

## MENINGITIS CAUSED BY *STENOTROPHOMONAS MALTOPHILIA*: CASE REPORT AND REVIEW OF THE LITERATURE

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*Stenotrophomonas* (formerly *Xanthomonas*), a gram-negative bacillus is noted for its high degree of antibiotic resistance and pathogenic potential. It can be isolated from water sources including rivers, wells, a hypertrophic lake, bottled water, sewage, sink traps, factory residues and a variety of soil, plant and food materials.<sup>1,2</sup> It is known to cause life-threatening infections in selected patients associated with immunosuppression, admission to the intensive care unit, advanced age, prolonged hospitalization, surgical procedures and prior antibiotherapy or corticosteroid therapy. Although it may cause a wide variety of infections, meningitis caused by *S. maltophilia* has been reported as extremely rare.<sup>3-10</sup> We report a case of post-neurosurgical meningitis caused by *S. maltophilia*, along with a review of the pertinent literature.

### Case Report

A 52-year-old Caucasian male was admitted to hospital with fever, severe headache, and increasing drowsiness. His medical history revealed previous hospitalization nine months earlier with subarachnoid hemorrhage due to an intracerebral aneurysm. During that hospitalization, he was placed with a ventriculoperitoneal (VP) shunt for hydrocephalus, and received phenytoin and dexametasone.

Five months later, he was re-admitted with fever and loss of consciousness. Following a clinical diagnosis of meningitis, empiric therapy consisting of meropenem + amikacin was begun. *Acinetobacter baumannii* was isolated from the CSF with automated Sceptor analysis and by classic culture methods, and was found to be sensitive to meropenem and amikacin, so the treatment was not altered. The VP shunt was removed. CSF culture on the seventh day of treatment did not grow any microorganism and the antibiotic treatment was continued for three weeks. Prior to discharge, the VP shunt was replaced. The patient was discharged from the hospital only to return a week later with fever and disorientation.

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TABLE 1. Antibiotic sensitivities of *S. maltophilia* isolated from blood and CSF.

| Antibiotic                  | MIC (µg/ml) | R/S/I |
|-----------------------------|-------------|-------|
| Ampicillin                  | =32         | R     |
| Piperacillin                | >64         | R     |
| Amikacin                    | 32          | I     |
| Gentamicin                  | 8           | I     |
| Ciprofloxacin               | 2           | I     |
| Cefotaxime                  | =64         | R     |
| Ceftriaxone                 | >32         | R     |
| TMP-SMX                     | =2          | S     |
| Ampicillin-sulbactam        | =32         | R     |
| Amoxicillin-clavulanic acid | >16         | R     |
| Aztreonam                   | =32         | R     |
| Cefoperazone                | =64         | R     |
| Cefotetan                   | >32         | R     |
| Trimetoprim                 | =16         | R     |
| Ticarcillin                 | =128        | R     |
| Ticarcillin-clavulonate     | >64         | R     |
| Tobramycin                  | =16         | R     |
| Imipenem                    | >8          | R     |
| Cefazolin                   | >16         | R     |
| Ceftazidime                 | =32         | R     |
| Cefuroxime                  | >16         | R     |

On physical examination, the patient was febrile (temperature 39.6°C) and had marked neck stiffness. Fundoscopic evaluation of the eye was normal. A complete blood count revealed leukocytosis (WBC 14600/mm<sup>3</sup>, 90% neutrophils, 10% lymphocytes) and the ESR was 24 mm/hr. Biochemical analysis was normal. Lumbar puncture yielded purulent, turbid fluid, and the following values were noted: WBC, 760 cells/mm<sup>3</sup> (92% leucocytes, 4% lymphocytes), glucose level 26 mg/dL (simultaneous blood glucose level 97 mg/dL) and protein level 128 mg/dL. Gram staining of CSF smear revealed gram-negative bacillus. CSF and blood cultures were obtained. Empiric therapy with meropenem + amikacin was initiated in view of the possibility of recurrent infection with *A. baumannii*. The VP shunt was removed and external ventriculostomy was performed. *S. maltophilia* was isolated from the CSF culture and blood cultures. Antibiotic sensitivities of the microorganism was resistant to the antibiotics except TMP-SMX (Becton Dickinson Auto Sceptor automated system) (Table 1). The susceptibility of the microorganism to TMP-SMX and

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TABLE 2. Summary of patients with meningitis caused by *S. maltophilia*.

