Oro-dental considerations in transplant recipients

Preeti Tomar Bhattacharya¹, Soumyabrata Sarkar¹, Rupam Sinha¹, Tanya Khaitan¹, Arpita Kabiraj², Soumi Ghanta¹

¹Department of Oral Medicine and Radiology, ²Department of Oral Pathology and Microbiology, Haldia Institute of Dental Sciences and Research, Haldia, West Bengal, India

Abstract

The modern scenario of ongoing successful organ transplantations has led to such patients presenting to their health care practitioners with oral complaints. Often these complaints are related to oral mucosal lesions or masses, which are either drug-induced or as a consequence of immunosuppression. Oral lesions in transplant recipients need to be identified, diagnosed, and treated efficiently in order to improve the quality of life and sense of well-being in these patients. This review appraises the recognition of plethora of oral problems that can arise in transplant recipients and their appropriate management by an oral physician.

Introduction

The field of organ transplantation is developing rapidly. Oral considerations in the transplantation population are vast, and new treatment strategies warrant continuous adaptation of oral care regimens to the changing scope of oral complications. Oral physician can come across with a variety of oral lesions in transplant recipients varying from oral infections, gingival overgrowths to neoplastic masses. The oral diagnosticians should have strong knowledge regarding the varied presentation of enormous lesions encountered in these patients and they must always keep themselves updated with the recent developments in the transplantation field to diagnose and treat any oral lesion. Nevertheless, the oral physician should also maintain an effective communication with the transplant team.

Oro-Dental Considerations [Table 1]

Infections

An organ transplant patient is more susceptible to oral infections of bacterial, viral or fungal origins, thus a comprehensive oral examination is a must. The clinical presentation of an oral infection appears to depend upon the patient’s ability to mount an immune response and level of immunosuppression. Oral infections must be diagnosed and treated early as local infections may lead to systemic involvement. Apart from this, systemic infections may also manifest orally. Culture and sensitivity testing of all types of infections are recommended in transplant recipients.

Bacterial infections

Bacterial infections such as dentoalveolar abscesses may not present in usual patterns in the transplant recipients. Bacterial infections are usually seen in the early postoperative period in solid organ transplantations. Both Gram-negative and Gram-positive bacterial species have been implicated. The increased incidence of dental caries in the post-transplantation period has been accounted but the actual cause is largely speculative. Even bacterial infections resembling pseudomembranous candidiasis have been reported in the literature.[1] This diverse presentation of bacterial infection with clinical resemblance to fungal infection delineates need of appropriate investigation in transplant recipients before initiating any treatment to avoid improper intervention.
amphotericin B.

Deep fungal infections may present as necrotic plaques on the palate of HCT recipients. The patient may succumb to these infections if not aptly managed. Deep fungal infections are arduous to manage and should be treated with intravenous amphotericin B.

Table 1: Oral manifestations in transplant recipients

<table>
<thead>
<tr>
<th>Disease</th>
<th>Oral manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial infections</td>
<td>Dentoalveolar abscesses, dental caries, bacterial infections resembling pseudomembranous candidiasis</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>Superficial - Angular cheilitis, pseudomembranous form, erythematous, hyperplastic type</td>
</tr>
<tr>
<td></td>
<td>Deep - Necrotic plaques.</td>
</tr>
<tr>
<td>Viral infections</td>
<td>CMV - Oral ulcerations - non-specific or aphthous-like, occur both on keratinized or non-keratinized oral mucosa, gingival overgrowth - hyperplastic gingivae, firm, lack of significant erythema, localized ulcerated areas</td>
</tr>
<tr>
<td></td>
<td>HSV - Clustered vesicles on an erythematous base, white plaques, ulcers at the junction of the vermilion of the lip</td>
</tr>
<tr>
<td></td>
<td>EBV - Hairy leukoplakia</td>
</tr>
<tr>
<td></td>
<td>Pseudohairy leukoplakia</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Squamous cell carcinoma, leukemias, lymphomas, Kaposi’s sarcoma</td>
</tr>
<tr>
<td>GVHD</td>
<td>Mucosal lichenoid hyperkeratotic lesions (striae, plaques, papules, and patches), erythema and inflammation, atrophy, pseudomembranous ulcerations, fibrosis, mucocceles, perioral fibrosis, salivary gland dysfunction, taste disorders, malignancies</td>
</tr>
<tr>
<td>Secondary to management of diseases</td>
<td>Gingival overgrowth, non-gingival soft tissue growths, aphthous ulcerations, mucositis, xerostomia, pain, bleeding, oral mucositis, paranasal sinusitis</td>
</tr>
<tr>
<td></td>
<td>In children - Enamel hypoplasia, enamel opacities, loss of lamina dura, teeth mobility, delayed teeth eruption, pulp narrowing and bony fractures, root hypoplasia, tooth agenesis or abnormalities, dentofacial abnormalities</td>
</tr>
</tbody>
</table>

