Review Article

Oral Manifestations of Renal Patients Before and After Transplantation: A Review of Literature

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ABSTRACT

Oral mucosa can be affected in many systemic diseases such as Chronic Renal Failure (CRF). Many metabolic and hematologic disorders develop in patients with CRF which can also affect oral cavity. Oral mucosa, teeth, salivary glands and jaw bones are affected. Although hemodialysis can improve many of systemic features but the best treatment is renal transplantation. In addition to previous features, several oral manifestations emerge as a consequent of transplantation. Here we reviewed these manifestations.

Keywords: Oral Manifestation, Renal Transplantation, Review.

INTROUDUCTION

Like any other systemic conditions, chronic renal failure (CRF) can cause oral manifestations.[1] Patients with CRF may present as unique signs of multi-system disease affecting the kidneys(such as vasculitis or diabetes mellitus) or as common oral pathologies found at an increased prevalence in patients with CRF.[2,3] The prevalence of oral lesions is affected by the accompanying systemic disease. For example diabetic uremic patient have more oral manifestations compared with non-diabetic uremic patients.[4] In pre-transplantation stage (PRTS), impaired renal function can lead to different hematologic and metabolic disorders[5] which involve oral cavity and jaw bones, can interfere with food intake and lead to increased catabolism and deterioration of the condition.[6]Some of the disorders reverse after dialysis and renal

transplantation but a group of them persist in spite of best medical treatments. Immunosuppressive treatment exacerbates the condition by increasing susceptibility to infections and malignancies. Here we reviewed oral manifestations in pre- and post-transplantation stages (PTS) in renal patients.

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Pre-trans plantation stage (PRTS)

Renal failure leads to a state of intoxication known as uremia, which is associated with accumulation of metabolic waste products and multi organ involvements. Hematologic, electrolyte, endocrine and skeletal disorders are the main changes.[7] These alterations lead to significant concern in dental management especially oral surgical procedures.[8] Approximately 90% of uremic patients have soft tissue and jaw bone changes.[2]

Dental disorders

Although total amount of saliva is decreased, [9] urea content is elevated which can decrease metabolic end products of bacterial plaque. This reduction results in increasing the buffering capacity of saliva and decreasing dental caries particularly in children,[10,11]in spite of poor oral hygiene, high sugar content of diet and low-protein in this group of patients.[1] If CRF begins earlier in life, enamel

hypoplasia may develop which[1,9,10,12] is due to disturbances in calcium and phosphate metabolism.[10] Long-term corticosteroid therapy can implicate the situation, too.[2] In developing dentition red-brown discoloration, delayed or altered eruption may be seen.[10,13-15] Due to frequent regurgitation and vomiting induced by uremia , medications and nausea related to dialysis severe erosions in lingual surfaces of teeth may occur.[1,12,16] As buffering capacity and flow rate of saliva decreases, erosion develops.[16] Tooth mobility and drifting result in malocclusion. Periapical radiolucencies and root resorption are associated with mobile teeth.[12] Painful responses to thermal and electrical tests and percussion can be seen.[2] Impaired calcium and phosphorus balance can cause narrowing of pulp chamber and increasing the incidence of dental calculus.[10] Routine follow up is required to diagnose pulp obstruction at early stage to prevent further complications specially in children.[10] Because of bone rarefaction the teeth appear more radiopaque in dental radiographs.

