Fusobacterium nucleatum: a rare cause of bacteremia in neutropenic patients with leukemia and lymphoma

A. Candoni[1], C. Fili[1], R. Trevisan[2], F. Silvestri[1] and R. Fanin[1]

[1]Division of Hematology and Bone Marrow Transplantation, Department of Medical and Morphological research, University Hospital and [2]Institute of Microbiology, General Hospital, Udine, Italy

Although anaerobic bacteremias are uncommon in oncohematologic patients, nevertheless they have been considered an emergent problem in the last few years. *Fusobacterium nucleatum* is an anaerobic Gram-negative bacillus commonly present in the oral cavity and in the respiratory and genito-urinary tracts. Over a 10-year period 18 episodes of *F. nucleatum* bacteremia in patients with hematological malignances (15 leukemias and 3 lymphomas) have been observed in our Department of Hematology. Predisposing factors included oropharyngeal mucositis and severe neutropenia owing to intensive chemotherapy. In our experience no septic shock occurred and the outcome of bacteremias caused by *F. nucleatum* was favorable.

Keywords *Fusobacterium nucleatum*; neutropenia, bacteremia, anaerobes

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Severe bacterial infections still represent the most common cause of morbidity and mortality in neutropenic patients with hematological malignancies. Although anaerobic bacteremias are uncommon, nevertheless an increasing number of anaerobic infections in this setting has been reported in the last decade and the type of anaerobes isolated from these patients suggests an oropharyngeal source of infection [1–6]. *F. nucleatum* is a Gram-negative anaerobic rod usually found in the gastrointestinal, oropharyngeal and respiratory tracts. Bacteremia caused by *F. nucleatum* is uncommon, accounting for less than 10% of all anaerobic bacteremias in adult patients without neutropenia [1,2,7]. Moreover, in the medical literature only a few cases of *F. nucleatum* bacteremia in neutropenic oncohematologic patients have so far been reported [4,5,8,9]. In this report we describe our experience with this rare infection.

To identify all cases of bacteremia caused by *F. nucleatum* we reviewed the records of all patients with hematologic malignancies hospitalized and submitted to chemotherapy at our Department of Hematology and Bone Marrow Transplantation between January 1992 and December 2001. Two or more sets of blood samples were obtained for aerobic and anaerobic cultures in each case of temperature higher than 38 °C, before starting the antibiotic therapy (most of the patients received piperacillin-tazobactam or imipenem as empiric first-line treatment). All venous blood samples that were drawn for culture were inoculated aseptically into media for processing on the BacT/Alert Fn System (Organon Teknika, Rome, Itlay). Blood-culture bottles were incubated at 37 °C and examined daily for 10 days. For the isolation of anaerobic bacteria after growth in the anaerobic culture bottle (Brain Hearth Infusion Blood Laked Agar-BHIBLA) a microflow anaerobic chamber (Anaerobic System MDH) was used and *F. nucleatum* was identified by conventional bacteriological methods (ID32 A system-Bio Merieux, Marcy-l'Etoile, France). Susceptibility to antibiotics was assessed by ATB-Ana system (Bio-Merieux).

Severe neutropenia was defined as an absolute granulocyte count of less than 100 cells/μL. Mucositis scores for each patient were obtained from the physicians' daily progress notes. The severity of

Corresponding author and reprints requests: Dr A. Candoni, Division of Hematology, University Hospital, P.le S. Maria della Misericordia, 33100 Udine, Italy
Tel: +39 432 559662
Fax: +39 432 559661
E-mail: candoni.a@tiscali.it

mucositis was graded from 0 (none) to 4 (life threatening) according to the classification system of the World Health Organization (WHO). All neutropenic patients received antimicrobial prophylaxis including oral ciprofloxacin or levofloxacin 500 mg/daily.

Eighteen episodes of bacteremia caused by *F. nucleatum* were identified in 18 different patients, a rate of 0.3 *F. nucleatum* bacteremias per 100 patient admissions. This accounted for 5% of all Gram-negative bacteremic episodes that occurred at our Department during the study period. In this group of patients 10/18 (56%) were male and 8/18 (44%) female with a median age of 34 years (range 17–69); 15 patients suffered from refractory/relapsed acute leukemia and 3 from refractory lymphoma. Sixteen patients (89%) had been treated with intensive chemotherapy (including anthracyclines and high-dose cytosine arabinoside) and 2 (11%) had been submitted to bone marrow transplantation (BMT). All patients were severly neutropenic at the onset of bacteremia caused by *F. nucleatum*, with granulocyte counts less than 100 cells/μL. Sixteen (89%) of patients had a severe oral mucositis at the time of bacteremia (WHO grade III–IV in 10 out of 18 cases). The *F. nucleatum* bacteremia occured after a median time of 12 days of severe neutropenia (range 5–15) and after a median time of 6 days of mucositis (range 4–9); 5/18 (28%) of bacteremic episodes were polymicrobial and the coinfecting organisms were a coagulase-negative *Staphylococcus* (3 cases) and *Escherichia coli* (2 cases). Pulmonary infiltrates were observed in only 2/18 (11%) of the patients, while in 16/18 (89%) of the *F. nucleatum* infections no focus could be found. However, it must be emphasized that 15/16 of these patients had an oropharyngeal mucositis (chemotherapy related) that might have served as a portal of entry for the systemic infection. The antibiotic treatment was piperacillin-tazobactam (nine patients), imipenem (four patients), meropenem (three patients) or amoxicillin-clavulanate (two patients). The median time of antibiotic therapy was 8 days (range 3–16); 15/18 (83%) cases responded to the first treatment and 2/18 (11%) to the second-line antibiotic therapy with imipenem. Only two patients received ceftazidime and vancomycin before the onset of *F. nucleatum* infection. The most active antibiotics in vitro were: piperacillin (100% of *F. nucleatum* were susceptible), amoxicillin-clavulanate (100% S), clindamycin (100% S), imipenem (100% S).

