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Article

Effects of Radiation on the Histology of the Tongue and Lip Mucosa in Rats : Preliminary Research

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Abstract. The tongue and lip mucosa, as tissues with high cell proliferation rates, are highly susceptible to injury caused by ionizing radiation. This study aimed to evaluate histological changes in the tongue and lip mucosa of rats after exposure to ionizing radiation at various doses. Nine rats were used, each consisting of three rats, divided into a negative control group (K) and three treatment groups receiving radiation doses of 13 Gy (30 seconds of radiation), 15 Gy (66 seconds of radiation), and 17 Gy (110 seconds of radiation). Samples of tongue and lip mucosa tissue were harvested after 7 days and processed for histological examination using Hematoxylin and Eosin (HE) staining at 100x objective magnification. The results of this preliminary study showed that radiation at 13 Gy caused epithelial erosion, loss of filiform papillae, subepithelial bullae formation, and acute inflammatory cell infiltration on the tongue. At 15 Gy, more extensive ulceration with subepithelial edema was observed. At 17 Gy, total epithelial loss with massive subepithelial edema and vascular dilatation occurs. This preliminary study concludes that the tongue mucosa exhibits greater radiation sensitivity than the lip mucosa, with a dose-dependent progression of damage ranging from erosion to total epithelial loss.

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1. Introduction

Radiotherapy is one of the primary modalities in the treatment of head and neck cancer. Although effective in targeting rapidly dividing malignant cells, the surrounding normal tissues are inevitably exposed to ionizing radiation, giving rise to various acute and chronic side effects. Among these complications, radiation-induced oral mucositis is one of the most clinically significant, greatly affecting the quality of life of cancer patients undergoing radiotherapy [1-3].

The oral mucosa is lined by stratified squamous epithelium which, due to its high cell turnover rate, is highly susceptible to the cytotoxic effects of ionizing radiation. Radiation-induced damage to the epithelial basal cells reduces the regenerative capacity of the tissue, subsequently leading to progressive epithelial thinning, erosion, ulceration, and in severe cases, total mucosal loss. These changes are typically accompanied by an acute inflammatory response characterized by neutrophil and immune cell infiltration [4-6]. Animal models, particularly rats, have been widely used to study oral tissue damage caused by radiation due to the anatomical and histological similarities of their oral mucosa to that of humans. Histological evaluation provides detailed information on the nature, extent, and progression of tissue damage at the cellular and structural levels [7-9].

The tongue, which is lined by specialized mucosa with filiform and fungiform papillae, and the lip mucosa represent two distinct oral microenvironments that may respond differently to radiation exposure. Understanding these differences in response is essential for developing targeted interventions to reduce oral complications from radiotherapy [1],[10-11]. Histological studies of the tongues of mice induced by mucositis using busulfan and infrared irradiation showed decreased epithelial thickness, lymphocyte infiltration, and a decrease in the number of blood vessels. These changes are consistent with previously reported animal models of oral mucositis. Albino mice receiving a single 13 Gy radiation dose to the head and neck showed significant oral mucosal damage. Histological examination of the tongues was performed using H&E staining to assess epithelial thickness and blood vessel count, and RT-PCR to assess apoptotic activity through bcl-2 expression. Animals receiving a cumulative dose of 40 Gy, partial to total erosion, edema, inflammatory infiltration, and ulceration were found, which damaged the structure and function of the tongue and lip mucosa (vermillion lip).

Histological assessment was carried out semi-quantitatively, including parameters such as erosion/ulceration, mucosal layer thickness, keratinization, lymphoid elements, and basal and suprabasal cell conditions). A single dose of 15 Gy exposure to the head and neck of rats resulted in severe morphological and functional changes in the salivary glands that were irreversible. The oral mucosa can also become dry and atrophic, causing ulceration and frequent recurrent injuries due to the loss of mucosal surface lubrication [12-15].This research is a preliminary study to determine the effective dose that will be used in further research which aims to to evaluate histological changes in the tongue and lip mucosa of rats after exposure to ionizing radiation at various doses.