GVHD: Graft versus host disease, CMV: Cytomegalovirus, HSV: Herpes simplex virus, EBV: Epstein barr virus

Fungal infections

The immunocompromised patients are more vulnerable to fungal infections, which may vary from superficial to deep fungal infections. These infections may manifest in a variety of patterns in the oral cavity. Seymour et al. quoted MacDonald and co-workers in their extensive review that due to accompanying neutropenia bone marrow transplant patients are prone to the higher occurrence of fungal infections than solid organ transplant recipients. Candidiasis remains the most frequently encountered fungal infection in these patients and more so in patients with concomitant diabetes mellitus. The candidal lesions can present as angular cheilitis, pseudomembranous form, erythematous or as hyperplastic type in hematopoietic cell transplantation (HCT) patients. It is imperative to keep in mind that candidiasis in these patients may not respond to usual antifungal drugs and may require treatment with amphotericin B.

Deep fungal infections may present as necrotic plaques on the palate of HCT recipients. The patient may succumb to these infections if not aptly managed. Deep fungal infections are arduous to manage and should be treated with intravenous amphotericin B.

Viral infections

High propensity to viral infections and reactivation of latent infections has long been recognized in the immunocompromised host.

The oral ulcerations coupled with cytomegalovirus (CMV) infection are either non-specific or aphthous like in clinical presentation and can occur both on keratinized or non-keratinized oral mucosa. Esophagus is the most commonly noted location in bone marrow transplant patients whereas lateral borders of the tongue can also be involved. Consequently, CMV should always be considered in the differential diagnosis for ulcerative lesions in immunosuppressed patients. CMV has also been implicated as a possible causative factor in gingival overgrowth, which is characterized by hyperplastic gingivae, firmness with the lack of significant erythema and localized ulcerated areas. Moreover, the infection of Kaposi’s sarcoma with CMV has also been outlined in the literature. Antifungal agents such as ganciclovir, valganciclovir or cidofovir have been used in the management of CMV infection.

Seymour et al. quoted various researchers regarding the relation between seropositivity and herpes simplex virus (HSV) infection. They stated that recurrent infections with HSV occur in more than 50% of the renal transplant recipients who are seropositive. The infections occur most frequently in the first 2 months after transplantation, last longer and are more severe than in seronegative patients. The HSV infections of the oral mucosa are characterized by clustered vesicles on an erythematous base. Characteristically, the vesicles later rupture and form an ulcerated area. HSV lesions may also manifest as white plaques that can be misdiagnosed as chronic hyperplastic candidiasis. Biopsy of such lesions is important to substantiate the diagnosis. The primary infection usually occurs in life and is asymptomatic. Oral recrudescent herpes lesions generally occur as vesicles or ulcers at the junction of the vermilion of the lip. Oral recrudescent human herpes viruses-1 infection is one of the major oral complications after bone marrow transplantation. These lesions are more extensive, aggressive, slow-healing, and painful in immunocompromised patients as compared to healthy patients. Management of herpes infection is directed toward pain control, supportive care, and definitive treatment. Antiviral drugs such as acyclovir and valacyclovir should be initiated at suppressive doses in HSV seropositive patients who are undergoing hematopoietic stem cell transplantation (HSCT) to suppress HSV reactivation. Acyclovir - resistant HSV is more frequently seen in this group of patients. In such cases, foscarnet is the drug of choice. Cidofovir has also been used in the treatment of multiresistant HSV infections.

