



## Prevalence of Oral Manifestations in Patients with Neutropenia, A Study in West of Iran

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### ABSTRACT

**Background:** Neutropenia is defined as abnormally decreased number of neutrophils in circulating blood. Various oral manifestations, including bacterial, viral, fungal lesions and oral ulcers may be seen in neutropenic patients. The purpose of this study was to investigate the prevalence of oral manifestations in neutropenic patients admitted to hospitals Sina and Fatemeh in 2006.

**Methods:** Eighty neutropenic patients were evaluated in this study. Data on age, sex, leukocyte count, etiology of neutropenia was obtained from patients' records. Oral examinations were conducted and the results were recorded.

**Results:** In studied patients, neutropenia was caused by medications and iatrogenic factors, stem cell disorders, and infections as 55%, 36.2%, and 8.8%, respectively. 53.8% of patients had no oral lesions and 46.2% of them had one or more types of oral lesions. The most common oral manifestation among these patients was oral ulcers in 25 cases. It was also observed angular cheilitis, petechiae, pseudomembranous oral candidiasis, gingivitis, erythematous candidiasis, NUG, and oral abscess in 10, 9, 7, 6, 5, 3, 3, and 2 cases, respectively.

**Conclusion:** according to this study, it can be concluded that oral lesions are observed in high prevalence in neutropenic patients. Of the most common oral lesions in neutropenic patients is oral ulcer.

**KEY WORDS:** oral lesions, neutropenia

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### INTRODUCTION

Neutropenia is defined as substantial reduction in number of neutrophils in circulating blood. Neutropenia or decreased neutrophil count is a complication that may occur because of various etiologic factors or may be congenital. The incidence of neutropenia has been reported as 3.4 million cases per year [1, 2, 3].

Regardless of the cause of its incidence, one of the problems of neutropenic patients is various infections. Of oral manifestations in these patients can be addressed to oral ulcers, gingivitis, bleeding gums, treatment refractory fungal infections, and in prolonged severe cases tooth mobility and alveolar bone loss. Oro-dental problems caused by pain and inflammation in various oral tissues, dental injuries, difficulty in chewing and dysphagia and consequently disrupted nutrition in these patients affect patients' oral health and general conditions and thereby the quality of their lives. In neutropenic patients, the oral cavity and mucous membranes are common places for infections, and oral ulcers, inflammation and periodontitis are of highly prevalent diseases [4]. Neutropenic ulcers are different from other oral ulcers, in this sense that these ulcers show no peripheral inflammation and are distinguished by necrosis. Because of dysfunction in anti bacterial defense mechanism, the ulcers turn into deep and irregular lesions that are extremely painful [5].

One of the problems in neutropenic patients is the incidence of infection regardless of its cause. Oral characteristics observed in such patients are gingivitis, gingival recession, tooth mobility, alveolar bone loss, and early loss of teeth including both milk-teeth and permanent teeth [6]. One of the common manifestations of neutropenia is the oral ulcer which may be its only clinical manifestation [7]. Infection is the major problem of this disease, commonly emerging as necrotic lesions in gums, palate, and mucosa of mouth, throat and other parts of the mouth. All of these lesions often reflect the overgrowth of microorganisms associated with a relatively weak neutrophil response [8]. The periodontal condition in these patients varies from a marginal gingivitis to a severe alveolar bone loss, highly resembling a prepubertal periodontitis. Fungal infections are of serious problems

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in the treatment of patients with hematologic malignancies. Neutropenic patients are at high risk of invasive fungal infections [9]. Candidiasis and Aspergillus infections are of the most common fungal infections in neutropenic patients [10]. Patients with invasive Aspergillus show undesirable prognosis and high mortality rate [11]. In addition, it is difficult to diagnose invasive Aspergillus and to select the appropriate medication [12]. Treatment and outcome of Aspergillus infections depend on severity of invasive fungi and host status. Neutrophil count is especially a key factor in determining the prognosis of these patients [13]. The sensitivity of these organisms to antifungal drugs is another important factor that affects the prognosis [14]. In neutropenic patients, it is important to prepare periodic culture, because it can assess the sensitivity of organism to medications as well as its genus [15].

