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## Case Report

### Ibuprofen induced neutropenia manifesting as oral ulcerations

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#### Abstract

Oral ulcerations of varied etiology are commonly seen in dental practice. Among all the causes of oral ulcers, those due to neutropenia are significant. Neutropenia can occur in many systemic conditions and also in patients on long-term therapy of certain drugs like Ibuprofen. Here, we report a case of a 40-year-old female patient who developed oral ulcerations secondary to Ibuprofen -induced neutropenia. Early diagnosis of the condition led to discontinuation of the offending drug and significant improvement in her blood picture and also prevented many other complications including systemic infections that neutropenia can cause.

**Keywords:** Neutropenia, Ibuprofen, ulcers

#### Introduction

Various systemic disorders are known to cause oral ulcerations.<sup>[1]</sup> Neutropenia is one of the disorders that manifests as multiple, irregular, deep and painful ulcers.

Neutropenia, by itself has no specific symptoms and is diagnosed on the basis of underlying infections in a neutropenic state. Among the various drugs that lead to neutropenia, Ibuprofen is an important example.

Here, we report a case of a 40-year-old female patient on Ibuprofen therapy who developed multiple, painful oral ulcerations secondary to the drug. Her blood picture revealed some abnormal values during Ibuprofen therapy and showed significant improvement within one month of discontinuation of the drug. The neutropenic state which had led to these oral ulcers was found out on a dental examination and prompt referral to the physician and discontinuation of Ibuprofen saved her from developing severe systemic infections.

#### Case Report

A 40-year-old female patient reported to our dental hospital with the complaint of difficulty in eating due to the presence of painful ulcers in her mouth since 15 days.

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The pain was severe and burning type in nature and continuous. She had been on completely liquid diet chiefly comprising milk, curd and fruit juices since the last 10-12 days. The ulcers in her mouth which had started 15 days back were small initially and had gradually increased to their current size. All the ulcers had developed almost at the same time. She had been unable to brush her teeth since the last 10 days owing to the painful oral ulcers. On general physical examination, the patient appeared weak and lethargic and had mild pallor. Her submental and left submandibular lymph nodes were palpable, tender, around 1.5 cm x 1.5 cm in size, discrete, movable and soft in consistency.

On intra-oral examination, multiple, irregular and deep ulcers were seen on the tip and left lateral border of the tongue, lower labial mucosa and buccal mucosae. Their average size was around 1.5 cm x 1 cm and the floor was covered with whitish slough. The ulcers were tender on palpation and characteristically, there was no inflammatory halo seen surrounding them. There was no bleeding from the ulcers and a coated tongue was seen.

Other intra-oral findings included missing 26, 27; attrited lower incisor teeth and chronic generalized marginal gingivitis

with localized periodontitis in relation to 31, 32 and 46. Based on history and physical examination, a provisional diagnosis of Recurrent Aphthous Ulcers of Major type was made.

The other differential diagnoses considered were oral ulcers secondary to systemic disorders (hematological, gastrointestinal), drug (Ibuprofen)-induced ulcers, pemphigus, mucous membrane pemphigoid, bullous pemphigoid and erosive lichen planus.

We also considered the differential diagnosis of oral ulcers secondary to hematological disorders. Also, considering that the patient was on Ibuprofen, we kept in mind the possibility of a toxic or allergic reaction to the drug which could have led to the oral ulcers. Pemphigus and pemphigoid, both are commonly seen in adult middle-aged women. They occur as vesicles or bullae which then rupture to form painful ulcers. Hence, we also considered the possibility of these two vesiculo-bullous lesions in the differential diagnosis. In erosive lichen planus, too, ulcerations can be seen involving the oral mucosa. Hence, it was also considered as a differential diagnosis.

The patient was sent for routine blood investigations and as palliative therapy,

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Benzydamine Hydrochloride (Tantum) mouth rinse was prescribed to be used three to four times in a day. Her blood picture revealed a reduced hemoglobin level at 6.5%, reduced RBC count at 2.2 million cells/ cu.mm, leucopenia at 2, 270 cells/ cu.mm and thrombocytopenia at 1,30,000 cells/cu.mm. The peripheral blood smear examination revealed normocytic, hypochromic blood picture with leucopenia, neutropenia, relative lymphocytosis and thrombocytopenia. Abnormal neutrophil band forms were also seen.

