Oral Mucositis: Pathophysiology; Biomarkers And Current Management Strtegies

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ABSTRACT –

Oral mucositis continues to be Among the most common and concerning adverse impacts of conventional chemotherapy and radiation treatments.it is an inflammatory condition of oral mucosa. In [1]immunocompromised patients, ulcerative mucositis is a risk factor for possible life-threatening local or systemic infection consequences.so for treating this condition from past few years different strategies are developed.The mucositis have a grading so the treatments going according to stages.

A complex interaction between cellular injury, inflammation, and tissue regeneration failure characterizes the pathophysiology of oral mucositis. Direct cytotoxicity to epithelial cells, the production of inflammatory mediators, and microbial infections are important contributing factors. Management is still primarily supportive, with pain management and dental care playing a key role, despite the exploration of numerous preventive measures and treatments, including as cryotherapy, antibacterial medicines, and growth factor-based therapies. New therapy strategies targeted at preventing or lessening the severity of mucositis have been made possible by developments in Comprehension of molecular processes underlying these condition. Improving patient outcomes requires multidisciplinary care, proactive prevention, and early diagnosis.

Keywords – Chemotherapy, Radiotherapy, lamina propria , pro-inflammatory cytokines, Osteopontin, Interleukins, Glycosylation, Erythema, ulcers, Monoclonal antibodies

INTRODUCTION-

The very incapacitating illness known as oral mucositis is Distinguished by ulceration, edema, and [2]erythema of the oral mucosa. In addition to causing swelling and ittitation in the oral cavity, mucositis is an extremely painful mouth sore that is caused by inflammation of the mucous membrane lining the alimentary system. It is a consequence of radiation therapy of cancer and head and neck ulcers. Additionally, hematopoietic stem cell transplantation and chemotherapy can damage the mucosal barrier brought on by lesions, which in extreme cases

[1] Immunocompromised- a patients weakened immunity

[2] Erythema – Redness

can result in oral cavity infection. Malnutritioin and poor dietary habits significantly impacting on the development of mucositis in the mouth.

It involves the study of physical examinations, management , pathopysiology and etiology of oral mucositis .oral mucositis may develop in 40% of patients receiving conventional chemotherapy. Radiation patients have a 30% to 60% probability of acquiring mucositis, particularly if they have head and neck cancer. 80% of head and neck cancer cases underwent radiation treatment, while up to 40% of cancer patients received chemotherapy. Oral mucositis have the stages in the last stages it can worsen the patients condition. And it may lead a death.The treatment like zonated water, lower level-laser therapy , some of the natural products like honey are used. We have the aim to cover the causes , signs , symoptoms , Biomarkers ,Grading , Novel treatment plans like stem cell therapy , matrix mettaloprotease blocker . mouthwash like benzdyamine and diphenhydramine ,natural treatment of the oral mucositis like curcuma longa and honey , prophylactic drugs like repifermin etc.[1]

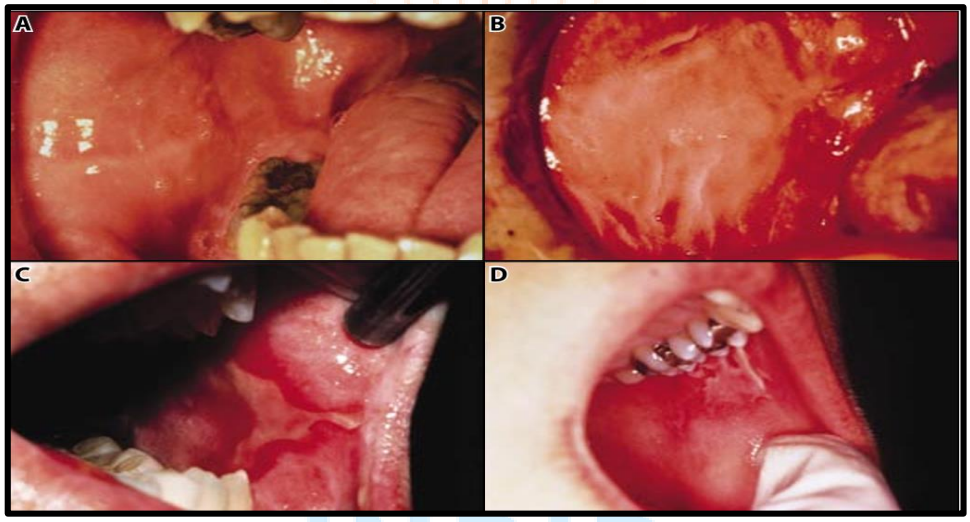

Figure 1. Representation of oral mucositis condition

Symptoms of OM

- Dry mouth [1]
- Ulceration , [3]itching
- Redness , swelling [2]
- Pain in the affected area
- Difficulty in Speaking , [4]swallowing , eating and drinking [3]

