Catheter-Related Bacteremia due to *Streptomyces* in a Patient Receiving Holistic Infusions

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Streptomyces species are rare causes of invasive infection in humans. We report the first documented case of a catheter-associated bacteremia due to *Streptomyces*. The most likely source of infection was unlicensed, injectable holistic preparations that the patient had received. We review reported cases of invasive infections caused by *Streptomyces* and comment on the potential infectious complications of parenteral holistic treatments.

Streptomyces species are aerobic actinomycetes best known for their production of antimicrobial substances. They infrequently cause human disease, most often manifesting as a localized, chronic suppurative infection of the skin and underlying soft tissue (1). Nonmycetomic infections caused by *Streptomyces* species are very rare.

We report the first documented case of a catheter-associated bacteremia caused by *Streptomyces*. The most likely source of infection was unlicensed, injectable holistic preparations that the patient had received. Identifying the use of alternative medicines by patients may be essential in evaluating cases or outbreaks of new or unusual organisms.

Case Report

A 49-year-old African-American woman had a 10-year history of breast cancer, for which she had declined chemotherapy; she opted to receive holistic treatments only. Her disease progressed; she underwent bilateral mastectomies and bone metastases developed. Approximately 1 year before admission, the patient had a subcutaneous central venous catheter placed to receive intravenous infusions of holistic preparations.

She reportedly received infusions of glutathion, germanium, superoxide dismutase, interferon (100,000 IU), manganese, selenium, zinc, magnesium chloride, calcium gluconate, potassium chloride, and vitamin C (25 g), as well as "NeyTumorin," a holistic preparation (2).

Three weeks before admission, the patient complained of feeling feverish after receiving an infusion at her provider's office. Her temperature was 38°C. Blood drawn through the subcutaneous catheter was sent for culture and was reported as growing "diphtheroids." Eleven days later, repeat blood cultures drawn through the catheter grew gram-positive bacilli, which a laboratory could not identify further. At that time the patient was referred to our hospital for admission.

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The patient's medications at the time of admission were pamidronate, a multivitamin, and the holistic infusions. She had no history of alcohol or illicit drug use. She denied HIV risk factors but had never been tested for HIV. She had not traveled recently and had no remarkable animal exposures. She had previously worked as a nurse.

On examination, she appeared nontoxic; her blood pressure was 143/83 mmHg, heart rate was 84 beats per minute, respiratory rate was 16, and temperature was 37.3°C. Physical examination revealed a subcutaneous port in her right anterior chest, which showed no signs of infection; well-healed bilateral mastectomy scars; and a grade II/VI systolic heart murmur.

After blood had been drawn for cultures, the patient was started empirically on vancomycin. Blood drawn peripherally and through the subcutaneous catheter on hospital days 1, 2, and 3 grew gram-positive elongated bacilli in the aerobic culture bottles. Her central venous catheter was removed on the fourth hospital day. Culture of the catheter tip was negative. A transthoracic echocardiogram showed no valvular vegetations.

When examined directly from liquid media, the organism appeared as long, branching, beaded, gram-positive bacilli. However, the organism grown on agar plates appeared more fragmented, as single, gram-positive bacilli. The isolate was catalase positive and modified acid-fast negative; aerial mycelia were present. There was no growth in lysozyme. The organism also hydrolyzed casein, xanthine, and tyrosine and yielded positive starch, gelatin, nitrate, and esculin reactions. Our laboratory identified the organism as a *Streptomyces* species. This isolate was sent to the Centers for Disease Control and Prevention (CDC) for confirmation of identification, and cell-wall analysis identified the peptidoglycan L-diaminopimelic acid, confirming that the isolate was a member of the genus *Streptomyces* (3).

The antibiotic regimen used to treat the patient was changed to intravenous ceftriaxone, 1 g every 24 hours, and oral clarithromycin, 500 mg twice a day. Her fever resolved, and she remained asymptomatic; repeat blood cultures were negative. A percutaneous indwelling central catheter was placed, and the patient was discharged to home with

recommendations to complete a 1-month course of ceftriaxone and a 6-month course of clarithromycin.

Three months after hospital discharge, the patient had no evidence of residual infection, and repeat blood cultures were negative. She was subsequently admitted to the palliative care unit for management of pain due to diffuse bone metastases and eventually died.