Death occured in 3/18 patients (17%), but the mortality related to *F. nucleatum* bacteremia was 5% (1/18). In fact, two patients died from cerebral hemorrage and only one from pneumonia with multiple abscesses caused by *F. nucleatum*. No septic shock occured.

When cases of *F. nucleatum* bacteremia were compared with the other anaerobic bacteremias that occured in our Department in the same period, there was a statistically significant increase of severe mucositis (P 0.001) and of severe neutropenia (P 0.04) in the group of *F. nucleatum* bacteremias (Table 1).

Although uncommon in this setting, Gram-negative anaerobic bacteremias represent a serious complication in neutropenic patients with hematological malignancies. However, over the last years an increase in the number of these infections has been observed and currently they are considered an emergent problem in patients with

Table 1 Clinical characteristics of *F. nucleatum* bacteremias compared to other anaerobic bacteremias that occurred in the same period (Jan 1992–Dec 2001)

***F. nucleatum* Bacteremias**	**Other Anaerobic Bacteremias[a]**	***P*[b]**	
No of cases	18	16	
Age-median (range)	34 (17–69)	37 (20–68)	n.s.
Male sex	8/18	8/16	n.s.
Leukemia	15/18	11/16	n.s.
Lymphoma	3/18	5/16	n.s.
Mucositis III-IV WHO	16/18	4/16	0.001
Neutropenia (<100 PMN)	18/18	10/16	0.04
Mortality related	1/18	4/16	n.s.

[a]8 Bacteroides species, 5 Peptostreptococcus species, 3 Clostridium species.
[b]Fisher's exact test.

oncohematologic diseases [3,4,6,9]. The main predisposing factors seem to be: intensive cytotoxic therapy with damage to normal mucous barriers, profound granulocytopenia and therapy with corticosteroids [3,4,6].

F. nucleatum is a Gram-negative anaerobic bacterium normally found in the oral cavity and commonly known as an agent of periodontal infections [10]. In the medical literature only a few cases (such as case reports or small series) of *F. nucleatum* bacteremia in neutropenic cancer patients have been reported; therefore, the real pathogenicity of this bacterium in this setting is not yet well defined. As an example, Lanstaad *et al.* described three cases of *F. nucleatum* bacteremia in neutropenic cancer patients with severe oral mucositis; one third of the patients died from bacteremia [9]. Brow *et al.* described two cases of *F. nucleatum* bacteremia in neutropenic cancer patients both with a favorable outcome [4]. Other single cases of *F. nucleatum* bacteremia are described in hematologic patients with oral mucositis, with or without neutropenia, with a variable outcome [5,11]. Many episodes of *F. nucleatum* bacteremia are reported in patients without cancer or neutropenia, suffering from different diseases (diabetes mellitus, intestinal, pulmonary, liver or gynecologic diseases) in which the oropharingeal, gastrointestinal, urogenital and respiratory tracts, commonly sites of *F. nucleatum* colonization, could become infection sources. In these series *F. nucleatum* bacteremia was frequently polymicrobial and nosocomial; the mortality was higher and correlated with the severity of the underlying disease [7,8]. In a recent paper Lark *et al.* reviewed their experience, over a 14-year period, with the incidence of anaerobe bacteremias among allogenic bone-marrow recipients; the predominant isolates were *F. nucleatum* (17 patients), followed by *Leptotrichia buccalis* (four patients) and *Clostridium* species (two patients). In this study infection-related mortality was 9% and the severity of oropharyngeal mucositis was identified as a risk factor for bloodstream infections [6].

Our data confirm the rarity of bacteremia owing to *F. nucleatum* in neutropenic oncohematologic patients. In fact, in our Department, over a 10-year period, this bacteremia accounted for only 5% of all Gram-negative bacteremic episodes and for only 1% of the total bacteremias. Nevertheless, this is one of the largest series of *F. nucleatum* bacteremia described in the literature in this type of patient. As reported by Lark *et al.*, our experience confirms that *F. nucleatum* bacteremia occurred in hematological patients with malignancies (leukemia and lymphoma) after intensive chemotherapy and, in most of the cases, in patients with oral mucositis. Antimicrobial susceptibility of *F. nucleatum* to beta-lactam and carbapenem antibiotics, frequently used in neutropenic patients, was very good. In our experience, the outcome of these bacteremias has been favorable, with a low mortality and without septic shock. Moreover, the course of *F. nucleatum* bacteremia seems to be more favorable than other bacteremias caused by *Fusobacterium* species such as *F. necrophorum*, which usually causes Lemierre Syndrome [12,13].

Even though *F. nucleatum* infections are rare, this bacterium should be considered as a possible cause of bacteremia in neutropenic oncohematologic patients with fever and severe oral mucositis following intensive chemotherapy [3,6,8,9]. In these situations blood cultures supporting the growth of anaerobic bacteria should be used routinely. Taking into account our experience we would emphasize the importance of mucositis prevention in these patients in order to avoid infections, and we would suggest the need for including antibiotics effective against anaerobes in their prophylactic/therapeutic antibiotic regimes [4,6,14]. Further multicentric studies are needed in order to increase our understanding on the epidemiology and the outcome of this unusual infection in oncohematologic Departments.

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