EPIDOMOLOGY AND PATHOPHYSIOLOGY OF OM-

Oral mucositis (OM) is a common and painful adverse consequences for patients undergoing cancer treatments like radiation therapy (RT) and chemotherapy (CT). The risk and severity of Oral mucositis vary depends on the type of treatment:

[3] Itching- tingle sensation
[4] Swallowing-chewing of eating of food

1. Radiation Therapy (RT): Nearly all patients receive RT for head and neck cancer develop OM. The severity can be worse with changes in RT schedules or when combined with chemotherapy.

2. Chemotherapy (CT)

Conventional-dose chemotherapy: Around 40% of these patients experience OM.

[5]Myeloablative chemotherapy (used for stem cell transplants) 75% of these patients develops severe om

3.Chemotherapy Drug: Some chemotherapy drugs are strongly linked to higher rates of OM. These include: Common drugs: Etoposide, methotrexate, cisplatin, doxorubicin, and 5-fluorouracil.

Others: Actinomycin D, docetaxel, chlorambucil, cytarabine, and many more.

Lamina propria is a strong layer of connectives tissue beneath the surface of the oral lining (epithelium). Its main job is to act as a barrier against infections and help maintain balance in the mouth. In the oral mucosa which is the tissue inside the mouth, you'll find:

Lymphoid tissue: This contains lots of immune cells like lymphocytes and plasma cells that help fight infections. Sensory receptors: These help you feel things like touch and temperature in your mouth.[3]

-Small salivary glands: These glands produce saliva to keep your mouth moist.

Cytokines are proteins that play a crucial role in the immune response and are involved in the development of oral mucositis (OM). The damage to the oral mucosa in OM is mainly due to an imbalance between the pro-inflammatory and the anti-inflammatory cytokines

1. The Pro-inflammatory cytokines (such as IL-1, IL-6, IL-8, TNF-α) are developed by cells in the mouth (like keratinocytes, which are skin-like cells in the mucosa). These cytokines trigger immune cells like Langerhans' cells to produce more cytokines.

2. Langerhans cells release llL-1, which then signals T cells to produce IL-2. This leads to more T cells being produced and activated, increasing inflammation.

3. T-helper cells (Th cells) are a type of immune cell that help regulate the immune response. There are two types:

Th1 cells: These are pro-inflammatory. When activated by cytokines like IL-12 a IFN-γ, they produce more pro-inflammatory cytokines (like IL-1, TNF, and others) and activate macrophages to cause inflammation.

Th2 cells These are more anti-inflammatory and help reduce the immune response.

So, in OM, the balance between these cytokines and immune cells can lead to either excessive inflammation (causing damage) or a protective response.[4]

that chemotherapeutic treatments target healthy tissues that divide quickly, such as the gastrointestinal tract and oral mucosa, recent research shows that submucosal components are damaged before the epithelial lesions show up In particular,

[5] Myeloblative – high dose of chemotherapy

fibroblast and vascular endothelial cell damage and death seem to occur before epithelial diseases.[5]

BIOMARKERS OF OM

The biomarkers utilized to assess the association between these biomarkers and the degree of mucositis, as well as predict the probability of oral mucositis in patients with head and neck cancer.[6]

1)Osteopontin (Opn) , a multifunctional glycoprotein	2)Salivary inflammatory mediator
3)N- Glycosylation of Alteration of serum and salivary globulin	4) a single nucleotide polymorphism
5) Apoptic and inflammation markers	6) Cytokines in saliva
7) The salivary alpha -1 antitrypsin and macrophage migration inhibitory factor biomarker	8)DNA methyltransferase gene

1) Osteopontin (Opn) , a multifunctional glycoprotein biomarker OM

[6]Osteopontin (OPN), a compound word made up of the words "osteo" and "pontin," was commonly used to describe the linking function of bone cells.