2. Experimental Section

2.1. Study Design and Animal Groups

This study was conducted at the Biomedical Laboratory of the Faculty of Medicine, Universitas Baiturrahmah, the Radiotherapy Installation of Universitas Andalas Hospital, and the Anatomical Pathology Laboratory of the Faculty of Medicine,Universitas Andalas. An experimental design was employed using Wistar rats divided into four groups. Nine rats were used, each consisting of three

rats, divided into a negative control group (K) and three treatment groups receiving radiation doses of 13 Gy (30 seconds of radiation), 15 Gy (66 seconds of radiation), and 17 Gy (110 seconds of radiation). All procedures were carried out in accordance with animal research ethical guidelines.

2.2. Tissue Processing and Histological Staining

Following irradiation, rats were sacrificed at predetermined time points. Tongue and lip mucosa tissues were harvested, fixed in 10% neutral buffered formalin, and routinely processed for paraffin embedding. Samples of tongue and lip mucosa tissue were harvested after 7 days. Tissue sections of 4–5 µm thickness were stained with Hematoxylin and Eosin (HE) and examined under a light microscope at 100x objective magnification.

2.3 Histological Evaluation Parameters

Histological preparations were evaluated based on the following parameters: integrity of the stratified squamous epithelium (E), condition of the subepithelial stroma (SE), presence and extent of erosion or ulceration, loss of filiform papillae (tongue-specific), formation of subepithelial bullae or splits, presence of necrosis, degree of acute inflammatory cell infiltration (primarily polymorphonuclear neutrophils), vascular changes including hyperemia and lymphatic dilation, and condition of the muscular layer (M). These histological parameters were evaluated directly by the laboratory anatomical pathologist.

3. Results and Discussion

3.1 Histological Changes in the Tongue Mucosa

Control Group (K): Histological preparations of the tongue in the control group showed normal architecture consisting of intact stratified squamous epithelium (E) with clearly visible filiform papillae on the surface, a well-defined subepithelial stroma (SE), and an organized muscular layer (M) beneath.

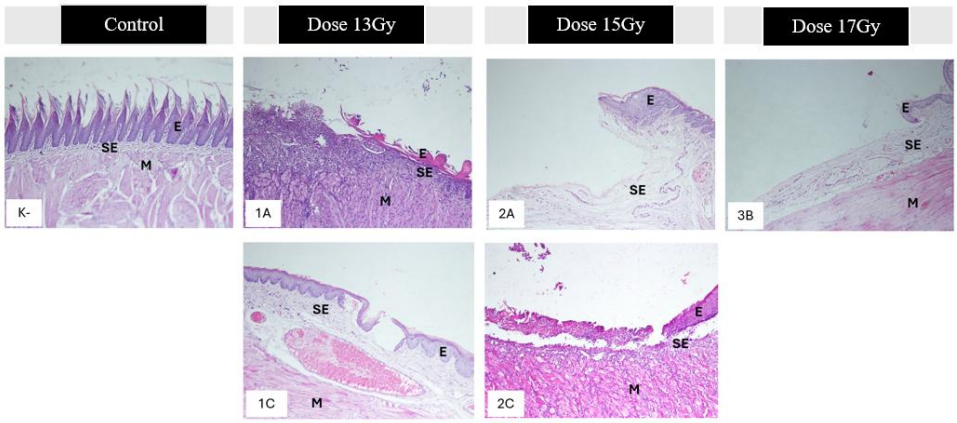

Figure 1. Histological Changes in Rat Tongue Tissue Following Radiation

The upper panel shows the negative control (K−) without radiation; 1A is the first sample given a radiation dose of 13 Gy; 2A is the first sample given a radiation dose of 15 Gy; 3B is the first sample given radiation at 17 Gy. The lower panel shows the third sample given a radiation dose of 13 Gy (1C), and 2C is the third sample given 15 Gy. No additional samples were available at 17 Gy. The rat tongue tissue shows stratified squamous epithelium (E), subepithelial stroma (SE), and muscularis (M).