Unfortunately, susceptibility test is not routine in most therapeutic centers. So there is little information available on the organism's sensitivity to the medication and also between the sensitivity and therapeutic effect, particularly in patients with immune deficiency [16]. Almost all patients receiving bone marrow transplants show oral complications. One of these complications is the risk of fungal infections of the oral mucosa, whose risk of incidence is associated with the severity and duration of neutropenia [17]. During the periods of neutropenia incidence, the patients are susceptible to oropharyngeal colonization of fungi especially *Candida*, and they may be affected by oral and systemic fungal infections in the later stages [18]. Herpes simplex is of the most prevalent oral viral infections in patients with neutropenia, which may occur as primary or secondary disease. Bacterial infections are detected in three areas in the mouth: gum, mucosa and teeth. Since there is not any normal symptom of infection and inflammation in patients with suppressed bone marrow and neutropenia, the diagnosis is based on the presence of oral lesions associated with fever and pain. Gum is the most common site of infection, particularly in patients with periodontal diseases. Here, infection occurs as necrotic gingivitis, clinically very similar to ANUG [19]. Given that few studies have been conducted in neutropenic patients with oral manifestations, and moreover, most of studies have been of case reports, blood diseases and neutropenia and oral manifestations are investigated in neutropenic patients.

## MATERIALS AND METHODS

In this descriptive cross sectional study, all patients with mild, moderate or severe neutropenia hospitalized in blood ward in Sina and Fatemeh hospitals in 2006 were selected by simple sampling method and evaluated in terms of oral lesions. The research process was explained to all patients and a written consent was obtained for participation in the study. While patients at any stage of the study were allowed to leave. Patients with verified neutropenia by WBC diff. test were enrolled in the study. In case of having other systemic diseases including diabetes, autoimmune diseases and other hematopoietic diseases or diseases with oral manifestations the patient was excluded from the study. Data such as age, sex, leukocyte count, percentage of neutrophils, etiology of neutropenia (congenital, acquired, medications and iatrogenic, associated with infection or stem cell disorders) were obtained from patients' records. Number of neutrophils was calculated as the leukocyte count multiplied by the percentage of neutrophils plus band cells. Oral examinations were conducted on the patients, and various types of lesions on lips, lips angle, gums, tongue and oral cavity were considered. Data obtained from medical records as well as results from oral examinations were recorded in an information form. Finally the data were analyzed by the software SPSS version 20, using descriptive statistics method

## RESULTS

In this study 80 patients with 3 to 85 years old and a mean age of 40 years old were evaluated in terms of oral lesions

The group consisted of 38 females (47.5%) with a mean age of 35.5 years old and 42 males (52.5%) with a mean age of 44 years old. Of 80 neutropenic patients, 43 patients (53.75%) had no oral lesions and 37 patients (46.25%) had one or more lesions. The present study found no case with congenital etiology. In descending order of frequency, the acquired causes of neutropenia consisted of medications and iatrogenic factors, stem cell disorders, and infections by 55%, 36.2%, and 8.8%, respectively. The frequency and percentage of patients with various oral lesions is shown in table 1. Table 2 shows the frequency and percentage of lesions seen in patients

**Table 1.**

<i>types of oral lesions</i>	<i>frequency</i>	<i>Percent</i>
One type	15	40.54
Two types	13	35.14
Three types	7	18.92
Four types	2	5.40
Total	37	100

**Table 2.**

<i>Type of oral lesion</i>	<i>frequency</i>	<i>percent</i>
Oral ulcers	25	31.25
Angular cheilitis	10	12.25
Petechiae	9	11.25
Pseudomembranous Candidiasis	7	8.75
Erythematous Candidiasis	3	3.75
Herpetic lesions in lips and mouths	6	7.5
Gingivitis	5	6.25
Oral abscess	2	2.5
NUG	3	3.75

Oral ulcer was the most common oral manifestation in the patients in the present study. It was observed in 25 patients, caused in frequency order by medication and iatrogenic reasons in 16 patients, by stem cell disorders in 8 cases, by infection in one patient. In general, oral ulcers constituted 35% of all oral lesions, observed in 31.25% of patients.

Meanwhile, two patients suffered from AML along with severe neutropenia and undesirable oral hygiene and CMM was diagnosed in another patient with moderate neutropenia. All three patients had unfavorable oral hygiene. Oral abscess also was reported in 2 cases, both of which had severe neutropenia and were in unfavorable status in terms of oral hygiene. Oral lesions were observed in female and male neutropenic patients by 50% and 42.9%, respectively. So oral manifestations were more common in women.

Oral lesions were also observed in neutropenic patients resulted from medication and stem cell disorders in 52.3% and 41.4% of cases, respectively. Infection-related neutropenic patients experienced oral lesions by 28.6%.

The incidence rate of oral lesions was enhanced by increased severity of neutropenia, so that the oral lesions were observed in patients with severe, moderate, and mild neutropenia by 53.8%, 36.7%, and 16.7%, respectively. Patients with undesirable and moderate oral hygiene suffered from oral lesions by 69.6% and 40%, respectively. In patients with favorable oral hygiene, this rate of incidence was considerably low (25%). Preserving oral hygiene can reduce the incidence of oral lesions in patients.