Based on these findings, a diagnosis of neutropenia (Ibuprofen induced) was made. Immediate discontinuation of Ibuprofen and iron supplements, b complex with lactobacillus resulted in marked improvement in her symptoms within seven days and the ulcers healed completely in 10 days time. After discontinuation of Ibuprofen therapy, she responded immediately and the ulcers disappeared.

The patient was periodically reviewed after 10 days, one month and then every month till the next six months. There has been no history of similar ulcers since then. It was during Ibuprofen therapy that the patient showed a reduced hemoglobin level, anemia, leucopenia, particularly neutropenia

and thrombocytopenia. Two months after the Ibuprofen therapy was discontinued, there was an overall significant improvement in her blood picture.

Based on these findings, we were able to give a final diagnosis of Oral Ulcerations due to Ibuprofen-induced Neutropenia.

### Discussion

Granulocytopenia may occur alone or as a part of a generalized suppression of the bone marrow. It chiefly results from a decrease in neutrophils referred to as neutropenia. Neutropenia is defined as an absolute neutrophil count of less than  $0.5 \times 10^9 / L$ . It can be classified as mild (count between 1000- 1500/ $\mu$ L), moderate (500-1000/ $\mu$ L) and severe (less than 500/ $\mu$ L). It can also be divided into acute neutropenia (occurring over hours to a few days) and chronic neutropenia (lasting months to years). Neutropenia leads to an increased susceptibility to infections. Causes of neutropenia are varied and can range from infections (due to Hepatitis A, Varicella Zoster, Septicemia, etc.) to Systemic Lupus Erythromatosus where there is increased sequestration of neutrophils. It can also be seen in patients on hemodialysis in whom there is activation of the complement system

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by dialysis membrane and most importantly in case of drug reactions.

Various drugs have been reported to affect the oro-facial structures thereby affecting the oral mucosa.<sup>[2]</sup> Ibuprofen has been reported to be one of them. Neutropenia secondary to drug reactions can be a result of a toxic reaction or due to an idiosyncratic reaction. Toxic drug reactions are those that occur predictably in all persons due to the exposure to an offending drug at sufficient doses for long periods of time. They bring about neutropenia by interfering with DNA synthesis, protein synthesis or mitosis. Ibuprofen is one of the drugs that can cause a toxic reaction-based neutropenia. Idiosyncratic reactions are not dose-related and occur in a small percentage of patients. They bring about neutropenia either by an immunologic reaction affecting the bone marrow or by an inherited inability to properly metabolize the drug. Examples of drugs that cause idiosyncratic neutropenia are phenothiazides, phenylbutazones, sulfonamides, chloramphenicol, cimetidine and Ibuprofen etc.

Clinical features of drug-induced neutropenia range from infection and mucocutaneous involvement to lymphadenopathy.

Drug-induced oral ulcerations are part of a complex reaction with cutaneous or systemic manifestations. Sometimes, one or more oral ulcerations appear as the main side-effect of a drug, or exceptionally as solitary lesions. Oral ulcerations due to neutropenia have some characteristic features. These occur as multiple, irregular and painful ulcers which lack an inflammatory component. These show dramatic improvement once the neutropenic state is corrected. It has been stated that usual therapeutic doses of drugs inducing neutropenia cause mucosal and cutaneous ulcerations. This patient on Ibuprofen showing the symptoms of neutropenia in the form of oral ulcers reflects an abnormal response of her bone marrow to the drug in a short span of time. However, early diagnosis of her neutropenia and prompt discontinuation of the offending drug saved the patient from severe systemic infections.

### **Conclusion**

The diagnosis of such cases is very difficult to because the various types of oral ulcers may appear clinically to be very similar. Features which are helpful in identifying the cause of ulcers are the associated constitutional signs and symptoms, presence of lesions on the skin

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and/or other mucosa, and the presence of bullae and vesicles. In some cases, however, laboratory procedures are required to make the diagnosis.<sup>[3]</sup>

The results indicate that careful history-taking goes a long way in establishing some unexpected diagnosis. This is to be supplemented with a thorough clinical examination, necessary investigations and adequate follow-up.

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