Compared with the control, post-irradiation at 13 Gy (1A) revealed epithelial damage characterized by loss of filiform papillae, epithelial erosion, necrosis, and acute inflammatory cell infiltration, while the third sample (1C) showed only disappearance of filiform papillae, subepithelial

bullae formation, and hyperemic blood vessels. After 15 Gy irradiation, erosion and edema in the subepithelial stroma were evident (2A), while the third sample (2C) displayed findings similar to 1A epithelial erosion, necrosis, and acute inflammatory cell infiltration but with more extensive epithelial and subepithelial detachment compared with the 13 Gy dose. Following 17 Gy irradiation, the epithelium was totally lost with edematous subepithelium and dilated vessels (HE, 100x objective magnification).

States that the oral mucosa consists of three types: lining mucosa, masticatory mucosa, and specialized mucosa each with its own histological, clinical, and functional characteristics. The oral surface of the lips, cheeks, floor of the mouth, and ventral surface of the tongue is lined by non-keratinized stratified squamous epithelium. The oral mucosa is rich in nerve endings and specialized taste receptors on the dorsal side of the tongue. Successfully established an animal model of radiation-induced glossitis in Sprague-Dawley rats using a single dose of 30 Gy of X-rays. On days 5 to 6 post-irradiation, patterned mucosal redness appeared; and on day 35, the epithelial structure began to reappear, but the epithelial layer was very thin. Granulation tissue was seen at the base of the ulceration during the recovery phase. Noted that tongue histopathology in the mucositis group showed intense lymphocytic infiltration, decreased thickness of the squamous epithelial cell layer, decreased number of blood vessels, cell necrosis, and pseudo membrane formation. These changes were assessed using hematoxylin and eosin (H&E) staining [12],[16-17].

3.2 Histological Changes in the Lip Mucosa

Control Group (K): The lip mucosa of the control animals showed normal stratified squamous epithelium, an intact subepithelial stroma, and organized muscularis, consistent with normal tissue architecture.