Serum OPN may be a diagnostic for the existence of [7]hematological malignancies during the Autologus peripheral stem cells transplantation , while salivary Osteopontin is a relatively unknown but non-invasive probe indicator for a number of mouth diseases, combining oral mucositis. Examining the various OPN isoforms in detail in light of post-translational changes such [8]glycosylation may also reveal information about the etiopathogenesis of OM, mucosal defense systems against aggressive microorganisms, and possible therapeutic targets.[7]

2) Salivary inflammatory mediator biomarker of OM-

Salivary inflammatory mediators, including prostaglandin E2, vascular endothelial growth factor, interleukin (IL)-1β, IL-6, IL-10, IL-12p70, and TNF, are responsible for mucosal dryness. The results showed that, in comparison to the pre-index group, there was a significant positive connection between OM grade and the levels of TNF, IL-6, and IL-10 in the saliva of cancer patients in the post-index group. Additionally, the salivary concentrations of IL-6, IL-8, and IL-10 were significantly higher in the post-index group than in the HV group.

[6] Osteopontin- bone sialoprotein
[7] Hematological malignancies-cancer that begins with blood forming tissue
[8] Glycosylation – a protein with glucose molecule

Additionally, it was demonstrated that oral mucosal dryness was much more prevalent in cancer patients than in the HV group, irrespective of whether the assessments were made prior to or following CTx and RT.[8,9]

3) N-glycosylation alteration of serum and salivary globulin biomarker as an OM - There are no biomarkers or specific treatments for oral mucositis . More than 1000 proteins, predominantly glycosylated, are found in saliva, which is a focus of ongoing biomarker research and a useful signal of changes in plasma contents (hormones, medications, etc.). Glycoproteins with a broad variety of functions are [9]immunoglobulins. The most common function of highly glycosylated IgA in mucosal protection[10]

4) Single nucleotide polymorphism –

Changes in genes involved in DNA damage repair have been the most extensively studied SNPs in non-inflammatory pathways. One process linked to radiosensitivity of a tumor in response and treatment-related to side effects is DNA damage repair. This process is essential for normal tissues to recover from RT-induced damage in between sessions, and changes to it might worsen toxicities and increase treatment variability across individuals. Polymorphisms in candidate gene that were formaly linked to radiosensitivity were assessed in the included articles. XRCC1, the most often investigated gene, is linked to the detection and restore of three of the most prevalent DNA errors: base excision repair, single-strand breaks, and double-strand breaks, which are more biologically significant.[11]

5) [10]apoptic and inflammation markers-

This study comprised 35 patients with head/neck cancer undergoing radiation therapy. Prior to radiation, patients were evaluated. Weekly reports of oral mucositis were made while undergoing radiation therapy. [11]Cytologic samples were taken from the mouth cavity using a brush. Immunocytochemical staining was performed using monoclonal antibodies for p53, BCl-2, MCl-1 TNF, and IL-1β. According to the findings, patients who develop mucositis after receiving radiation treatment for head and neck cancer see an increase in oral mucosal

[9] Immunoglobulin-cells of immune system
[10] Apoptic-breaking of cells
[11] Cytologic – examination of body cells under a diagnose

Inflammation.[12]

6) cytokines in saliva as a biomarker in OM -

Free radicals triggered by CTx and RT are said to be in charge of upregulating specific genes through the NF-κB pathway, which results in an overabundance of inflammatory mediators like prostaglandin E2 (PGE2), interleukin (IL)-1b, IL-6, and tumor necrosis factor (TNF). Patients with head and neck cancer were found to have higher levels of these inflammatory mediators in their saliva. [13]

7) The Salivary alpha -1 antitrypsin and macrophage migration inhibitory factor -

Salivary A1AT and MIF abundance is correlated with OM brought on by cancer treatments. MIF's physiological pro-inflammatory function seems to be consistent with its association with severe OM. The utilization of salivary MIF and A1AT levels as predictive indicators for successful treatment interventions, like photo [12]biomodulation therapy, patient-controlled analgesics, or customized medications, is greatly expanded by these findings.[14]

8) DNA methyltransferase gene -

[13]The post-mucositis phase is linked to the DNMT1 methylation profile. Higher creatinine levels seem to be linked to the DNMT3A methylation profile linked to the CC genotype of (SNP rs7590760). Furthermore, there seems to be a correlation between elevated creatinine levels and the DNMT3B unmethylated profile linked to the CC genotype (SNP rs6087990). [15]

Stages of mucositis

ORAL TOXICITY SCALE - (WHO)

Grade 0	No Alteration
Grade l	Pain and erythema
Grade ll	Erythema and ulcers
Grade lll	Ulcers (liquid diet only)
Grade lV	Unable to feed

[16]

- **Grade 0**

little or nonexistent symptoms, no need for intervention, and the patient can eat continues normally.

[12] Biomodulation- the changes in the cells or tissue

- **Grade l**

The patient needs a modified diet and has moderate pain or an ulcer that doesn't affect their ability to swallow.

