



## Case report

# Mucositis and oral infections secondary to gram negative rods in patients with prolonged neutropenia



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## ABSTRACT

Patients with prolonged neutropenia are at risk for a variety of complications and infections including the development of mucositis and oral ulcers. The changes in oral flora during chemotherapy and its effects on the development of infections of the oral cavity have been studied with inconsistent results. However, there is evidence that supports the colonization of gram negative rods in patients undergoing chemotherapy. In this report, we present two leukemic patients who developed oral ulcers secondary to multi-drug resistant *Pseudomonas aeruginosa*. It is important to suspect multi-drug resistant gram negative rods in patients with prolonged neutropenia who develop gum infections despite appropriate antibiotic coverage.

## Introduction

It has been proposed that the oral flora in prolonged neutropenic cancer patients on prophylactic antibiotic therapy is different from the normal oral flora. These patients are thought to be at a higher risk of colonization with gram negative rods (GNR). However, there is a paucity of literature that describes the changes that occur in the oral flora of patients undergoing chemotherapy, and the study results have been inconsistent [1,2]. We describe two leukemic patients with prolonged neutropenia who developed multi-drug resistant (MDR) gum infections.

## Case report

Our first patient is a 67 year old male with acute myeloid leukemia (AML) receiving cladribine, cytarabine, filgrastim, and mitoxantrone (CLAG) therapy. He had prolonged neutropenia and was on prophylactic ciprofloxacin. He presented with a gingival ulcer. On physical exam he was febrile with a temperature of 101.8 °F, pulse 93 beats/min, blood pressure 95/59 mm Hg, respirations 20 breaths/min, and oxygen saturations of 94% on room air. A 1.5 centimeter purpuric lesion was noted on the left upper gum line. The left cheek was tender with erythema and swelling. Left cervical lymphadenopathy was present. His heart sounds were regular without murmurs, and his lungs were clear to auscultation. His abdomen was soft and non-tender. No other cutaneous

lesions were noted and the rest of his physical exam was unremarkable. Laboratory studies revealed a white blood cell count of 0.16 k/ $\mu$ L, hemoglobin of 6.7 g/dL, platelets of 8000/ $\mu$ L, blood urea nitrogen of 9 mg/dL, and creatinine of 0.6 mg/dL. The absolute neutrophil count (ANC) was less than 500 and this was the fourteenth day of severe neutropenia. A facial computerized tomography (CT) was negative for an abscess. Clindamycin was added to his antibiotic regimen to which he did not respond. Swab culturing the effected gum grew pan-sensitive *Pseudomonas aeruginosa* (PSA) and he was treated with piperacillin plus tazobactam. The mean inhibitory concentration (MIC) for piperacillin plus tazobactam was 8. His oral lesion improved and he was continued on piperacillin plus tazobactam as prophylaxis for persistent neutropenia.

Three weeks later he presented with fevers of 102.0 °F, pulse 92 beats/min, blood pressure 92/59 mm Hg. His ANC remained less than 500. On oral examination he had developed a large gingival ulceration with features consistent with associated facial cellulitis. He also developed purpuric papules on the right shoulder. A resistant GNR infection was suspected and piperacillin plus tazobactam was switched to meropenem and tobramycin to which he responded well. Blood cultures revealed PSA resistant to piperacillin plus tazobactam. Biopsy of the skin lesions from the right shoulder was performed, pathology revealed thrombotic vessels with dermal necrosis and granulation tissue with focal septal panniculitis with numerous bacterial forms which was consistent with ecthyma gangrenosum. The tissue culture grew PSA

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which was also resistant to piperacillin plus tazobactam. He completed a course of meropenem with resolution of the infection.

Our second patient was a 29 year old female with refractory AML receiving CLAG chemotherapy. She had prolonged neutropenia and presented with gingivitis. On physical exam the temperature was 99.1 °F, pulse 88 beats/min, blood pressure 94/51 mm Hg, respirations 16 breaths/min, and oxygen saturations of 98% on room air. There was an oral ulcer of the upper palate. Her heart sounds were regular without murmurs, and her lungs were clear to auscultation. Her abdomen was soft and non-tender. Laboratory studies revealed a white blood cell count of 8.06 k/ $\mu$ L, hemoglobin of 7.6 g/dL, platelets of 6000/ $\mu$ L, absolute blasts 7.74 k/uL, absolute neutrophils 0.00 k/uL, blood urea nitrogen of 12 mg/dL, creatinine of 0.7 mg/dL. She had been neutropenic for greater than 3 months. Gum cultures grew pan-sensitive *Pseudomonas aeruginosa* (PSA) and she was treated with ciprofloxacin to which she responded well. The MIC to piperacillin plus tazobactam was 32.

She presented 3 months later with a new gingival ulcer. In the interim her course was complicated by fusariosis and was treated with liposomal amphotericin B. On examination her temperature was 101.7 F, pulse 126 beats/min, blood pressure 96/64 mm Hg. There was a small darkly pigmented ulcerative lesion of the right lower gum line. Laboratory studies revealed a white blood cell count of 18.31 k/ $\mu$ L, hemoglobin of 6.7 g/dL, platelets of 12,000/ $\mu$ L, absolute blasts 16.59 k/uL, absolute neutrophils 0.00 k/uL. She was on piperacillin plus tazobactam for prophylaxis for prolonged neutropenia. A MDR GNR infection was suspected and she was switched to meropenem. Gum and blood cultures grew MDR PSA susceptible only to tobramycin. She was treated accordingly but died 2 days later due to PSA septic shock, chronic disseminated fusarium, and refractory leukemia.

