Successful Treatment of Meningitis Caused by Highly-Penicillin-Resistant *Streptococcus mitis* in a Leukemic Child

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In recent years, viridans streptococci have been reported with increasing frequency to cause infections in neutropenic cancer patients. *Streptococcus mitis*, one of the species included among viridans streptococci, is the most resistant to beta-lactam antibiotics in this group. Bacterial meningitis presenting without pleocytosis in the cerebrospinal fluid (CSF) is rare, and this situation could be confusing to physicians. It is also an uncommon infectious complication in leukemic patients with neutropenia. In patients with leukopenia caused by myelosuppression after chemotherapy, bacterial meningitis must be considered a possibility when a patient develops meningeal signs, even if no pleocytosis is found in the CSF.

We report on a 6-year-old boy with leukemia and neutropenia who developed sepsis and meningitis caused by *S. mitis* with high-level resistance to penicillin and cephalosporins (MIC of both, >2 mg/l); he was a long-term survivor receiving chronic trimethoprim-sulfamethoxazole prophylaxis. The patient was successfully treated with a combination of vancomycin, ceftriaxone, and granulocyte-colony-stimulating factor. *(Chang Gung Med J 2002;25:190-93)*

Key words: ***Streptococcus mitis*, penicillin resistance, vancomycin, ceftriaxone, granulocyte-colony-stimulating factor**

In recent years, viridans streptococci and other alpha-hemolytic streptococci have been reported with increasing frequency to cause infections in neutropenic cancer patients.[1-4] Patients receiving high-dose cytosine arabinoside are especially at an increased risk to such infections.[1-3] Traditionally viridans streptococci have been considered susceptible to beta-lactam antibiotics, tetracyclines, and macrolides, but in recent years the prevalence of antibiotic resistance has increased.[3,4] By the end of the 1980s, the majority of these streptococcal isolates still could be inhibited by 0.12 μg/ml of penicillin, and no strain was found with a minimal inhibitory concentration (MIC) of 4 mg/l.[3,4] However, in a recent survey in the US, the percentage of high-level resistance to penicillin (defined as MIC=4 mg/l or higher) in strains isolated from blood was as high as 44% among neutropenic patients with cancer.[4]

Streptococcus mitis, one of the species included among viridans streptococci, is the most resistant to beta-lactam antibiotics of this group.[5] Meningitis due to *S. mitis* in patients with cancer is uncommon.[6] We herein report on a case of meningitis caused by a highly-penicillin-resistant strain of *S. mitis* in a leukemic child. This patient was subsequently cured with a combined therapy of vancomycin, ceftriaxone, and granulocyte-colony-stimulating factor (G-CSF).

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CASE REPORT

A 6-year-old boy was diagnosed as having acute nonlymphocytic leukemia (ANLL) (FAB: M5a) on July 11, 1994. He had been receiving induction chemotherapy with cytarabine, epirubicin, and 6-thioguanine. Complete remission was achieved 1 month after initiation of therapy. His history showed that he had previously suffered from 4 episodes of bacteremia associated with severe neutropenia: Salmonella group B bacteremia in July 1994, *Pseudomonas aeruginosa* bacteremia in April 1995, *Escherichia coli* bacteremia in November 1995, and viridans streptococcus bacteremia in April 1996. MICs of antibiotics to the viridans streptococcus that caused the bacteremia in this patient in April 1996 were: ampicillin 4 mg/l, penicillin 4 mg/l, erythromycin 16 mg/l, ceftriaxone 0.5 mg/l, and vancomycin 0.25 mg/l. The patient was treated with a 7-day course of vancomycin therapy. His fever subsided soon after initiation of therapy, and he was discharged when his granulocyte count increased to $>0.5 \times 10^9$/L.

About 2 months later, the patient developed the 5th episode of neutropenic fever. He presented with fever and chills just 3 days after he had completed a course of chemotherapy with cytarabine, epirubicin, and 6-thioguanine. An examination revealed that the child was undernourished without neurodevelopmental disability. He was disoriented, and his neck was rigid. His pupils were isocoric, and no eruption was found on the skin. Ophthalmologic examination showed venous engorgement, suggesting the presence of increased intracranial pressure. A hemogram revealed a white blood cell (WBC) count of $<0.1 \times 10^9$/L with agranulocytosis. Computed tomography of the brain showed brain swelling without focal lesions. Lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis disclosed a WBC count of 5×10^6/L (100% lymphocytes); no bacteria were seen on Gram-stained smears. Other relevant data included glucose 4.4 mmol/L, protein 248.4 g/L, and lactate 72.8 mg/dl. Latex agglutination tests for meningococcal and pneumococcal antigens were negative. Both blood (1 set) and CSF cultures subsequently yielded viridans streptococcus, which was further identified as *S. mitis* using a biochemical identification kit (ID32 STREP, bioMerieux Vitek, Inc., MO, USA). Both blood and CSF isolates showed the same susceptibility pattern and antibiotic MIC values as those of the streptococcal isolate derived from this patient in April 1996. He was treated with intravenous vancomycin (15 mg/kg/dose 4 times daily) plus ceftriaxone (100 mg/kg/dose 2 times daily) for 3 weeks. Trough and peak serum bactericidal titers for the organism were 1:16 and 1:32, respectively. Because of the profound neutropenia, the patient was given 3 doses of G-CSF (5 μg/kg daily) for 3 successive days; its effect was demonstrated by a gradual increase in the granulocyte count in peripheral blood.

