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Manifestations of Renal Disease: 'Uremic Syndrome': Review Article

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ABSTRACT

Renal disease mostly affects the middle aged and elderly population, and has a normally chronic course. The oral manifestations of thisproduce a variety of signs and symptoms, that when properly recognized and diagnosed is very helpful in their management. Soft tissue as well as bone changes occurs in the renal disease patients causing uremic stomatitis and renal osteodystrophy. A careful case history taking and examination of all the patients becomes mandatory in order to find out an underlying serious renal disease and to avoid any potential complications.

Key words: Uremic stomatitis, renal osteodystrophy, Dialysis, End stage renal disease.

INTRODUCTION

'Mouth is the mirror of the body which reflects systemic diseases' wrote Sir William Osler, famous physician. True to the statement many illnesses manifest in the oral cavity producing a variety of signs and symptoms which when properly investigated leads us to the diagnosis of systemic diseases.

Manifestations of renal disease results in uremic syndrome,comprising biochemical disturbances, gastrointestinal symptoms, neurologic signs and symptoms,hematologic problems,calcium and skeletal disorders(renal osteodystrophy), cardiovascular manifestations, respiratory symptoms, immunologic changes, and oral manifestations.

Two groups of symptoms affect the patients,' one leading to altered regulatory and excretory function, fluid volume,electrolyte abnormalities,acid-base imbalance,accumulation of nitrogenous waste and anemia and the other symptoms affectthe cardiovascular and gastrointestinalsystems and also produce hematologic syndromes and others.

Biochemical Disturbances

Metabolic acidosis is the common biochemical disturbance in renal failure patients. In metabolic acidosis hydrogen ion concentration decreases, leading to systemic acidosis resulting in lower plasma pH and bicarbonate ion.Due to reduced nephron mass ammonia excretion decreases. Symptomslike anorexia, lethargy, nausea,and the deep sighing respirationcalled kussmaul's breathing,with increased CO_2 excretion occurs. Potassium balance is affected leading to hyperkalemia. A normally functioning kidney shows great flexibility by excreting and conserving sodiumin response to changing intake. At End Stage Renal Disease (ESRD)oliguria results leading tosodium retention. This leads to edema, hypertension and congestive heart failure.

Gastrointestinal Symptoms

There occur a myriad of symptoms involving theoesophagus, stomach, duodenum and the pancreas. The most commonsymptoms arenausea,vomiting and anorexia.In the late stage of renal failure gastrointestinal inflammations like gastritis, deodinitis and oesophagitis result. Digestion of hemorrhagic blood causes a rapid increase in Blood Urea Nitrogen (BUN) levels.

Neurologic Signs and Symptoms

Central as well as peripheral nervous systems may be involved. The degree of cerebral disturbance roughly parallels with the degree of azotemia.The electroencephalogram (EEG) is abnormal and is commensurate with metabolic encephalopathy. With progressive disease, asterixis, myoclonic jerks, central nervous system (CNS) irritability and seizures may occur. The predominant patient complaints are paresthesia or "burning feet" that may progress to muscle weakness, atrophy and paralysis.

Hematologic Problems

Anemia and increased bleeding. Anemia is usually normocytic and normochromic due to decreased erythropoiesis in the bone marrow. In dialysis patientsanemia results due to frequent blood samplingand loss of blood in hemodialysis tubing and coils.Bleeding is a significant problem in end stage renal disease (ESRD).

Calcium and Skeletal Disorders (Renal Osteodystrophy)

Skeletal changes that result from chronic kidney diseasecausedisorders incalcium and phosphorous metabolism,abnormal vitamin D metabolism and increased parathyroid activity.Kidneys are unable to convert vitamin D into its active form.So,in early renal failure,intestinal absorption of calcium decreases.On Sunlight Exposure,7-dehydroxycholesterol present in the skinis converted to Cholecalciferol (vitamin D3) which is metabolized in the liver.25-hydroxycholecalciferol (25-HCC)a biologically active form, is further converted in kidney parenchyma, to1, 25-dihydroxycholecalciferol (1, 25-DHCC) or21, 25-dihydroxycholecalciferol (21, 25-DHCC).When serum calcium level is high, 25-HCC is metabolized to 21, 25-DHCC; conversely, a hypocalcemic state initiates the conversion of 25-HCC to 1, 25-DHCC.Impaired calcium absorptiondue to chronic kidney disease causephosphate retentionand a decrease in serum calcium level resulting in hypocalcemia. This results in compensatory parathyroid activity leading to the production of paratharmone which increase the excretion of phosphates,and decrease the excretion of calcium, and augments the release of calcium from bone.