## Discussion

Mucositis is a common complication in neutropenic patients undergoing immunosuppressive chemotherapy which may lead to oral infectious ulcers and periodontal infections [2–4]. Mucositis affects the entire gastrointestinal tract including the mouth [5]. Cytotoxic agents lead to mucositis by several mechanisms including damaging normal barrier function, reducing immunologic protection due to neutropenia and increased inflammatory reaction leading to direct tissue damage [1,6].

There is some research that describes the complex relationship between oral bacteria and immune reactions that may contribute to mucositis. Three pathways have been associated with the development of mucositis and the oral flora which include nuclear factor kappa B (NF $\kappa$ B), toll-like receptor (TLR) and mitogen-activated protein kinase (MAPK) signaling. Bacterial ligands are thought to stimulate the TLR and MAPK pathways which ultimately leads to the release of inflammatory cytokines and cell death, clinically resulting in mucositis. It has been proposed that due to the expected change in oral flora following chemotherapy, certain bacterial ligands may be more prevalent and therefore can directly affect the TLR pathway causing an increased inflammatory reaction. However, this is minimally studied and further research should be done to elucidate the pathophysiology of the complex interactions in this subset of patients [6].

Along with understanding the immune response associated with bacteria and mucositis, it is important to be aware of the organisms that make up the oral flora in order to choose the best treatment options for this population. It is predicted that normal oral flora consists of greater than 500 bacterial species which are typically harmless [1]. However in patients with mucositis, organisms found within the oral flora have been shown to prolong mucosal healing and lead to secondary oral infections [7,8]. Napeñas et al. reviewed the literature and described the oral flora in patients undergoing chemotherapy. They were unable to make a conclusion regarding changes in the oral flora in this population due the lack of studies and the large amount of variability in the

populations which were studied including the type of chemotherapy given, the methods for culturing, and the duration of chemotherapy received when cultures were collected. However, the majority of the studies they reviewed isolated gram-negative rods in patients undergoing chemotherapy which included *Klebsiella*, *Enterobacter*, *Pseudomonas* and *E. coli* in adults. Prior to chemotherapy gram positive organisms were more commonly isolated [1]. A study performed by Wahlin et al. revealed changes in oral bacterial resistance patterns in patients undergoing chemotherapy compared to a control population [9]. In cancer patients there has been a rise in MDR gram negative infections with increased recognition of carbapenem-resistant enterobacteriaceae, MDR *Acinetobacter baumannii*, trimethoprim-sulfamethoxazole-resistant *Stenotrophomonas maltophilia* and fluoroquinolone-resistant *E. coli* and *P. aeruginosa* [10]. A recent study by Laheij et al. found an association between ulcerative mucositis and *P. gingivalis*, *P. micra*, *T. denticola*, and *F. nucleatum*. Anaerobic oral organisms are also important to consider as a cause of mucositis in immunocompromised patients. *Fusobacterium* is an anaerobe present in the oral flora that has also been associated with gingival disease along with systemic infections including bacteremia [11,12]. *Capnocytophaga* is a facultatively anaerobic organism found in normal oral flora that has been associated with mucositis, gingival hyperplasia and invasive infections [13,14]. Fortunately, data currently supports low bacterial resistance patterns for *Fusobacterium* and *Capnocytophaga*. However, there is concern for antibiotic resistance development of *Capnocytophaga* due to  $\beta$ -lactamase production [12,15,16]. It is also important to consider other infectious etiologies such as fungal infections particularly candidiasis. Less common fungal organisms including *Fusarium* have been associated with primary gingivitis leading to disseminated disease [17]. Viral infections such as herpes simplex virus, varicella zoster virus, and cytomegalovirus are common etiologies to consider in this population [18]. Good oral hygiene and preventative dental care is important to reduce infectious bacterial complications associated with mucositis [5,19]. A relatively new development in the management of neutropenic patients receiving induction chemotherapy is to consider the degree and duration of mucosal barrier injury when choosing antibiotic therapy [20]. Antibiotic de-escalation is increasingly considered in patients with prolonged neutropenia who are far enough out from the receipt of chemotherapy that MBI is considered resolved therefore reducing their risk for the development of infections [20].

## Conclusion

Neutropenic patients are at increased risk of developing oral lesions due to GNR. Anaerobic bacteria contributing to mucositis in neutropenic patients receiving ciprofloxacin or cefepime are the central concern. However, prolonged antibiotic therapy in these patients can lead to development of MDR GNR in the oral cavity and subsequent infections. MDR GNR should always be suspected in such patients who develop gum infections or worsen despite appropriate and gram negative coverage. Swab culture of the area with susceptibility should be obtained immediately to guide antibiotic therapy. While awaiting culture susceptibilities broader antibiotic coverage should be considered to address possible resistance patterns. Prevention of oral infections may reduce morbidity and likely mortality in this population. Early diagnosis of MDR infections is also crucial in preventing further complications. Finally mucosal barrier injury is a newly realized factor in determining antibiotic therapy in patients with prolonged neutropenia.

## Conflicts of interest

The above authors do not have any potential conflicts of interest to disclose.

## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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