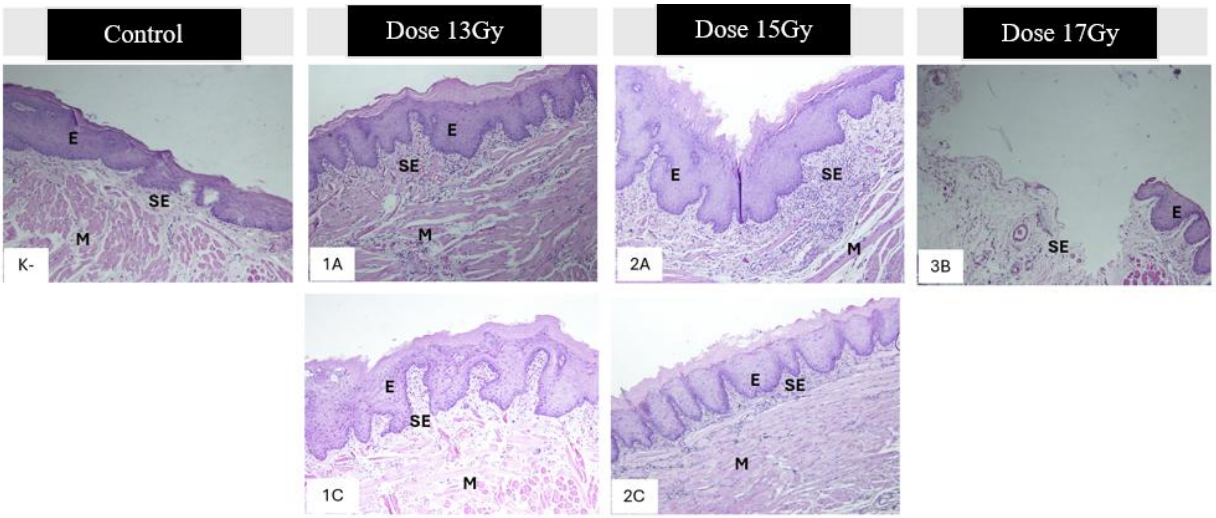

Figure 2. Histological Changes in Rat Lip Mucosa Tissue Following Radiation

The upper panel shows the negative control (K−) without radiation; 1A is the first sample given a radiation dose of 13 Gy; 2A is the first sample given a radiation dose of 15 Gy; 3B is the first sample given radiation at 17 Gy. The lower panel shows the third sample given a radiation dose of 13 Gy (1C), and 2C is the third sample given 15 Gy. No additional samples were available at 17 Gy. The rat lip mucosa tissue shows stratified squamous epithelium (E), subepithelial stroma (SE), and muscularis (M). Compared with the control, samples 1A, 1C, 2A, and 2C post-irradiation showed no marked differences except for inflammatory cell infiltration visible in the subepithelial stroma, while sample

3B showed loss of the epithelium down to the subepithelial stroma, representing ulceration (HE, 100x objective magnification).

This study demonstrated clear dose-dependent histological changes in the oral mucosa of rats following ionizing radiation exposure. The tongue mucosa displayed a more pronounced radiation response than the lip mucosa at lower doses, indicating a difference in radiosensitivity between these two types of oral tissue [1],[5],[7]. At doses of 13 Gy and 15 Gy, the tongue exhibited a progressive pattern of radiation-induced mucosal injury, including subepithelial splitting, vesicobullous lesion formation, necrosis, and ulceration with acute neutrophilic infiltration. These pathological changes resemble burn-type injury at the tissue level. The subepithelial splits observed in the early stages are consistent with disruption of hemidesmosomal adhesion between the epithelial basal cells and the underlying basement membrane, a known consequence of radiation-induced oxidative stress [4-6],[18].

The neutrophilic infiltration found in ulcerated areas reflects the body's acute inflammatory response to epithelial necrosis and exposure of the subepithelial connective tissue. Neutrophils serve as the primary defense mechanism through phagocytosis of necrotic debris and bacterial pathogens. Clinically, these histological changes correspond to the stomatitis or aphthous ulcers frequently observed in patients undergoing head and neck radiotherapy, and underscore the importance of standardized management protocols [2-3],[11],[19]. At 17 Gy, total loss of the epithelial layer made histological evaluation more challenging. Massive necrosis resulted in widespread tissue fragility, which likely contributed to additional mechanical damage during grossing and microtomy. These findings indicate that at higher radiation doses, the depth and extent of necrosis increase substantially, making tissue preservation and processing more technically demanding [1],[5],[7].

The relative resistance of the lip mucosa to low-dose radiation (13–15 Gy) compared with the tongue is likely attributable to several factors. The lip mucosa, unlike the specialized tongue mucosa, lacks papillary structures and may have a different epithelial turnover rate. In addition, regional differences in vascularization, tissue oxygenation, and basal cell proliferation rates may contribute to the observed difference in radiosensitivity [18],[20-21]. The vascular changes observed including hyperemia and lymphatic dilation are consistent with early radiation-induced vascular injury and increased vascular permeability, contributing to the subepithelial edema and blister formation that was observed. These findings align with the well-established pathophysiology of radiation-induced tissue injury, which involves oxidative damage to endothelial cells and disruption of microvascular supply [6,18]. Overall, these findings reinforce the clinical relevance of dose selection in radiotherapy planning for head and neck tumors. The tongue appears to be a particularly sensitive area, necessitating closer monitoring and early intervention to manage acute mucosal complications during and after radiation treatment [1],[3],[10].

The external surface of the lips is lined by skin (stratified keratinized squamous epithelium with hair follicles), the core is formed by skeletal muscle (orbicularis oris muscle), and the internal surface is lined by mucosal epithelium (stratified non-keratinized squamous epithelium). The mucosa is covered by the lamina propria, and the submucosa contains small salivary glands (labial salivary glands). The vermilion zone of the lips has long connective tissue papillae containing superficially located capillaries, which contribute to the clinically red appearance. The labial mucosa displays non-keratinized epithelium with a relatively flatter junction between the epithelium and connective tissue, in contrast to the vermilion zone which has more prominent connective tissue papillae.

