infection for splenectomized TM patients. Clinically, *C. meningosepticum* is not a common pathogen in cases of bacterial meningitis in adults; and this infection usually occurs in patients with significant underlying diseases or conditions, such as malignant neoplasms, neutropenia, tuberculosis, aplastic anemia, diabetes, bone marrow and solid organ transplantation, and other immunosuppressive conditions (4, 16–18). This patient had many infections as a result of risk factors other than the splenectomy. These risk factors included regular blood transfusions, iron overload, and desferrioxamine chelation therapy for 14 years. Desferrioxamine therapy might have predisposed the patient to the infection by mobilizing iron from

tissue depots. An in vitro study showed improved neutrophil phagocytosis in the presence of desferrioxamine in patients with thalassaemia major (2, 10). In this patient, deferiprone treatment was begun 6 months before the *C. meningosepticum* infection. Agranulocytosis is the most serious undesirable effect of deferiprone treatment. The mechanism of deferiprone-induced agranulocytosis and of milder neutropenia is unknown. It does not appear to be dose dependent but is idiosyncratic and unpredictable (3). Cohen et al. pointed out that neutropenia was frequently observed in patients with an intact spleen (6). When our patient was admitted to the hospital, however, an elevated absolute neutrophil count was detected.

In the literature, most of the reported cases of *C. meningosepticum* infection are hospital acquired and usually occur in immunodeficient patients. The infection described here, however, was considered community acquired, because the patient came to our hospital acutely ill, with the initial cultures at the time of presentation yielding positive results. The patient had no history of travel or other activity prior to this illness. Therefore, the source of the microorganism could not be found. *Chryseobacterium meningosepticum* is widely distributed in nature, so its role in the pathogenicity of community-acquired infections is reasonable in immunocompromised patients (1, 16, 17).

The appropriate choice of antimicrobial agents effective for the treatment of chryseobacterial infections is difficult to make. *Chryseobacterium* spp. are inherently resistant to many antimicrobial agents commonly used to treat infections caused by gram-negative bacteria (aminoglycosides, beta-lactam antibiotics, tetracyclines, and chloramphenicol) but are often susceptible to agents generally used to treat infections caused by gram-positive bacteria (rifampin, clindamycin, erythromycin, trimethoprim-sulfamethoxazole, quinolones, and vancomycin) (22). The choice of an effective drug for the empirical treatment of infections due to *C. meningosepticum* is sometimes difficult. According to the results of the SENTRY Antimicrobial Surveillance Program, the agents most active against *C. meningosepticum* are the quinolones, rifampin, and trimethoprim-sulfamethoxazole, while the susceptibility of the organism to aminoglycosides, beta-lactams, carbapenems, and glycopeptides is low (13). The susceptibility of our strain resembled these findings. It was susceptible to fluoroquinolones and trimethoprim-sulfamethoxazole, but it was also susceptible to vancomycin. *Chryseobacterium meningosepticum* is usually resistant to multiple antibiotics. These resistance phenotypes could be explained by the presence of beta-lactamases, including extended-spectrum beta-lactamases and metallo-beta-lactamases (24). Our strain produced a chromosomally mediated inducible beta-lactamase. This helps explain the multiresistance pattern of the isolate.

Because of the multiresistant nature of this species, the choice of the optimal therapeutic regimen for the treatment of a *C. meningosepticum* infection is usually limited. Previous studies have shown that the combination of vancomycin and rifampin appears to be the most appropriate therapy for *C. meningosepticum* infections, based on clinical outcomes (9). Recent studies, however, have shown that many different results have been obtained when vancomycin is used to treat patients with infections caused by *C. meningosepticum*. Some reports have documented the successful use of vancomycin, and it has been recommended as a therapeutic choice. Several

other reports, however, showed that vancomycin has poor activity against *C. meningosepticum* isolates (9, 17, 24). Our patient was successfully treated with vancomycin.

In conclusion, the case described here shows that *C. meningosepticum* infections should be considered when bacterial meningitis occurs, especially in immunocompromised patients. Although the clinical or laboratory manifestations are not unique, physicians should be suspicious of *C. meningosepticum* infections when gram-negative rods are detected on Gram stain and culture, the microbiological features of the organism recovered are similar to those described above, and the organism is also susceptible to antimicrobial agents with activities against gram-positive bacteria. Although there is no recommended antibiotic for use for the initial treatment of *C. meningosepticum* meningitis in adults, vancomycin can be effective as empirical therapy.

