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Reviews

Irradiation Mucositis: A Reappraisal

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Irradiation mucositis is a complication of anticancer therapy. It is regarded as an unavoidable consequence of treatment. Recent studies have shown that this condition is probably a consequence of abnormal Gram negative bacillary carriage in the oral cavity. If this abnormal carriage is avoided then prevention or amelioration of irradiation mucositis may be possible.
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INTRODUCTION

IRRADIATION MUCOSITIS is an inflammatory reaction of the oral mucosa in response to irradiation of the oral tissues. Clinically its appearance is variable. It may present initially as a white patch on the mucosa that may appear to be hyperkeratinised [1, 2]. Alternatively, it can appear as erythema or hyperaemia due to vascular dilatation of the arterioles [3–5]. The lesions once established tend to lead to severe symptons as the therapy progresses. Often pseudomembranes form with concomitant ulceration and bleeding [3, 4]. Irradiation mucositis often results in the necessity for nasogastric feeding and difficulties in sleeping due to pain. The complications of irradiation mucositis may be so severe that a change in the planned treatment may be necessary [6].

THE AETIOLOGY OF IRRADIATION MUCOSITIS

The cause of irradiation mucositis is still not proven. In experimental animals, that have been irradiated, irradiation mucositis can be shown to be associated with a depletion in the progenitive layers of the oral epithelium [7]. This result in animals is not completely comparable with the condition in humans as in order to induce mucositis in animals high doses of irradiation must be used. It is acknowledged however, that the early responses to irradiation are in the cells of the oral mucosa that are rapidly dividing [8, 9].

The changes that occur in the oral tissues during irradiation also deplete the oral defence systems. There is a diminution in salivary flow with a concomitant change in its composition [10]. Amongst the changes in saliva is a decrease in salivary immunoglobulin A which is a potent regulator of the oral microbial population [11]. There are also changes in the sialoperoxidase and lysozyme activity in saliva [11]. There is some impairment of the mobility of the oral tissues which is especially marked when the irradiation mucositis is severe and painful. This leads to stagnation areas on the mucosa with consequent changes to the oral flora. This may lead to rampant caries and inflammatory periodontal disease.

The alteration in the oral mucosa is not confined to the progenitive layers. Changes have been shown in the surface of the oral mucosa. These changes lead to changes in the receptor sites for micro-organisms. The precise nature of these surface changes have still to be fully elucidated but fibronectin diminution and low intramucosal pH have been recorded [12]. Some of these changes have been attributed to macrophage activity, in particular to the production of elastase [13].

In health the oral mucosa has a number of distinct habitats which are colonised by micro-organisms that are able to establish a homeostatic community [14]. These homeostatic microbial communities are protective for the host by preventing or interfering with the colonisation of exogenous pathogens; this potent defence mechanism is called "colonisation resistance" [15, 16]. When the oral tissues are irradiated the colonisation resistance is practically abolished. Irradiation mucositis is caused by a combination of alteration of the normal oral microflora with concomitant changes in the tissues [17].

THE ROLE OF YEASTS IN IRRADIATION MUCOSITIS

There has been considerable interest in the role of yeasts in irradiation mucositis [18, 19]. The reason for this interest is that as irradiation progresses yeast numbers, in particular *Candida* spp. appear to increase. In addition, some clinicians thought that the formation of oral mucosal pseudomembranes was caused by the development of acute pseudomembraneous candidosis (thrush). Candidosis does occur in irradiated patients but it is probably not as common as was hitherto believed. Accurate measurement of oral yeast carriage show wide fluctuations in numbers which are probably related to salivary neutrophil concentrations and activity [20]. Accurate systematic trials with topical or systemic antifungals have consistently failed to prevent the development or to cure irradiation mucositis although these antimicrobials are still widely prescribed during radiation therapy [18].

GRAM-NEGATIVE BACILLI AND IRRADIATION MUCOSITIS

In a healthy patient the oral flora is composed of a mixture of facultative viridans streptococci, anaerobic rods such as *Prevotella*, *Porphyromonas* and *Fusobacterum* species together with imperfect yeasts and treponemes [15]. The use of irradiation therapy radically changes this flora allowing Gram-negative Enterobacteria and Pseudomonads to predominate [21].

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Extensive epidemiological studies have shown that Gram-negative bacilli opportunistically colonise only where there is underlying disease [22]. The presence of Gram-negative bacilli in the mouth represent abnormal carriage and contributes to the morbidity and mortality of the mucosa. The bacilli may also migrate to the gastrointestinal tract or to the trachea and lungs and cause life-threatening consequences. In addition, these micro-organisms release powerful endotoxins which themselves cause both systemic and local effects on the host [23].

PREVENTION AND TREATMENT OF IRRADIATION MUCOSITIS

If the role of Gram-negative bacilli in the aetiology of irradiation mucositis is recognised then it may be possible to prevent, treat or ameliorate the deleterious effects of irradiation mucositis.

Prevention could be achieved by preventing the Gram-negative colonising the mucosa. Such a concept has been called "selective decontamination" [17]. The use of this technique has been used to good effect in two clinical trials [23]. The agents used to achieve this effect were polymyxin E and tobramycin applied locally four times daily. Such a regimen has not yet been fully evaluated for treatment of existing irradiation mucositis but it holds much promise.

CONCLUSION

There is wide-spread belief that irradiation mucositis is an inevitable consequence of radiation therapy. If the concept of the role of Gram-negative bacilli in this process is accepted then treatment and preventative modalities can be designed to prevent this distressing complication of oral cancer treatment.

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