Soft tissue and salivary changes

One of the early symptoms may be a bad metallic taste and unpleasant odor in the mouth particularly in the morning.[12] This uremic fetor, an ammoniacal odor is a typical sign of all uremic patients which is caused by the high concentration of urea in the saliva and its subsequent breakdown to ammonia.[12, 17, 18] Salivary urea level correlates well with the BUN so that saliva can be used as a non invasive diagnostic tool.[19]An acute rise in BUN (>150 mg/dl) may result in uremic stomatitis which disappear 2 to 3 weeks after medical intervention and decreasing BUN. [12] Uremic stomatitis is considered as a kind of chemical burn. The red burning mucosa is covered with gray exudates and would be ulcerative later. Four types of uremic stomatitis have been described: erythemo-pultaceous, ulcerative, hemorrhagic and hyperkeratotic.[12]This lesion is painful and appears on the ventral surface of tongue and anterior mucosal surfaces.[2] Another rare outcome of excessive BUN level (>55 mg/dl) in oral cavity is uremic frost, white patches, which are remaining urea crystals after evaporation of saliva.[2]The most prevalent mucosal finding is pale mucosa as a result of normochromic/normocytic anemia[2,12] caused by decreasing of erythropoietin but increasing hemolysis due to dialysis procedure and uremic toxins.[7,2,20,21]Lichenoid reaction(drug induced) and pyogenic granuloma are frequently observed in CRF patients .[12,22] Caroten –like material deposition gives oral mucosa an orange-red color. There is controversy related to gingival and periodontal inflammation. In some studies low frequency of periodontal diseases has been reported due to suppressed immune system after transplantation and uremia[10, 23] but the other studies showed higher frequency of periodontal diseases specially in children.[7,24]Metastatic calcifications occur when calcium –phosphate exceeds 70 mg/dl.

The frequent sites are sclera, eye canthous and other subcutaneous tissues, like perioral area. Skeletal, cardiac muscles and blood vessels don't spare this entity. Severe xerostomia is a common finding[13] with a prevalence of 73.2%. Its possible cause is a combination of salivary gland involvement, inflammation, drug side effects (especially anti-hypertensive drugs), dehydration and mouth breathing (kussmaul's respiration).[9,12] In some cases salivary gland swelling and retrograde parotitis[23] can be seen as a result of xerostomia. Impaired salivary function has been related with more prevalence of oral manifestations.[25]Epstein et al. suggested that saliva can be used as a diagnostic index to aid in maintaining renal patients at appropriate fluid balance.[26] Dysgusia is another finding.[9] Previous reports indicated that sour and sweet tastes were more seriously affected than bitter and salty tastes.[27,28] High levels of urea, dimethyl and trimethyl amines and low level of zinc may be implicated factors.[27]

Gingival bleeding, petechia and echymosis develop in labial and buccal mucosa, soft palate and tongue borders as a result of qualitative and to a lesser degree, quantitative platlet defects.[12,9,29,8]Anticoagulants used for hemodialysis can be a predisposing factor.[30]

Since lymphocyte number and function, neutrophil chemotaxis and phagocytosis decrease, delayed healing and susceptibility

to infections occurs.[31]Although dialysis improves several mucosal alterations, but some disorders such as uremic odor, taste alteration and xerostomia persist.

Jaw bone alterations

Other oral manifestations of renal disease are related to renal osteodystrophy(RO), a common condition which is considered as a dysfunctional mineral homeostasis.[32] These manifestations appear in late stage.[1] Disorders in calcium and phosphorus metabolism, abnormal vitamin D metabolism and increased compensatory parathyroid activity are the main causes.[33] Secondary hyperparathyroidism develops when the kidney secretes more phosphate ions and also osteoblastic and osteoclastic activity increases.[33]

Radiographic features of RO in mandible or maxilla are bone demineralization, loss of trabeculation, ground glass appearance, total or partial loss of lamina dura, abnormal socket healing, giant cell lesions or brown tumors and metastatic calcifications.[21,34] These changes appear most commonly superior to the mandibular canal or in molar region .Generalized rarefaction is secondary to osteoporosis. Malocclusion due to tooth mobility and collapsed tempromandibular structures can be seen.[35] Bone loss is present but there is no apparent periodontal pocket formation. In areas such as floor of the antrum, lamina dura and angle of the mandible, the compact bone becomes thin .It has been proposed that decreased thickness of mandibular angle correlates well with the degree of RO. Lack of lamina dura, resorption and deposition of sclerotic bone after dental extractions called "socket sclerosis "may be observed as a result of abnormal bone metabolism.[34]This may remain for years after tooth extraction.[36] There are few reports of macrognatia.[37] Pathologic fractures of jaw bones may occur which complicate dental extractions and periodontal surgical procedures.[21,23,32] These findings in addition to osteomalacia of jaw bones needs accurate evaluation of renal patients before any oral and maxillofacial surgery specially implant replacement.[38] Cortical expansion and gingival swelling originated from giant cell lesions may occur.[34]

Post-transplantation stage (PTS)