#### REFERENCES

- Bloch, K. C., R. Nadarajah, and R. Jacobs. 1997. *Chryseobacterium meningosepticum*: an emerging pathogen among immunocompromised adults: report of 6 cases and literature review. *Medicine* 76:30–41.
- Cantiniaux, B., C. Hariga, A. Ferster, M. Toppet, and P. Fondu. 1990. Desferrioxamine improves neutrophil phagocytosis in thalassaemia major. *Am. J. Haematol.* 35:13.
- Ceci, A., P. Baiardi, M. Felisi, M. D. Cappellini, V. Carnelli, V. De Sanctis, R. Galanello, A. Maggio, G. Masera, A. Piga, F. Schettini, I. Stefano, and F. Tricta. 2002. The safety and effectiveness of deferiprone in a large scale, 3-year study in Italian patients. *Br. J. Haematol.* 118:330–336.
- Chiu, C. H., M. Waddington, W. S. Hsieh, D. Greenberg, P. C. Schreckenberger, and A. M. Carnahan. 2000. Atypical *Chryseobacterium meningosepticum* and meningitis and sepsis in newborns and the immunocompromised, Taiwan. *Emerg. Infect. Dis.* 6:481–486.
- Clinical and Laboratory Standards Institute. 2005. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 6th ed. Approved standard M7-A6. Clinical and Laboratory Standards Institute, Wayne, Pa.
- Cohen, A. R., R. Galanello, A. Piga, A. Dipalma, C. Vullo, and F. Tricta. 2000. Safety profile of the oral iron chelator deferiprone. A multicentre study. *Br. J. Haematol.* 108:305–312.
- Cone, L. A., T. J. Cronin, M. Curti, and D. Friscia. 1998. Osteomyelitis due to *Chryseobacterium (Flavobacterium) meningosepticum*. *Antimicrob. Infect. Dis. Newsl.* 17:60–62.
- Dwyer, J., C. Wood, J. McNamara, A. Williams, W. Andiman, L. Rink, T. O'Connor, and H. Pearson. 1987. Abnormalities in the immune system of children with beta thalassaemia major. *Clin. Exp. Immunol.* 68:621–629.
- Fraser, S. L., and J. H. Jorgensen. 1997. Reappraisal of antimicrobial susceptibilities of *Chryseobacterium* and *Flavobacterium* species and method for reliable susceptibility testing. *Antimicrob. Agents Chemother.* 41:2738–2741.
- Ghosh, K., S. Daar, D. Hwase, and N. Nusrat. 2000. Primary *Pseudomonas* meningitis in an adult, splenectomized, multitransfused thalassemia major patient. *Haematologia* 30:69–72.
- Hansen, K., and D. B. Singer. 2001. Asplenic-hyposplenic overwhelming sepsis: postsplenectomy sepsis revisited. *Pediatr. Dev. Pathol.* 4:105–121.
- Hsueh, P. R., J. C. Chang, L. J. Teng, P. C. Yang, S. W. Ho, W. C. Hsieh, and K. T. Luh. 1997. Comparison of E-TEST and agar dilution method for antimicrobial susceptibility testing of *Flavobacterium* isolates. *J. Clin. Microbiol.* 35:1021–1023.
- Kirby, J. T., H. S. Sader, T. R. Walsh, and R. N. Jones. 2004. Antimicrobial susceptibility and epidemiology of a worldwide collection of *Chryseobacterium* spp.: report from the SENTRY Antimicrobial Surveillance Program (1997–2001). *J. Clin. Microbiol.* 42:445–448.
- Kutukuler, N., O. Kutlu, G. Nisli, S. Oztop, N. Cetingul, and S. Caglayan. 1996. Assessment of neutrophil chemotaxis and random migration in children with thalassemia major. *Pediatr. Hematol. Oncol.* 13:239–245.
- Li, C. K., M. M. K. Shing, W. K. Chik, V. Lee, and P. M. P. Yuen. 2001. *Klebsiella pneumoniae* meningitis in thalassemia major patients. *Pediatr. Hematol. Oncol.* 18:229–232.
- Lim, L. C., J. A. Low, and K. M. Chan. 1999. *Chryseobacterium meningosepticum (Flavobacterium meningosepticum)*—a report of five cases in a local hospital. *Ann. Acad. Med. Singapore* 28:858–860.
- Lin, P. Y., C. Chu, L. H. Su, C. T. Huang, W. Y. Chang, and C. H. Chiu. 2004. Clinical and microbiological analysis of bloodstream infections caused by *Chryseobacterium meningosepticum* in nonneonatal patients. *J. Clin. Microbiol.* 42:3353–3355.
- Lu, C. H., C. R. Huang, N. W. Tsai, C. S. Chang, Y. C. Chuang, P. Y. Lee, C. B. Lei, H. C. Wang, and W. N. Chang. 2004. An adult case of *Chryseobacterium meningosepticum* meningitis. *Jpn. J. Infect. Dis.* 57:214–215.
- Peng, C. T., C. H. Tsai, J. H. Wang, C. F. Chiu, and K. C. Chow. 2000. Bacterial infection in patients with transfusion-dependent beta-thalassemia in central Taiwan. *Acta Paediatr. Taiwan* 41:318–321.
- Scher, K. S., F. Wroczynski, and J. A. Coil. 1982. The effect of splenectomy on gram-negative bacteremia. *J. Trauma* 22:407.
- Schreckenberger, P. C., M. I. Daneshvar, R. S. Weyant, and D. G. Hollis. 2003. *Acinetobacter*, *Achromobacter*, *Chryseobacterium*, *Moraxella*, and other nonfermentative gram-negative rods, p. 749–779. In P. R. Murray, E. J. Baron, J. H. Jorgensen, M. A. Tenover, and R. H. Tenover (ed.), *Manual of clinical microbiology*, 8th ed. ASM Press, Washington, D.C.
- Steinberg, J. P., and C. D. Rio. 2000. Other gram-negative bacilli. In G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), *Principles and practice of infectious diseases*, 5th ed. Churchill Livingstone, Philadelphia, Pa.
- Sztajn bok, J., and E. J. Troster. 1998. Community-acquired *Chryseobacterium meningosepticum* pneumonia and sepsis in a previously healthy child. *J. Infect.* 37:310–312.
- Vessillier, S., J. D. Docquier, S. Rival, J. M. Frere, M. Galleni, G. Amicosante, G. M. Rossolini, and N. Franceschini. 2002. Overproduction and biochemical characterization of the *Chryseobacterium meningosepticum* BlaB metallo- $\beta$ -lactamase. *Antimicrob. Agents Chemother.* 46:1921–1927.