- **Grade l**

[14]Excruciating discomfort that prevents oral intake

- **Grade lll**

[15]Life-threatening outcomes that call for immediate action

- **Grade lV**

May causes death [17]

Prophylactic drugs used for OM

- REPIFERMIN-

The human keratinocyte growth factor 2 (KGF-2) is called repifermin. In a phase II experiment, this material was investigated in patients who underwent conditioning chemotherapy prior to autologous HSCT. The incidence of grade 2 to 4 mucositis was considerably reduced by Repifermin.[19 ,20,]

- SAFORIS-

(AES-14)-

Aesgen Inc., Princeton, NJ, USA, manufactures AES-14 (SaforisTM), an oral suspension that uses a [16]proprietary vehicle to deliver concentrated L-glutamine to the oral mucosa. Based on research demonstrating a reduction in mucositis severity in [17]BMT patients and a quicker recovery period following radiation, the [18]FDA granted this system fast-track approval in January 2003.[21,22,23]

- GELCLAIR-

In 2002, the FDA authorized Gelclair® as a medical equipment of class 1. The gel is bioadherent. that covers mucosal lesions to create a covering. Gelclair is made up of glycerrhetinic acid, hyaluronic acid, and polyvinylpyrrolidone. This chemical is believed to have anti-inflammatory properties. It has been demonstrated that this preparation effectively reduces pain and mouth discomfort in patients with mucositis and is well tolerated and simple to administer.[2]

[14] Excruciating- extremely painful
[15] Life threatening – is the situation where can kill
[16] Proprietory-relating to ownership
[17] BMT- bone masrrow transplant
[18] FDA- food and drug administration

❖ DIPHENHYDRAMINE MOUTHWASH-

When compared to the placebo mouthwash, the diphenhydramine with a -lidocaine-antacid mouthwash dramatically decreased the oral mucositis pain in the first few hours of following treatment.[26,27]

NOVEL TREATMENTS ON OM-

- **Stem cell therapy-**

[19]**T**he two main characteristics of stem cells that set them apart from other types of cells containing in the body are their capacity for self-renewated, which allows them to divide repeatedly while staying undifferentiated, and differentiation, which allows them to develop into specialized cell types. Stem cells contain immune modulatory, regenerative, and anti-inflammatory properties.[28,29]

- **Lower level – laser theray-**

Lower-level laser therapy (LLLT) has been demonstrated in numerous studies to lessen the seriousness of OM, while the precise mode of action is unknown. It has been [20]hypothesized that LLLT may lower reactive oxygen species and/or pro-inflammatory cytokine levels.[28-30]

- **Zonated water -**

Ozone's anti-inflammatory, antibacterial, It is a molecule with clinical applications in medicine and dentistry due to its biosynthetic (activator of lipid, protein, and carbohydrate metabolism), antihypoxic, bioenergetic, hemostatic, and analgesic properties.In situations of stomach ulcers brought on by stress, ozonated water was utilized. [28-30]

Antimicrobial agents

The findings in the literature for the usage of chlorhexidine are incongruous. A evaluation of a clinical trials employing chlorhexidine in a child patients slated for chemotherapy was carried out by [21]Nashwan . Four of the five trials that satisfied the inclusion requirements indicated a

[20] Hypothesized- strongest matches , imaginary

significant protective effect against the onset and higher grade of oral mucositis. Other research, however, suggests the chlorhexidine is ineffective at lessening the higher grade of mucositis.The findings of in the literatures for the usage of chlorhexidine are incongruous. A evaluation of clinical trials employing chlorhexidine in pediatric patients slated for chemotherapy was carried out by Nashwan . Four of the five trials that satisfied the inclusion requirements indicated a significant protective effect against the onset of action high grade of oral mucositis. [28-30]

- **Analgesics and anesthetics (pain treatment)**

Despite the fact that no medication has been proven to effectively treat mucositis, Strong analgesics (morphine rinses, sublingual methadone, or fentanyl patches) and anesthetic solutions (diphenhydramine, viscous xylocaine, and lidocaine) may help patients feel better by reducing their pain symptoms.[28-30]

