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# Fusobacterium Nucleatum, a New Invasive Pathogen in Neutropenic Patients?

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Three chemotherapy-induced neutropenic hematologic patients with severe systemic infection caused by *Fusobacterium nucleatum*, a Gram-negative anaerobic rod, are described. Anaerobic infections are not very common in this patient category, but in a short period of time, several such patients were seen. The infection was considered to be caused by a combination of chemotherapy-induced mucositis, which served as a portal of entry for the systemic infection, and the antibiotic regime used in these patients. This is a serious infection with a high mortality. In hematological neutropenic patients suffering from severe mucositis and fever, antibiotic therapy should cover anaerobic bacteria.

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## INTRODUCTION

Anaerobic bacteria infrequently cause systemic infection in hematological patients with neutropenia following chemotherapy (1). Recently 3 neutropenic patients with severe oropharyngeal mucositis developed systemic infection caused by *Fusobacterium nucleatum*, a Gram-negative anaerobic rod.

## CASE REPORTS

### Case 1

Patient A, a 44-year-old female, underwent an autologous bone marrow transplantation as a consolidation treatment for a refractory anemia with blast excess. Myelo-ablative chemotherapy consisted of etoposide and dimethylbusulphan. As standard infection prophylaxis, oral ciprofloxacin 2 × 500 mg, oral amphotericin-B 4 × 500 mg and benzylpenicillin 4 × 10<sup>6</sup> IU i.v. was given, the latter to prevent streptococcal septicemia. On day 12, mucositis grade 4 on the WHO scale developed. On day 14, penicillin was replaced by vancomycin because of high fever and the suspicion of a central venous catheter associated infection. On day 29, an inspiratory stridor developed and intubation was necessary. Blood cultures were positive for *F. nucleatum*. Antibiotic therapy was changed to metronidazole and cephalothin. Mucosal damage progressed and a pulmonary infiltrate developed. The bone marrow remained aplastic. On the 36th day after transplantation the patient succumbed. Post-mortem examination revealed a damaged and necrotic mucosa of the throat and the upper respiratory tract, which contained many fusiform Gram-negative rods.

### Case 2

Patient B was a 29-year-old female with a myelodysplastic syndrome requiring a large number of blood transfusions, and severe thrombocytopenia. Chemotherapy consisted of idarubicin, ara-c and etoposide. Standard infection prophylaxis was given. On the 16th day, she developed fever with grade 3 mucositis and swelling of the neck. The neutrophil count at that time was  $<0.1 \times 10^9/l$ . Blood cultures revealed only *Staphylococcus epidermidis* and vancomycin was given. The fever abated and the general condition of the patient improved, although the mucositis and bone marrow aplasia persisted. On the 46th day she again developed higher fever. Blood cultures revealed *F. nucleatum* for which clindamycin

4 × 600 mg i.v. was added. Fever and bone marrow hypoplasia persisted and she developed pulmonary infiltrates for which treatment was started with amphotericin-B i.v. She died on the 77th day. Postmortem examination revealed pulmonary aspergillosis.

### Case 3

Patient C was a 44-year-old man with a secondary myelodysplastic syndrome after treatment for Hodgkin's disease. Chemotherapy consisted of idarubicin, etoposide and Ara-C. He received standard infection prophylaxis, but because of penicillin allergy, vancomycin was given. On the 16th day, grade 4 mucositis (WHO) developed, followed by high fever. Blood cultures revealed *F. nucleatum* for which he was treated with cephalothin. After 5 days the temperature normalized and his mucositis and neutrophils recovered. He achieved complete remission.

### Microbiological data

*F. nucleatum* was identified by conventional bacteriological methods and by gas-liquid chromatography. The strains were susceptible to benzyl penicillin, cephalothin, clindamycin and metronidazole, but resistant to ciprofloxacin and erythromycin. They were all  $\beta$ -lactamase-negative.

## DISCUSSION

Three patients with systemic infection caused by *F. nucleatum* are described. All had severe chemotherapy-induced neutropenia and high fever. In the only patient surviving the infection, bone marrow recovery was probably a significant factor. There is resemblance to post-anginal septicemia (Lemierre's Syndrome, 2) described in 1936 in healthy young adults, usually caused by *F. necrophorum*.

*F. nucleatum* is a strictly anaerobic Gram-negative rod normally found in the gastrointestinal, genito-urinary and respiratory tracts. We have no reason to assume that this sudden increase is due to better culture methods, to transmission by personal contact, or to contaminated food.

All 3 patients received our standard infection prophylaxis. For various reasons, penicillin was replaced by vancomycin to prevent endogenous streptococcal infections. This

infection prophylaxis is not active against *F. nucleatum* and may have resulted in a selection and overgrowth of it.

All patients received very intensive chemotherapy leading to a severe mucositis. *F. nucleatum* might have exacerbated an oropharyngeal mucositis that could serve as a portal of entry for the systemic infection.

In patients with fever and severe mucositis, early treatment with antibiotics directed at anaerobes should be considered.

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