Epstein barr virus (EBV) had also been related to the presence of oral hairy leukoplakia. Oral mucosa serve as a reservoir for EBV and immunosuppression result in cellular alterations which finally leads to differentiation of lingual epithelium. The duration of immunosuppression, CD4/CD8 ratios or serum concentrations of cyclosporine have no relation
with the development of hairy leukoplakia in organ transplant patients and in most instances is an incidental finding. The lesion usually remains symptom-free or can go into remission intermittently. Thus, the patient should be kept under observation. Clinically, it is important to differentiate between hairy leukoplakia and chronic candidal infections as these two conditions can have similar clinical patterns. Parallel infections of EBV and HSV in bone marrow transplant recipients may also occur. In such cases, prophylactic usage of acyclovir has been suggested. Oral hairy leukoplakia has been regarded as a marker for progression to AIDS by many researchers. On the contrary, no association between seropositivity and occurrence of oral hairy leukoplakia has also been reported.

A lesion with clinical and histopathological similarity to hairy leukoplakia has been referred to as "pseudo hairy leukoplakia." The condition is not associated with EBV and HIV infection. Both renal and bone marrow transplant recipients have shown the presence of "pseudo hairy leukoplakia." This again outlines the need of biopsy of all the lesions in these patients.

Malignancy

Organ transplant patients also appear to be more vulnerable to the development of malignant neoplasms. Solid tumors particularly squamous cell carcinoma arises more commonly in patients who develop graft versus host disease (GVHD), however, the patients undergoing allogeneic HSCT are at high risk of developing secondary neoplasms, particularly leukemias and lymphomas.

It is believed that chronic antigenic stimulation from the presence of the allograft may be responsible for the increased frequency of lymphomas. Apart from this, viral oncogenesis may also play a significant role as these patients are more susceptible to viral infections owing to their immunosuppressed status. Oncogenic viruses such as human papillomaviruses may contribute to squamous cell carcinoma of the buccal mucosa after HSCT. Many authors have strongly suggested that, irradiation is a major risk factor for post-transplant malignancies. A case of rapid progression of leukoplakia to squamous cell carcinoma in a liver transplant recipient has also been accounted in literature thus emphasizing the fact that premalignant lesions of oral cavity may also serve as a potent risk factor apart from immunosuppression in developing malignancies.

Smoking, alcohol, male gender, and older age are considered the most important risk factors of oral cancer.

The renal transplant patients are particularly prone to develop lip cancer, especially if there is increased exposure to sunlight. Lip cancer may be superficial, multiple or atypical in appearance in these patients. Kaposi’s sarcoma and squamous cell carcinoma can arise in gingival overgrowths in organ transplant patients. Post-transplantation lymphoproliferative disorder is a well-documented complication of solid organ or bone marrow transplantation. It ranges from benign B-cell hyperplasia to malignant lymphoma. A case of EBV-associated non-Hodgkin’s lymphoma presenting as a gingival ulceration has been reported. The delineation of an atypical presentation of oral malignancies in this group of patients.

The increased incidence of malignancy involving the mouth and associated structures in organ transplant recipients would vindicate a regular screening program. Patients should be examined every 6 months and any suspicious lesion must be biopsied. The patient should be advised to avoid smoking, sun exposure, sunbeds and to use lip protective emollients.

GVHD

GVHD is a clinical syndrome where donor-derived immunocompetent T-cells react against patient tissues directly or through exaggerated inflammatory responses following allo-HCT. The primary target organs of GVHD classically have been those of skin, liver, and gastrointestinal tract. However, the oral cavity is also frequently involved, possibly only second to cutaneous involvement. Acute GVHD can occur as early as 1 week post-HCT or following donor lymphocyte infusion (DLI). In contrast, chronic GVHD (cGVHD) can have an onset of 70 days or later post-HCT or DLI and continue many years. Clinically, acute and chronic oral GVHD are characterized by mucosal lichenoid hyperkeratotic responses (striae, plaques, papules, and patches), erythema and inflammation, atrophy, pseudomembranous ulcerations, fibrosis, mucoceles, perioral fibrosis, and salivary gland dysfunction and taste disorders. Oral cGVHD may obscure or mimic oral dysplasia and malignancies and biopsy can only discriminate between the two conditions. The goals of oral GVHD management center primarily on ameliorating symptoms (such as pain, sensitivity, and oral dryness), maintaining oral function, and treatment of ulcerative lesions as applicable.