- **Matrix Metalloprotese blocker**

Excessive levels of proteolytic enzymes, including matrix metalloproteases (MMPs), are known to be present in all chronic ulcers. In order to clear the ulcers and create a favorable environment for cells development, MMPs are in charge of proteolyzing protein [22]debris. Unfortunately, they also proteolyze cell matrix proteins. To provide a base for the new cells during the recovering process of new mucosal cells should stick to a matrix that the mother cells release before cell division Nonetheless, this matrix is unique to each cell and contains different proteins in predetermined amounts, including collagen, fibronectin, hyaluronic acid, elastin, and laminin. Ulcers cannot heal without this matrix because daughter cells are unable to proliferate and adhere. In actuality, MMPs inhibit daughter cell attachment and hence prevent cell proliferation in OM ulcers by destroying cellular matrix. An osmotically active hypertonic solution containing particular protease-inhibiting plant procyanidins (OROSOL) was used in one trial as a novel therapeutic strategy for the treatment of OM. It was able to cleanse the ulcers, eliminate impurities, and promote cell development. The OROSOL group shown significantly greater improvement during burning sensation, discomfort, infection grade, feeding abilities, and general mucositis when compared to the standard treatment groups; nevertheless, the rate of new ulcer development did not reduce.[28-31]

[22] Debris – distress

TREATMENTS ON ORAL MUCOSITIS-

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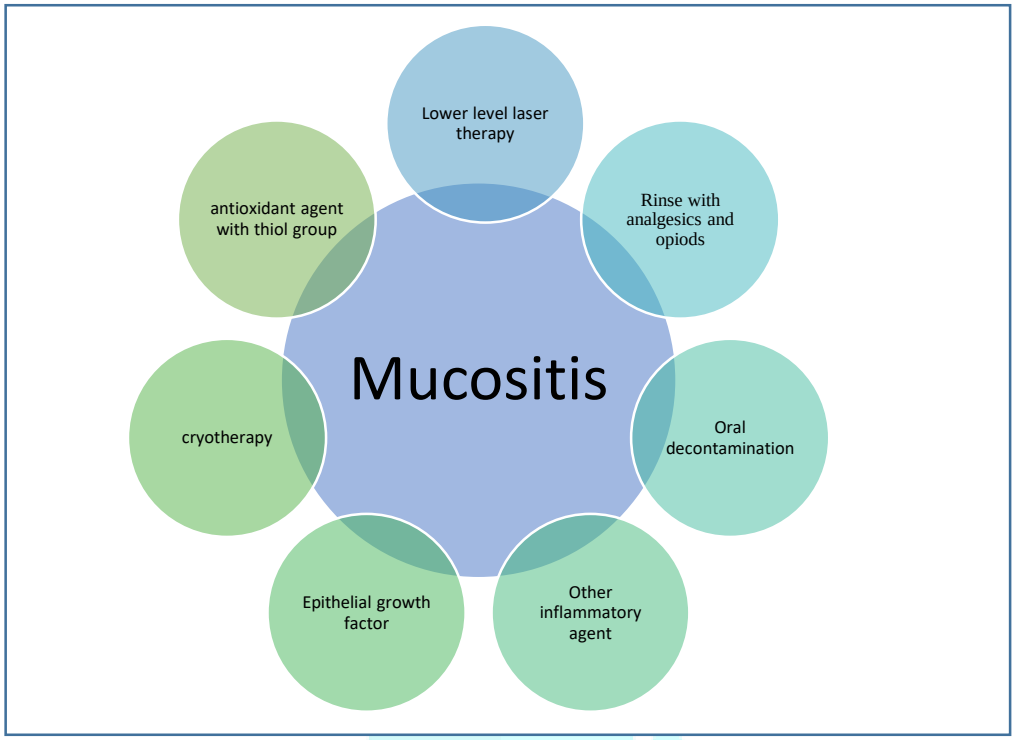

Figure 2 Treatment on oral mucositis

Natural products are used in om

1) *The bees products* [32-40]
2) *The Propolis* [33,34]
3) *The Royal jelly* [33-,35]
4) *The Aloe vera* [43,44]
5) *The Spondias mombin* [47]
6) *The Calendula officinalis* [48-51]

CONCLUSION-

In conclusion , oral mucositis is a very painful condition that commonly affects the patients undergoing treatments like chemotherapy and radiotherapy. It is characterized by inflammation, ulceration, and tissue damage to the mucosal lining of the mouth, which can lead to significant discomfort, difficulty in eating, swallowing, and speaking, as well as an increased risk of infections. The management of oral mucositis typically involves a combination of preventive measures, symptomatic relief, and supportive care to reduce pain and promote healing.

The detection of this disease some of the biomarkers like OPN and salivary cytokines are used. The prophylactic drugs like genclair and diphenhydramine mouthwashare used. Some of the natural product like honey and turmeric are used. Some of the novel

treatment are lower Level laser therapy and zonated water and for preventing the disease oral hygience maintenance is necessary.

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