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ORAL HYPERPIGMENTATION IN END-STAGE CKD PATIENTS UNDERGOING HEMODIALYSIS: A CASE REPORT

Fanni Kusuma Djati[1*], Nanda Asta Minullah[1], Sherly Octivany[1], Niken Febriharsari[2], Aditiawarman[2], Yunanto Dwi Nugroho[2]
[1]Department of Dentistry, Faculty of Medicine, Jenderal Soedirman University, Purwokerto
[2]Internal Medicine RSUD Prof. Dr. Margono Soekarjo, Purwokerto

ABSTRACT

Chronic kidney disease (CKD) is a progressive disease characterized by gradual and irreversible loss of kidney function over several months or years. According to Riskesdas 2018, the incidence of CKD in Indonesia is 0.38% (713,783 people) with 19.33% (2,850 people) undergoing hemodialysis therapy. Many CKD patients have related oral lesions, but attention to oral healthcare remains insufficient, especially in developing countries with higher rates of CKD patients. Several oral manifestations of CKD described in the literature include mucosal inflammation, mucosal petechiae, ecchymosis, skin and mucosal hyperpigmentation, fissured tongue, and coated tongue. A 51-year-old male with CKD was hospitalized in Mawar ward, Prof. Dr. Margono Soekarjo Regional Public Hospital. The patient presented of brown patches on his lips and oral cavity. Intraoral examination revealed lesions presenting as irregularly shaped macules with smooth brown margins on the lips and buccal mucosa. The patient was diagnosed with oral hyperpigmentation. Another case involved a 48-year-old female with stage 5 CKD who routinely underwent hemodialysis, presenting with brown patches on the lips, indented lesions on the lateral and dorsal tongue, and yellowish coloration on the dorsal tongue, diagnosed as fissured tongue and coated tongue. The manifestations that appear may be influenced by the kidney disease itself, consumed medications, or the therapy provided. Oral hyperpigmentation, coated tongue, and fissured tongue are some of the oral manifestations commonly found in end-stage CKD patients undergoing hemodialysis, with therapy aimed at improving patients' quality of life.

Keywords: chronic kidney disease, oral hyperpigmentation, fissured tongue, coated tongue, hemodialysis.

Corresponding author:

Fanni Kusuma Djati
Department of Dentistry Unsoed, Faculty of Medicine, Jenderal Soedirman University,
Jl. Dr. Soeparno, Karangwangkal, North Purwokerto, Banyumas, Central Java
Email: fanni.djati@unsoed.ac.id

INTRODUCTION

The kidneys function to excrete excess glucose and harmful substances from the blood while maintaining fluid balance. Impaired kidney function occurs when the body cannot maintain metabolic processes and electrolyte balance, leading to urea and nitrogen waste retention (Cahyani et al., 2022). Chronic kidney disease (CKD) is a progressive disease in which the kidneys gradually and irreversibly lose their function over several months or years (Glick, 2015). A person with a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m², or evidence of kidney damage such as micro or macro albuminuria, persistent hematuria, or radiological abnormalities for more than three months can also be diagnosed with CKD (Piliang et al., 2022).

The global prevalence of CKD is >10% of the general population worldwide, with approximately 843.6 million patients (Kovesdy, 2022). According to the Basic Health Research/ *Riskesdas* 2018, the incidence of CKD in Indonesia is 0.38% (713,783 people) with 19.33% (2,850 people) undergoing hemodialysis therapy (Ministry of Health RI/ *Kementerian Kesehatan Republik Indonesia*, 2018). CKD is commonly suffered by elderly patients, more frequently in women than men, in minority races, and in patients with diabetes mellitus and hypertension (Kovesdy, 2022). CKD is one of the leading causes of death worldwide and is one of the non-communicable diseases whose mortality rate has increased over the last 2 decades (Aditama et al., 2023). Triggering factors for CKD generally stem from unhealthy lifestyles such as rarely drinking water and frequently drinking coffee, habits of consuming fast food and excessive sweet foods, busyness that causes stress, and prolonged sitting habits such as sitting all day in the office (Ministry of Health RI, 2023).

Management of CKD patients generally involves hemodialysis or kidney transplantation. Among renal replacement therapies, hemodialysis remains the most widely performed treatment (Kacaribu et al., 2018). The principle of hemodialysis is to remove excess nitrogen products and urea contained in metabolism as well as toxins from the blood through a dialyzer device (Piliang et al., 2022). Complications may arise due to the disease condition and hemodialysis process, requiring multidisciplinary cooperation, including dentists, to handle patients comprehensively (Oyetola et al., 2015). CKD can cause various systemic changes, one of which is the appearance of changes in the oral cavity. Research reveals that at least 90% of patients with stage 5 CKD show oral signs and symptoms that affect both soft and hard tissues of the oral cavity (Costantinides et al., 2018). Additionally, hemodialysis procedures also affect the oral cavity because this process causes physiological and biochemical changes in the body. Some effects of hemodialysis on the oral cavity include xerostomia due to medication side effects and fluid restriction, halitosis due to accumulation of nitrogen waste products in the blood causing a characteristic ammonia-like breath odor, and pigmentation/mucosal lesions that may also be caused by medications such as antihypertensives or diuretics (Costantinides et al., 2018).