CSF findings

| Reference no. and year | Age/Sex     | Underlying condition                  | Neurosurgical procedure                   | WBCs/mm <sup>3</sup> protein (% PNL) (mg/dL) | Glucose (mg/dL) | Therapy  | Result        |       |
|------------------------|-------------|---------------------------------------|---|--|-----------------|--|---------------|-------|
| 3 (1975)               | 70 years/M  | Emphysema                             | NA  | 92 (96)                                      | 70 200          | Sulfadimidine + chloramphenicol 12 days            | Cured         |       |
| 4 (1977)               | 8 months/M  | None                                  | NA  | Numerous                                     | NR              | Ampicillin + colistin                              | Died          |       |
|                        | 13 months/F | None                                  | NA  | 460 (NR)                                     | NR              | Chloramphenicol + sulfadoxine                      | Cured         |       |
| 5 (1982)               | 55 years/F  | Breast cancer + meningeal involvement | Ommaya reservoir placement                | 442 (90)                                     | 86              | 16 Chloramphenicol + gentamicin + removal of drain | Cured         |       |
| 6 (1984)               | 7 days/M    | Prematurite                           | NA  | NR   | NR              | NR   | None          | Died  |
| 7 (1987)               | 65 years/F  | Intraventricular bleed                | Placement of external ventricular drain   | 650 (100)                                    | 348             | 42 TMP-SMX+ removal of drain                       | Cured         |       |
| 8 (1993)               | 28 years/F  | Brain tumor                           | Posterior fossa operation                 | NR   | NR              | NR   | Ciprofloxacin | Cured |
| 9 (1994)               | 64 years/M  | Meningioma                            | Temporal resection and VP shunt placement | 253 (96)                                     | 65              | 521 TMP-SMX+IT gentamicin + removal of VP shunt    | Cured         |       |
| 10 (1997)              | 36 years/F  | Melanoma + meningeal involvement      | Ommaya reservoir placement in two cases   | 120 (76)                                     | 48              | 333 TMP-SMX + ceftazidime + vancomycin             | Cured         |       |
|                        | 41 years/M  | Lymphoma + CNS involvement            |   | 14 (NR)                                      | 77              | 163 TMP-SMX + amikacin                             | Cured         |       |
| Our case               | 52 years/M  | Subarachnoid hemorrhage               | VP shunt placement                        | 760 (92)                                     | 26              | 128 TMP-SMX  | Cured         |       |

WBC=white blood cells; NA=not applicable; NR=not reported.

ticarcillin/clavulanic acid (TIC/CL) which were the only treatment option was confirmed by *E* test (AB Biodisk). The MIC values of TMP-SMX and TIC/CL were  $\leq 2 \mu\text{g/mL}$  and  $\geq 128 \mu\text{g/mL}$  for the isolate, respectively. TMP-SMX (trimetoprim 320 mg + sulfamethoxazole 1600 mg IV, at 6 h intervals) was initiated, prompt defervence was noted on the fourth day, and the patient began to communicate and respond on the sixth day of the TMP-SMX treatment.

Analysis of CSF was carried out on the seventh day of treatment and revealed the following values: WBC  $40 \text{ mm}^3$ , glucose 35 mg/dL (simultaneous blood glucose 105 mg/dL), and protein 28 mg/dL. CSF was sterile on culture. Repeated blood cultures were negative. Antibiotic treatment was further continued to cover a complete three weeks. Following re-insertion of VP shunt, the patient was discharged from the hospital. No signs of infection were noted in the follow-up for eleven months.