Other oral manifestations

It is well recognized that long-term administration of both cyclosporine and calcium channel blockers is associated with gingival overgrowth. The prevalence of gingival overgrowth increase to 50% when patients are medicated with the combination of cyclosporine and nifedipine. The gingival overgrowth usually occurs within 3 months and the labial gingiva with canine region appears to be the predilection site. Age is also an important factor for this unwanted effect since children are more susceptible than adults. The pathogenesis of either cyclosporin or nifedipine induced gingival overgrowth is still under research. The recent studies indicate that cyclosporine affects signaling molecules in gingival fibroblasts inducing an increase in activator protein 1, interleukin 6, transforming growth factor β1, which increase the expression of fibrinogenic molecules and promote gingival overgrowth. Good oral hygiene should be maintained because inflammatory components may aggravate the condition. Surgical intervention may be unavoidable in severe cases.

Non-gingival soft tissue growths have also been asserted in allogeneic HCT recipient. These lesions can be seen in the buccal mucosa, alveolar mucosa, and elsewhere. The proposed mechanism is the dual effect of cyclosporine and chronic inflammation or trauma. Cyclosporine may play a role in
disturbances due to altered vitamin D, calcium, and phosphate in children with chronic kidney diseases. Other distinguished ulcerations.

Oral mucositis may occur more frequently in bone marrow transplant recipients. It can be triggered by the use of antimicrobial drugs. A significant resolution of oral mucositis and concomitant oral infections after 1 week of commencing chlorhexidine mouth rinses has been reported. A significant resolution of oral mucositis and concomitant oral infections after 1 week of commencing chlorhexidine mouth rinses has been reported. A significant resolution of oral mucositis and concomitant oral infections after 1 week of commencing chlorhexidine mouth rinses has been reported. A significant resolution of oral mucositis and concomitant oral infections after 1 week of commencing chlorhexidine mouth rinses has been reported. A significant resolution of oral mucositis and concomitant oral infections after 1 week of commencing chlorhexidine mouth rinses has been reported.

There is an increase in the occurrence of enamel hypoplasia in children with chronic kidney diseases. Other distinguished disturbances due to altered vitamin D, calcium, and phosphate metabolism are enamel opacities, loss of lamina dura, teeth mobility, delayed teeth eruption, pulp narrowing, and bony fractures. Apart from these depictions, tooth agenesis or abnormalities, root hypoplasia and dentofacial abnormalities have been reported in children who have undergone HCT. It has been postulated that pre-transplant long-term high-dose chemotherapy may be responsible for these disturbances.

Pre and Post-transplantation Considerations

A detailed clinical examination of the dentition, periodontium, and oral mucosa as well as the head and neck areas, including the lymph nodes and the salivary glands, is paramount. The patient should be taught to maintain appropriate hygiene and perform an oral examination on regular basis at home. This procedure enables the patient to constantly monitor his or her own condition and aids the health care professional in early diagnosis of any pathology. Medical consultation should be sought before any dental treatment. All necessary treatments should be performed before anticipated transplantation. Any elective treatment should be undertaken only in stable post-transplantation period under appropriate antibiotic prophylaxis. The patient’s medical history should be updated with each dental appointment and the oral physician must maintain appropriate communication with the surgical transplant team. The details of the basic oral care have been listed in Table 2.

Conclusion

Oral considerations in the transplantation population are vast. It is now well recognized that immunosuppressed organ transplant patients are more susceptible to various oral infections and malignant neoplasms, with the mouth and associated structures being the “target area.” It is essential that the dentist familiarize himself or herself with the special needs of these patients. Since these patients can present with atypical manifestations, advanced investigations should be used to ascertain the diagnosis. This is important not only for instituting specific therapy but also for avoiding the inappropriate empiric treatment of such lesions. Prevention and/or diagnosis and management of oral complications in transplant recipients by the dental team can improve the success of a transplant by reducing morbidity, improving the quality of life, and reducing the cost of care.

Authors Contributions

Dr. Preeti Tomar Bhattacharya: Concept, manuscript preparation, editing; Dr. Soumyabrata Sarkar: Designing and formatting, manuscript preparation; Dr. Rupam Sinha: Manuscript preparation, references; Dr. Tanya Khaitan: Manuscript preparation and editing; Dr. Arpita Kabiraj: Manuscript preparation and editing; Dr. Soumi Ghanta: Manuscript preparation, references.
References