His condition was complicated with subglottic stenosis due to prolonged intubation. A tracheostomy was performed in August 1996. He eventually recovered from this severe infection, as well as emerging from coma, and has been in remission for over 7 years since the initial diagnoses of ANLL in July 1994. This patient has remained free of leukemia, whereas long-term ophthalmologic follow-up showed he has impaired visual acuity, most likely due to retrobulbar optic neuropathy.

DISCUSSION

Physicians caring for patients who are neutropenic and febrile need to be aware of the risk of meningitis and bacteremia due to organisms usually regarded as commensals. A cell count in the CSF for a diagnosis of bacterial meningitis is unreliable if that patient is severely neutropenic. In the absence of pleocytosis in the CSF, other parameters such as glucose, protein, lactate, Gram staining, and cultures for bacteria have important roles in the diagnosis of meningitis in neutropenic patients.

Viridans streptococci are normal inhabitants of the human oral cavity. The portal of entry for the organisms is usually an oral lesion. Systemic infections can still occur in patients without overt oral lesions, and this is especially true in neutropenic cancer patients. The emergence of viridans streptococci highly resistant to penicillin, *S. mitis* in particular, as a cause of sepsis and meningitis in patients with cancer has been an issue of concern.[1-6] The relevant mechanism of penicillin resistance in viridans streptococci might be the same as that in *S. pneumoniae*, i.e., alternations in penicillin-binding proteins with

lowered affinity for beta-lactam antibiotics.[4,5] So far, there are no guidelines or consensus for the treatment of meningitis due to penicillin-resistant viridans streptococci in neutropenic patients. Since meningitis due to penicillin-resistant pneumococci generally requires combination therapy consisting of vancomycin and cefotaxime or ceftriaxone, if the organism is susceptible to these third-generation cephalosporins,[7] we reasoned that meningitis caused by penicillin-resistant, but ceftriaxone-susceptible, viridans streptococci could also be treated with a combination therapy of vancomycin and ceftriaxone. It is because this patient had been "colonized" with penicillin-resistant streptococci for such a long time that a 7-day course of vancomycin therapy for an earlier episode of streptococcal bacteremia did not seem sufficient to eradicate the bacteria that had colonized his body. However, eradication was finally achieved following a 3-week combination therapy using vancomycin and ceftriaxone for the meningitis, as evidenced by the fact that during a 7-year period of follow-up, no recurrent episode of streptococcal infection was observed. The success of the treatment also implies a role in attempting to limit the duration of neutropenia by G-CSF. This may be another important factor affecting the outcome of such patients.[3]

The emergence of antimicrobial resistance complicates the therapy for viridans streptococcal infections in cancer patients with neutropenia. However, on the basis of data from the present as well as previous reports,[4,6] it is suggested that definitive therapy for such infections can be guided by in vitro susceptibility results and clinical guidelines currently used for treatment of resistant pneumococcal infections.[7] The development of ophthalmologic sequelae in spite of eradication of bacteria in the present case illustrates the virulence of this opportunistic pathogen in neutropenic patients and suggests the importance of prophylactic buccal decontamination, although this is still a controversial issue. De Jong et al. suggested that penicillin be used prophylactically in cancer patients at risk for viridans streptococcal infections,[8] while other studies have shown that resistance to penicillin among viridans streptococci increased following the use of penicillin prophylaxis.[9] Careful monitoring of the incidence and outcomes of bacteremia and meningitis due to viridans streptococci, and of their susceptibility to penicillin and cephalosporins is important for further evaluation of the real benefits of prophylaxis against viridans streptococci in neutropenic patients, and of the optimal therapeutic regimen for treatment of these infections.

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成功治療由高抗藥性和緩鏈球菌(*Streptococcus mitis*)所引起的敗血症及腦膜炎

江東和 邱政洵 洪悠紀

近年來，草綠色鏈球菌 (viridans streptococci) 已成爲癌症患者因顆粒球下降而致感染的主要致病菌，其中又以和緩鏈球菌 (*Streptococcus mitis*) 常呈現對盤尼西林類抗生素有抗藥性，對治療造成困難。尤其當白血病患者處於白血球減少時期，如罹患細菌性腦膜炎時，其腦脊髓液內白血球數目的變化常不明顯。我們報告一位6歲白血病病童，因顆粒球下降而併發和緩鏈球菌敗血症及腦膜炎，從病人血液及腦脊髓分離出來的和緩鏈球菌對盤尼西林及頭孢素類有高抗藥性 (penicillin最低抑菌濃度=4 mg/L)，我們成功地併用vancomycin、ceftriaxone及顆粒球群落刺激因子 (granulocyte-colony stimulating factor)治療此感染。(長庚醫誌 2002;25:190-93)

關鍵字：和緩鏈球菌、抗盤尼西林、vancomycin、ceftriaxone、顆粒球群落刺激因子。

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