### Review and Discussion

There seem to be a wider variety of clinical entities associated with *S. maltophilia* than is generally known. Despite the difficulties confronted in the isolation of this microorganism and in deciding whether to consider it as a coloniser or a pathogen, recent reports emphasize its role in nosocomial infections and community-acquired infections. However, along with the isolation of microorganism, establishment of strict criteria for the definition of infection will determine it as a true pathogen.<sup>1,2</sup>

In the pertinent literature reviewed, only 11 cases (including the one described here) have been reported so far, the latest report being published in 1997. The rarity of *S. maltophilia* meningitis results in various clinical

problems in diagnosis and treatment due to lack of experience. Analysis of the cases reported in the literature revealed that four were community-acquired and seven were related to neurosurgical procedures (Table 1). Three patients belonged to the pediatric age group and seven were adults. The mean age in the pediatric age group was  $28.3 \pm 25.7$  weeks, and in the adult group it was  $51.4 \pm 15.1$  years. The clinical signs of meningitis was overt in all the patients, and the CSF findings were not very different from typical or nonspecific bacterial meningitis such as pleocytosis, as well as increase in the proteins, and decrease in glucose levels. In the reported cases, the mean values of CSF findings were  $348.9 \pm 272.7 \text{ cells/mm}^3$ , glucose level  $59.1 \pm 21.2 \text{ mg/dL}$ , protein level  $212 \pm 158.8 \text{ mg/dL}$  (Table 2).

The underlying factors complicating the primary disease were determined as prematurity, neurosurgical procedures, intracranial hemorrhage, and malignancy. It is interesting to note that more than half the cases were related to neurosurgical procedures, especially with shunts/drains in six cases.<sup>5,7-10</sup> Carbapenem treatment has also been suggested as a risk factor for infection/colonization with *S. maltophilia* as may have happened in our case.<sup>11,12</sup> The antibiotic treatment in these cases was combined with the removal of the shunt in four cases. In two patients with Ommaya reservoir, medical therapy alone was sufficient for cure.<sup>8</sup> The antibiotics used as a single agent or in combinations for the treatment of *S. maltophilia meningitis* are given in Table 2.

A number of publications have reported the variability in susceptibility results for *S. maltophilia* according to

medium, incubation period and time. Agar or broth dilution methods are recommended for susceptibility tests to *S. maltophilia*. Because these methods are time-consuming, *E* test is recommended as an alternative method.<sup>1,13</sup>

*S. maltophilia* is resistant to beta-lactam antibiotics (including carbapenem), having the ability to produce various beta-lactamase enzymes (metallo-beta-lactamase, L2-cephalosporinase). Furthermore, with the active efflux property, the bacteria is especially resistant to tetracycline, along with quinolones and chloramphenicol.<sup>13</sup> Multiple-drug resistance is linked to the expression of an outer membrane protein (OMP54) and energy-dependent efflux mechanism both in an experimental model system and in multi-drug resistant clinical isolates.<sup>13,14</sup> Of particular interest is the fact that *S. maltophilia* is resistant to most of the antibiotics frequently used in the empiric treatment of nosocomial infections. Despite the reported weak activity of beta-lactam-beta-lactamase inhibitor combinations against this organism, some authors have reported successful results with ticarcilline-clavulonate combination.<sup>1,15</sup> With a few exceptions,<sup>16,17</sup> most studies have found TMP-SMX to be active against most strains of the bacterium, and this drug has long been regarded as the agent of choice for the therapy of *S. maltophilia* infection.<sup>1,18</sup> The strain isolated from the present patient was resistant to ticarcillin-clavulonate but sensitive to TMP-SMX.

It is of note that the overall mortality rate of this disease is 18.18% (2/11) and none of the patients who did not receive appropriate empiric antibiotic treatment survived. The high mortality rate along with its severe clinical course calls for consideration in the differential diagnosis of meningitis in patients with predisposing factors and nosocomial infections. The fact that only 21 *S. maltophilia* cases were reported before 1990 compared with 55 cases within the last 10 years may be a strong indicator of the increasing recognition of this pathogen in the clinical settings.

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