Disseminated soft tissue infection and sepsis with *Stenotrophomonas maltophilia* in a bone marrow transplant patient

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JH LIPTON, KS MACDONALD. Disseminated soft tissue infection and sepsis with *Stenotrophomonas maltophilia* in a bone marrow transplant patient. *Can J Infect Dis* 1996;7(6):383-385. A 32-year-old female presented with aplastic anemia and subsequently underwent a one-antigen mismatched bone marrow transplant from her brother. She failed to engraft and a second graft was attempted. Protracted neutropenia of three months' duration despite the use of broad spectrum antibiotics occurred. *Stenotrophomonas (Xanthomonas) maltophilia* metastatic cellulitis developed that did not respond to appropriate antibiotics.

Key Words: Bone marrow transplanation, Metastatic cellulitis, Soft tissue infection, *Stenotrophomonas*, *Xanthomonas*

Infection disséminée des tissus mous et septicémie à *Stenotrophomonas maltophilia* chez une patiente ayant subi une transplantation de moelle osseuse

RÉSUMÉ : Une patiente de 32 ans, souffrant d'anémie aplasique et ayant par la suite reçu une transplantation de moelle osseuse de son frère mésappariée à l'égard d'un antigène. La première greffe a échoué et une a été tentée. Une neutropénie prolongée d'une durée de trois mois s'est installée malgré l'emploi d'antibiotiques à large spectre. Une cellulite métastatique à *Stenotrophomonas maltophilia* (xanthomonas) est apparu et n'a pas répondu aux antibiotiques appropriés.

Infectious complications following bone marrow transplantation are a major side effect causing significant morbidity and mortality (1,2). Developments in the management of fever and infection have resulted in major improvements in the therapy of immunosuppressed and neutropenic patients (3-5), but changes in antimicrobial selection for prophylaxis and

therapy and increasing and more prolonged immunosuppression have resulted in different infectious profiles and complications. One organism being found more frequently in the immunocompromized host is *Stenotrophomonas maltophilia*, previously called *Xanthomonas maltophilia*. Recently a series of mucocutaneous and soft tissue infections with this organ-

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Figure 1) *Metastatic cellulitis due to Stenotrophomonas maltophilia*

ism have been reported (6). We report the sixth such fatal case of 'metastatic cellulitis', a newly described syndrome, occurring in a patient undergoing bone marrow transplantation for aplastic anemia.

CASE PRESENTATION

A 32-year-old female was well until two weeks before admission when she developed fatigue, dyspnea on exertion and bleeding gums. She was found to be pancytopenic, and bone marrow examination revealed aplastic anemia. Chromosome studies were normal. Etiology was uncertain, but the patient was hepatitis B surface antibody-positive. A brother was found to be one histocompatibility leukocyte antigen mismatched (B blank, DR mismatch). Her course pretransplantation was complicated by perioral herpes simplex virus treated with acyclovir and culture-negative febrile neutropenia treated with ceftazidime, tobramycin and vancomycin. At the time of bone marrow transplantation five weeks after diagnosis, she was afebrile and on prophylactic acyclovir and cotrimoxazole. After conditioning with cyclophosphamide 50 mg/kg/day for four days and total body irradiation (300 cGy in one fraction at 53.5 cGy/min), she underwent transplantation in October 1994. Prophylaxis for graft-versus-host disease was cyclosporine and methotrexate. She became profoundly jaundiced on day 1 post-transplantation. This was initially thought to be caused by a hemolytic reaction (donor blood type O negative, recipient A positive). The jaundice improved and then worsened at two weeks because of veno-occlusive disease of the liver, but resolved. *Clostridium difficile* toxin was detected in stool on day 8, and the patient was treated with metronidazole. *Candida albicans* was cultured from a mouth swab from day 9. Bronchoalveolar lavage for pulmonary infiltrates on day 17 was culture-negative. She remained otherwise well until day 24, when, again, culture-negative fever developed that responded to ceftazidime, tobramycin and vancomycin. Coagulase-negative staphylococcus sensitive to clindamycin and vancomycin was cultured from one blood sample taken on day 25. On day 31 of engraftment, *C. albicans* was found in

one blood culture completed after a repeat temperature spike. The patient responded to amphotericin B. She remained neutropenic, and a bone marrow aspirate done on day 30 revealed a failure of engraftment. Routine surveillance cultures were not done. Computed tomography scan of the abdomen on day 45 revealed ascites only.