## DISCUSSION

Neutropenia is characterized by considerably reduced neutrophils caused by factors such as medications, stem cell disorders and infections. Oral manifestations may be included oral ulcers, bacterial, fungal and viral infections. Such manifestations are sometimes stated even as the first symptom and chief complaint and can result in major problems for patients, including secondary infections, particularly septicemia [20]. Oral manifestations vary among patients with neutropenia in terms of type, severity and etiology of neutropenia as well as patients' oral health. In studies conducted so far, there has been reported very little information about the prevalence of oral manifestations [20, 21]. In studies conducted on oral manifestations caused by neutropenia, there has been investigated usually patients with congenital neutropenia [4, 6]. Most of these studies have been of case reports, and a few of these studies has investigated a significant number of patients. In addition, previous studies have mentioned no relationship between oral manifestations and oral hygiene and severity of neutropenia in neutropenic patients. Thus, comparing the rate of incidence and prevalence reported in various studies does not provide much information; rather they have dealt with the pathogenesis and diagnostic and therapy approaches

In the present study, patients generally suffered from moderate and severe disorders that caused them to be hospitalized. Of two major causes of neutropenia, that is congenital and acquired, the present study found no case with a congenital etiology.

The results of presented study showed a prevalence of 46.3% of oral manifestations in patients with neutropenia. The results also showed that oral lesions and angular cheilitis and petechiae are of the most common oral manifestation in neutropenic patients whereas oral abscess and NUG are of the rarest ones

The incidence of petechiae in these patients was mainly caused by thrombocytopenia resulted from suppressed bone marrow cells. Pseudomembranous Candidiasis (7 cases, 8.75% of patients) and Erythematous Candidiasis (3 cases, 3.75% of patients) were observed in 12.5% of patients in total.

In a study on 72 neutropenic patients by Azad [20] in Tehran, it was reported the incidence of oral symptoms as 48% in general, the incidence of petechiae was reported in 9% and oral ulcers in his study by 38%. Therefore the results of the present study match Azad research in terms of oral manifestations, oral lesions and petechiae prevalence. Thus it can be said that over 40% of patients with neutropenia presented with oral manifestation and oral lesions are the most common finding in patients with neutropenia.

According to Myoken *et al.* [21], 84.6% of neutropenic patients caused by bone marrow transplantation showed ulcerative oral mucositis. Also they [21] reported the incidence of oral candidiasis (Pseudomembranous or Erythematous) in 115 neutropenic patients as 14.8%, in spite of antifungal prophylaxis.

Consequently it can be said that the results of the present study is consistent with Myokens *et al.* (21) study. However the prevalence of oral findings is significantly different in these two studies. The reasons for this can be the difference in duration of illness at the time of study and cultural level of participants.

Of other reasons for high degree of oral lesions in Myoken *et al.* study, it can be addressed to the severity of neutropenia and the patients' failure in preserving proper hygiene. In addition to neutropenia, older age of studied patients, use of artificial dentures, possible vitamin deficiency, and anemia may be involved as interfering factors. In the present study oral lesions were more common in female patients with neutropenia.

This relatively small difference may be due to differences between male and female groups in terms of factors causing neutropenia, the severity of neutropenia, and also their different oral hygiene status.

It is noteworthy to state about patients under chemotherapy regime that chemotherapy drugs are causing oral lesions in two direct (affecting epithelial cells of the mouth) and indirect (decreasing neutrophils). The direct effects of such drugs may affect the results of the study. However, we tried to distinguish between them in the present study through patients' early examinations at the entry to the study and associating the duration of symptoms emerging during treatment with direct and indirect effects.

The results of present study showed that medication and stem cell disorders are the most common reason for neutropenia, incidence rate of oral lesions was enhanced by increased severity of neutropenia and preserving oral hygiene can reduce the incidence of oral lesions in patients.

Of the advantages of this research was the concurrent study of oral findings, oral health and their interaction with each other. Since few studies on neutropenic oral manifestations exist. The limitations of this study to compare the results with similar studies can be named. Ultimately it is suggested to conduct similar studies with larger sample sizes in other regions of Iran and also parts of the world.

## Conclusions

The results of the study showed: Oral lesions are of high incidence in neutropenic patients. Drugs and stem cell disorders are of the main factors resulting in oral lesions in neutropenic patients. Oral ulcers are considered as the most common oral lesions in neutropenic patients. Oral hygiene in neutropenic patients can be effective in reduction of oral lesions.

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