Immunosuppressants used to prevent transplant rejection. Although have serious complications but its benefits outweigh risk. Perhaps gingival enlargement (GE) is the most known complication of renal transplantation. Different studies have established such a finding with a prevalence of 22 to 81%[39-41] in patients.[42,43] The main cause of GE is cyclosporine, but an immunosuppressant and calcium channel blockers such as Niphedipine can exacerbate GE as well.[39,40,44,45] In a study GE was more severe in patients taking both drugs.[39] Although some studies failed to find a relation between dose of drug and GE, in one survey a clear relationship was observed.[39]

Some investigators have reported resolution of GE after drug dose reduction.[47] Periodontal status can get worse after GE. Bacterial, viral and fungal infections may be silent due to suppressed immune response. Non-pathogen organisms can be pathogen for these patients. Common viral infections are caused by CMV (Cytomegalovirus), VZV(varicella zoster virus), HSV (herpes simplex virus) and EBV(Epstein-Barr Virus).[2] They appear as ulcers (CMV,HSV,VZV,...), masses (HSV,CMV,..) and hairy leukoplakia (EBV).[2] HSV is the most common pathogen in oral cavity and along with CMV are the major causes of death and morbidity in recipients of organ and tissue transplants and affect 50 to 70 % of the patients.[48]

CMV infection occurs in the first few months after transplantation coinciding with maximal immunosuppresion.[10]Some authors have found a relationship between CMV infection and severity of GE.[49]Hairy leukoplakia (HL) develops in lateral borders of tongue and usually is a marker of HIV-related immunodeficiency[50,51] with a prevalence of 9.2 to 20%.[52,53] and also in PTS patients its prevalence is about 11.3%. The etiology of this lesion is Epstein - Barr virus (EBV). Although some previous reports, focused on the reactivation of EBV (latent in basal

epithelial layers) [54] but some investigations established a primary infection limited to upper epithelial layers mediated through B-lymphocytes.[39, 55] Oral leukoplakia is considered as a precancerous condition in normal population.The prevalence is reported from 2% to 17% in different ethnic groups.[56]In one study the prevalence was 10.7%(compared with 5.6% in healthy controls).[39] Interestingly the difference was more significant between two groups in women (16.4% vs 3.4%).[39]

The exact cause remains obscure, but drug therapy and immunosuppressants should be concerned. Candida and deep seated fungal infections can cause disseminated or systemic infections that can be fatal if neutropnia exists. Oral candidosis is also a fairy common oral finding. The prevalence has been reported about 10.1 %. [39]

Smoking and alcohol are suggested risk factors in otherwise healthy patients but it is not the case for PTS patients. Despite the high prevalence of skin warts in PTS patients[58] oral warts are not so common (only 1.2%).[39]Another concern is high risk of malignancy due to deficient antitumoral and antiviral function of the immune system. The frequency of post-transplantation tumors is 2 – 4 folds compared with the non-transplanted population and the distribution of tumors is also different. [59]

The most frequent tumors are non-melanoma skin cancer lymphoma (especially non-Hodgkin lymphoma),[12] Kaposi's sarcoma, (especially in Middle East), [60] oral cancer and anogenital tumors which are often associated with oncogenic viruses (e.g.HHV8 in Kaposi's sarcoma and HPV in anogenital cancers). [33] Tumors in head and neck region include skin, lip, oral and thyroid cancers. [61] Other risk factors for tumor development are gender, age (older adult), the presence of preformed antibodies before transplantation and the time of immunosuppressant therapy. Non- melanoma skin cancers are more prevalent in PTS patients (21.9%) but it is not yet documented for intraoral malignancies. [39, 62] Since there is a relation between duration of immunosuppressive drug therapy and skin cancers, [63]by increasing the survival rate of transplanted patients ,higher prevalence of oral cancers could be expected.[39] However, two cases of malignant changes in drug-induced GE have been reported.[62,64] Over immunosuppresion can cause mucositis and unusual bone loss.[65] Bleeding appearance presents as petechia and echymosis.[8] High frequency of caries is observed ,in which drugs, end organ diseases, xerostomia or decreased salivary IgA levels have been suggested as etiology.[39] The high frequency of intraoral lesions in PRTS and PTS patients mandates a regular screening of oral mucosa and lips.

SUMMARY

Like any other systemic disease, chronic renal failure has oral manifestations .Being familiar with these manifestations is important for oral health care workers.

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