After repeat conditioning with antithymocyte globulin (AT-GAM, Upjohn, Michigan) 40 mg/kg/day for four days, she underwent repeat transplantation from the same donor on December 1, 1994. Graft-versus-host prophylaxis was with cyclosporine and methylprednisolone, and granulocyte colony-stimulating factor was administered from day +1. On day +4 after being afebrile for eight days without positive cultures, antibiotics were switched to oral ciprofloxacin. However, on day +6, she again became febrile and developed right upper quadrant pain and hepatomegaly (but no peritoneal signs), and ceftazidime, tobramycin, metronidazole and amphotericin B were started in view of concern about both intra-abdominal sepsis and a recurrent candidal infection. Continuing jaundice and ascites were noted. On day +7 a cellulitis was noted, and antibiotics were switched to clindamycin, ceftriaxone and intravenous ciprofloxacin. Subsequently two red firm nodular lesions with necrosis which enlarged rapidly developed on her buttock. Intravenous ciprofloxacin was continued, and imipenem was added to her regimen for a Gram-negative organism on Gram stain of a blood culture. Ultimately, a skin biopsy from day +8 and four of six blood cultures taken both peripherally and through a central venous catheter grew *S. maltophilia*. Antibiotics were subsequently switched to high dose cotrimoxazole, intravenous ciprofloxacin and ticarcillin/clavulanic acid. Amphotericin B was continued. On testing, the organism was sensitive to cotrimoxazole with a minimum inhibitory concentration (MIC) of less than 0.5 µg/mL, and resistant to ceftazidime with an MIC of greater than 128 µg/mL using microbroth dilution. The skin lesions progressed to cover her buttocks and left thigh (Figure 1). She developed hypotension, pneumonia and progressive renal failure. She died on day +13.

DISCUSSION

S. maltophilia colonization and infection have been shown to be strongly associated with prolonged broad spectrum antibiotic use, particularly imipenim, but also third-generation cephalosporins (6,7). Pulmonary infections have predominated in most series but increasingly septicemia and line infections have been observed (8).

A recent review of skin and mucous membrane infections in cancer patients showed that different mechanisms involving direct inoculation or hematogenous dissemination accounted for distinct clinical syndromes (6). Vartivarian et al (6) reported five patients with a previously undescribed syndrome metastatic cellulitis characterized by multiple tender hard nodules associated with bacteremia in neutropenic patients on broad spectrum antimicrobial therapy. This differs from ecthyma gangrenosum in that the central nodules are not well demarcated, there is no central necrosis and the nodules spread rapidly to generalized necrosis.

Prolonged neutropenia and antimicrobial use in this patient and the clinical presentation are consistent with this newly described syndrome. Of interest, imipenem was not employed in this patient initially; however, ceftazidime and ciprofloxacin both were used, and other recent reports suggest that they are risk factors for subsequent *Stenotrophomonas* infection (6,9). This patient initially received cotrimoxazole as prophylaxis, the drug of choice for the treatment of *S. maltophilia* infections, but for the four weeks before the *Stenotrophomonas* bacteremia she had not been on cotrimoxazole.

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The increasing use of fluoroquinolone prophylaxis (10) and prolonged use of broad spectrum antimicrobials in the face of prolonged neutropenia almost certainly sets the stage for colonization of patients with this ubiquitous and somewhat opportunistic pathogen. In this setting, it has been shown to be highly virulent and fatal when disseminated infection develops. This report confirms the clinical syndrome of this characteristic metastatic cellulitis and underscores the need to consider *S. maltophilia* as well as other organisms including fungal pathogens in neutropenic patients presenting with rapidly progressive soft tissue infections.