Compensatoryhyperparathyroidism (HPTH) occur leading to skeletal changes. These changes can appear before and during treatment with hemodialysis.In some cases, renal osteodystrophy becomes worse during hemodialysis.Hemodialysis is a life saving therapy but, does not correct the crucialcalcium-phosphate imbalance.Some of the bone changes that result arebone remodeling,osteomalacia,osteitis fibrosa cystica,(a rarefying osteitis + fibrous degeneration + cystic spaces) and osteoscelerosis.

Bone lesions may involve the digits, clavicle,acromioclavicular joint and lesions like mottling of the skull,erosion of distal clavicle and margins of symphysis pubis,rib fractures andnecrosis of femoral head. Jaw manifestations involve bone demineraralization,decreased trabeculation,and "ground glass" appearance,loss of lamina dura,radiolucent giant cell lesions,and metastatic soft-tissue calcifications. In children, it results in osteomalacia, bone softening leading to deformities of the ribs, pelvis and femoral neck (renal rickets). Early changes aredetectable only byhistological orbiochemical means.For bone changes to be detectable it needs more than 30% bone mineral loss.Treatment consists of protein restricted diets, phosphate binders, and vitamin D supplements.If it fails parathyroidectomy is indicated.

Cardiovascular Manifestations

Hypertension and Congestive Heart Failure are common manifestations of uremic syndrome.Alterations in sodium and water retention account for 90 % of cases of hypertension in chronic renal failure patients.

Respiratory Symptoms

Kussmaul's respiration,the deep sighing breathing seen in response to metabolic acidosisis seen withUremia.Initially,there is dyspnea on exertion.Other respiratory complications like pneumonitis and "Uremic Lung"result from pulmonary edema associated with fluid and sodium retention and or Congestive heart failure.

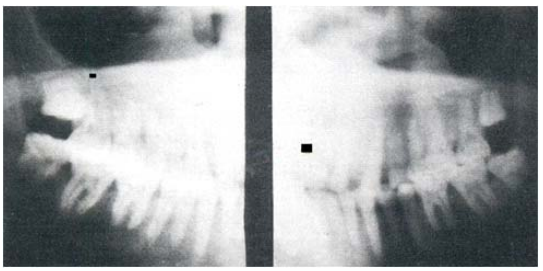
Immunologic Changes

Altered host defense and reduced immunocapacity due to uremic toxemia. Uremic plasma contains nondialyzable factors that suppress lymphocyte responses that are manifested at the cellular and humoral levels, such as granulocyte dysfunction, suppressed cell-mediated immunity, and diminished ability to produce antibodies. Also impaired or disrupted mucocutaneous barriers decrease protection from environmental pathogens.

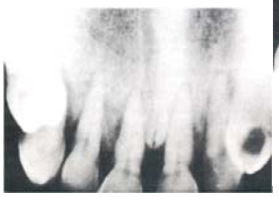
Oral Manifestations

Foul odor, bleeding tendency, xerostomia, renal osteodystrophy, uremic stomatitis, gingival hyperplasia, periodontal problems, enamel hypoplasia, severe erosions and candidal infections tend to occur in chronic renal failure patients under hemodialysis and in renal transplant patients[7].Chronic renal disease leads to 'uremic stomatitis.' It was first mentioned by Lancereaux in 1887 and described by Barie in 1889[3].The clinician may detect an odor of ammonia or urine in the patient's breath[10]. There may be a variety of changesas disease progresses through an azotemic to uremic state. In renal patients 90% show oral symptoms ofuremia. Presenting signs are ammonia like taste and smell, stomatitis,gingivitis,hypo-salivation, xerostomia and parotitis. There is bad taste and odor in the mouth, particularly in the morning. This uremic fetor an ammoniacal odor is due to high concentration of urea in the saliva and its subsequent breakdown to ammonia.Salivary urea levelscorrelateto blood-urea-nitrogen (BUN) levels.An acute rise in BUN level to a value > 150mg/dL, may result in uremic stomatitis, regarded as a chemical burn or as a general loss of tissue resistance and inability to withstand normal and traumatic influences, and which may appear asan 'erythemopultaceous form characterized byred mucosa covered with a thick exudate and a pseudomembrane or as an ulcerative form characterized by frank ulcerations with redness and pultaceous coat.'Rarely white plaques called 'uremic frost'may form intraorally as in the skin, due to 'residual urea crystals left on the epithelial surface after skin perspiration evaporates or as a result of decreased salivary flow.'[1] The clinical appearance occasionally has been known to mimic oral hairy leukoplakia.[10]