Conclusions

The most common manifestation of *Streptomyces* infection, mycetoma, typically results from inoculation of the microorganism through an injury caused by a thorn and usually involves the legs and feet (4). Invasive *Streptomyces* infections are extremely rare. A Medline search from 1966 to 2000 identified only 10 cases of invasive *Streptomyces* infection, defined as infection other than mycetoma or superficial skin infections (1,5); in none of the cases was infection caused by catheter-associated sepsis. Previous cases included four cases of pneumonia and one each of lymphadenitis, pericarditis, brain abscess, peritonitis, endocarditis, and intraspinal mycetoma. Five of the patients had underlying conditions identified: four were HIV infected, and one had a prosthetic aortic valve. In only two of the nine cases (one of pneumonia and one of endocarditis) was *Streptomyces* cultured from the blood.

Treatment recommendations for *Streptomyces* infections are generally based on in vitro data and analogies from data on the treatment of *Nocardia* infections (1). McNeil et al. performed in vitro tests of the susceptibility of aerobic actinomycetes species, including 28 isolates of *S. griseus* referred to CDC from October 1985 to February 1988 (6). These data suggest that the best antimicrobial options for visceral *Streptomyces* infection include macrolides, minocycline, doxycycline, ceftriaxone, and imipenem (6). Twenty-nine percent of *S. griseus* species tested at CDC were resistant to trimethoprim/sulfamethoxazole, the drug of choice for treatment of *Nocardia* infections (6).

A variety of antimicrobial regimens were used in the previously reported cases, and in most the outcome was good, with resolution of infection. However, the optimal choice of antimicrobial agent and duration of therapy for *Streptomyces* visceral infections remain to be determined.

Our patient had clearance of bacteremia after removal of the indwelling central catheter and a course of ceftriaxone and clarithromycin. While the catheter tip culture was negative and hence an alternate focus cannot be entirely excluded, the patient's fever resolved and blood cultures promptly cleared after catheter removal, supporting the inference that the infection was catheter associated.

The previous reports of invasive *Streptomyces* disease do not mention putative sources of the infections. For our patient, who had no history of travel or unusual agricultural exposures, a possible source of infection was the unlicensed, injectable holistic preparations that she had received. Attempts to obtain samples of the intravenous holistic preparations for culture were unsuccessful, as were attempts to assess whether other patients had received this preparation and whether any other infectious complications had occurred. Information on any measures used to ensure product sterility was unavailable.

Three times a week, our patient was receiving infusions of a preparation that included a compound called NeyTumorin, which reportedly consists of "a combination of peptides and proteins of 15 different organs from fetal and young pigs or cows" (2). The inventor of NeyTumorin claims that "physiologic repair aids" from the cytoplasm of healthy animal organs result in immunogenic and immunomodulatory effects that improve a patient's biologic response to malignancy (2). However, the specific components of NeyTumorin are not defined, the claimed mechanism of action has not been proven, and there is no evidence of clinical efficacy. Clinical studies are described as inconclusive "because of false or insufficient documentation" (2).

The use of alternative and herbal medicines in the United States has increased steadily over the past decade (7,8). Patients frequently believe that if a substance is "natural," it is safe; likewise, providers often assume that such substances are unlikely to be harmful (9). However, recent data have demonstrated that some holistic medicines may result in a variety of undesirable effects. Acute rejection has been reported in two heart transplant patients due to a metabolic interaction between cyclosporine and St. John's wort (*Hypericum perforatum*), which induces the 3A4 isoform of the cytochrome P450 enzyme system (10). Through a similar drug-to-drug interaction, St. John's wort has been shown to lower plasma levels of the protease inhibitor indinavir, potentially placing patients at risk for antiretroviral resistance and treatment failure (9).

Alternative remedies may also directly cause adverse drug effects; interfere with laboratory assays; contain unrecognized, potentially harmful contaminants; and, if nonsterile, transmit infections (9-11). Distribution of an unlicensed injectable preparation, purported to contain adrenal cortex extract contaminated with *Mycobacterium abscessus*, led to a multistate outbreak of soft-tissue abscesses (11). Our case may represent another instance of an infection transmitted by the injectable use of a holistic preparation.

To create an environment that is conducive to open communication and education, physicians should discuss alternative therapies nonjudgmentally with patients to identify what substances patients may be using (7). Given the increased use of alternative medicines, including those administered parenterally, increased vigilance in monitoring patients for potential infectious complications of such treatments is needed. Clinicians should be aware of data addressing the safety and efficacy of alternative and herbal preparations and of reliable data sources such as the National Institutes of Health's National Center for Complementary and Alternative Medicine (nccam.nih.gov) and the Office of Dietary Supplements (odp.od.nih.gov/ods).

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