The stratified squamous epithelium covering the lips is divided into four zones: an orthokeratinized epidermis with appendices (hair follicles, etc.), an orthokeratinized vermilion with a more prominent rete pattern, a parakeratinized intermediate zone that is PAS-positive, and a non- or parakeratinized labial mucosal epithelium. The thickness of the epithelium increases gradually from the cutaneous side to the mucosal side. The cytokeratin pattern changes across the intermediate zone with the loss of CK 1 and 10 from the cutaneous side, and CK 4, 13, and 19 from the mucosal side. Histological examination of gingival tissue in rats irradiated with 5 × 15 Gy showed

hyperkeratinization, not only in the oral gingival epithelium, but also in the gingival pocket epithelium. This animal model successfully demonstrated physiological and histological changes consistent with radiation injury in humans, and could be used for future therapeutic evaluation [16],[22-23].

Male Wistar rats were irradiated using X-rays at two different doses (8 Gy and 26 Gy) to induce low- and high-grade oral mucositis. H&E staining was used to determine the severity of mucosal damage, measuring the degree of epithelial defects, distortion of normal mucosal structures, and inflammatory cell infiltration. Tongue tissue was sectioned at 5 μm thickness and assessed by a pathologist blinded to the treatment. Macroscopic and microscopic examinations included the skin, lips, salivary glands, and oral mucosa. Oral mucositis on the tongue appeared as ulceration on the ventral surface of the tongue for doses of 75–85 Gy. Irradiated rats showed significantly reduced saliva production compared to controls. This preclinical model successfully replicated various normal tissue responses observed in head and neck cancer patients.

Ionizing radiation directly induces DNA double-strand breaks and generates reactive oxygen species (ROS) which in turn damage important biomolecules. Ferroptosis has been identified as the primary mode of cell death responsible for radiation-induced depletion of oral mucosal epithelial cells. Radiation-induced oral mucositis is clinically characterized by mucosal atrophy or ulceration, severe pain, and impaired barrier function. Found significant hyperkeratosis of the oral epithelium and fibroblast activation in the lamina propria of the oral mucosa in both exposed groups. Dermal fibrosis and lamina propria fibrosis significantly increased in the 60-day exposure group, and vascular congestion was observed in the parotid gland [24-27].

Exposure to ionizing radiation induces oxidative stress in the tongue, characterized by increased levels of malondialdehyde (MDA) and decreased total antioxidant capacity (TAC), superoxide dismutase (SOD), and catalase (CAT) activities. In addition, radiation exposure increases inflammatory cytokines TNF-α and IL-6, along with overexpression of NF-κB mRNA which plays an important role in lingual mucosal damage. Expression of proinflammatory cytokines and chemokines occurs transiently within 1–4 hours after irradiation, returns to normal levels at 24 hours, then reappears on days 3 to 5 and increases significantly on day 7, which coincides with the severity of histological tissue damage.

This new X-ray irradiation-induced glossitis model in mice is stated to be useful for investigating the pathophysiology of oral mucositis. An oral mucositis model in mice was created with various irradiation doses. Tongue tissue was analyzed using histological staining, immunohistochemistry, and Western blot. This study established that keratinocyte necroptosis via the RIPK3/MLKL pathway is an important mechanism contributing to the pathogenesis of radiation-induced oral mucositis. Mucositis is caused by the early effects of radiation on rapidly dividing mucosal basal cells, due to the impact of radiation on DNA replication and mucosal cell proliferation, resulting in decreased basal epithelial regeneration and ultimately mucosal atrophy, collagen damage, and ulceration of the tongue and lip mucosa [28-31].

4. Conclusion

The conclusion of this study indicates that ionizing radiation induces dose-dependent histological changes in the oral mucosa of rats. The tongue mucosa is more radiosensitive than the lip mucosa, showing progressive changes ranging from subepithelial bullae and erosion at lower doses to total epithelial loss at 17 Gy. This study is a preliminary test study so further research is needed for better results.

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