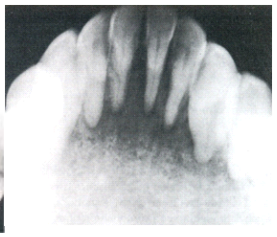
Radiological features of renal osteodystrophy



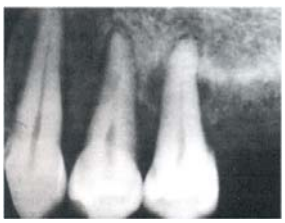
OPG showing trabecular changes Erupted 3rd molars – without fully developed root formations



Maxillary anteriors
Loss of trabeculation



Mandibular anteriors
Loss of trabeculation



Loss of lamina

OPG showing socket sclerosis of extraction sites; Teeth extracted – 6 years before the OPG and 2 years before the diagnosis of ESRD

More commonly, there is significantxerostomiadue to direct gland involvement, chemical inflammation, dehydration and kussmaul's breathing. Salivary adenitis may also be seen. In children, there islow caries activitydespite high sugar intake and poor oral hygiene, suggesting an increased neutralizing capacity of the urea arising from ureal hydrolysis.

Patients report a metallic taste or the sensation of an enlarged tongue. Apart from urea, other factors possibly implied are the increase in the concentration of phosphates and proteins and changes in the pH of saliva. Also, these patients can refer sensitive disturbances, like altered taste sensations, especially, sweet and acid flavours. These can be due to the high levels of urea, the presence of dimethyl- and trimethyl- amines, or low zinc levels (due to the malabsorption derived from gastrointestinal disorders).[6]

An asymptomatic entity called Saburral tongue may occur.It is non-scrapable yellowish-white plaque on tongue dorsum with slightly elongated filiform papillae and bacterial accumulation.It is caused by retention of desquamated epithelial cells and dead leucocytes on filiform papillae, and by volatile sulfurous compounds produced by anaerobic bacteria.It has also been described as filiform papillae enlargement, with bacteria accumulation due to factors such as a water-restricted diet, low saliva flow, poor oral hygiene, and even the emotional condition of the dialysis patient[8].

Because of their immune compromised state, hemodialysis patients and allograft recipients have increased susceptibility to candidal infections, such as pseudo membranous, erythematous and chronic atrophic Candidiasis.[2]

Chronic periodontal inflammation may contribute to the chronic systemic inflammatory burden associated with chronic renal disorder. There is evidence to support a mechanistic link among inflammation, atherosclerosis and inflammatory biomarkers such as C–reactive protein and interleukin–6, have been shown to be elevated in chronic renal disorder.[2]Development of uremic stomatitis is by hydrolysis of urea in saliva by urease, when intraoral concentration of urea exceeds 30 mmol/ l.[4]

Uremic stomatitis may clear within a few days after renal dialysis, although such resolution may take place in 2 - 3 weeks. In order to assist lesion healing, a mildly acidic mouth rinse, such as 10% hydrogen peroxide gargles (1:1 in water), 4 times a day, can be given to clear the oral lesions.[6]For control of pain, while the lesions heal, patients may be given palliative therapy with ice chips or a topical anaesthetic such as viscous lidocaine or dycionine hydrochloride.[3]The gingivae can be pale due to anemia with possible loss of demarcation of the mucogingival junction and when there is platelet dysfunction, the gingivae may bleed easily.[5]

Histopathological signs of uremic stomatitis are not specific and pathognomonic and the role of histopathology is only to exclude other pathologic conditions. The definitive diagnosis is made by combining history, clinical and haematological findings alone.[9]

Other oral manifestations are related to renal osteodystrophy or secondary HPTH.Classic signs in the mandible or maxilla are bone demineralization, loss of trabeculation, ground-glass appearance, total or partial loss of lamina dura, giant cell lesions or brown tumors, metastatic calcifications. Lesions mostly involve the mandibular molar regions,superior to mandibular canal.Rarefaction is secondary to generalized osteoporosis.Radiolucent lesions of HPTH are called "Brown tumors."They contain areas of old hemorrhage and appear brown on clinical inspection.

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