Areas of the oral cavity where manifestations of systemic diseases can be found include the lips, labial commissures, labial mucosa, buccal mucosa, gingiva, palate, floor of the mouth, and tongue. Oral manifestations that usually appear in CKD include uremic fetor, dysgeusia, periodontitis, candidiasis, pale mucosa, petechiae, ecchymosis, uremic stomatitis, xerostomia, enamel hypoplasia, angular cheilitis, and gingival enlargement and

bleeding (Ravissankar et al., 2020). Pigment changes in CKD patients have been reported in the literature as hyperpigmentation, pale skin, brownish discoloration, and yellowish skin. This abnormal pigmentation often occurs on the lips and face of patients undergoing hemodialysis. Additionally, hyperpigmentation can also be caused by several medications commonly consumed by chronic kidney disease patients (Hussein et al., 2022).

Based on Hussein's (2022) research examining 131 CKD patients undergoing hemodialysis, 115 people were found to have oral hyperpigmentation. Mahay's (2024) research found that 33.3% of studied patients had oral pigmentation manifestations, 36% had fissured tongue, and 51.3% had coated tongue. Oral hyperpigmentation can occur because in CKD there is impaired excretion and metabolism of hormones that should be eliminated through the kidneys. β-MSH (Beta-Melanocyte Stimulating Hormone) increases in circulation because the kidneys fail to clear it properly. This hormone stimulates MC1R receptors on melanocytes, thereby increasing melanin production. Excessive melanocyte stimulation appears in the basal cell layer of oral epithelium and results in hyperpigmentation (Hussein et al., 2022). Additionally, damaged kidneys cannot eliminate pigments such as urochrome, carotenoids, and phenolic compounds. These pigments accumulate in the skin and cause skin coloration to become blackish, yellowish, or dull. Poor oral hygiene and decreased salivary flow rate can lead to fissured tongue and coated tongue conditions.

Oral hyperpigmentation in CKD patients can be distinguished from physiological oral pigmentation. Physiological oral hyperpigmentation usually appears in dark-skinned individuals referring to genetics or certain races and is not related to any disease. Physiological oral hyperpigmentation usually appears limited to the gingiva, especially anterior gingiva and labial mucosa, is visible from a young age or childhood, and has no accompanying symptoms because this condition is normal. In contrast, oral hyperpigmentation in CKD patients tends to appear widely distributed in the oral mucosa including buccal mucosa, tongue, and palate, appearing along with disease progression especially in advanced CKD stages, and is usually accompanied by other systemic complaints such as anemia, uremia, and skin color changes (which can be confirmed by laboratory tests).

In this case report, we report several oral manifestations in patients with stage 5 CKD. This report was made for learning purposes in detecting signs of oral problems that indicate CKD, especially in detecting early CKD manifestations in managing oral complications due to hemodialysis at Prof. Dr. Margono Soekarjo Regional Public Hospital.

RESEARCH METHODS

The research design used descriptive observational approach. The research sample consisted of stage 5 CKD patients hospitalized in Mawar ward and Soepardjo Ratman (SR) ward of Prof. Dr. Margono Soekarjo Regional Public Hospital on September 25, 2024, using purposive sampling technique. The research instrument used observation sheets. Verbal informed consent was obtained before data collection.

Case Reports

Case 1

A 51-year-old male patient was hospitalized in the Internal Medicine Department of Prof. Dr. Margono Soekarjo Regional Public Hospital, Purwokerto, Central Java, complaining of brown patches on his lips and inner cheeks. The lesions were asymptomatic. The patient had received no prior treatment for these lesions and rarely brushed his teeth during hospitalization. The patient's family disease history was unknown. The patient had systemic diseases including hypertension (165/94 mmHg) and stage 5 CKD routinely undergoing hemodialysis twice weekly.

Laboratory examination included hematological and clinical chemistry tests. Laboratory findings revealed decreased hemoglobin of 8.7 g/dL (reference value: 13.4-17.3 g/dL), decreased hematocrit of 22% (reference value: 40-50%), decreased leukocyte count of 4,480/mL (reference value: 4,500-11,000/mL), and decreased platelet count of 148,000 mcL (reference value: 150,000-450,000 mcL). There was elevated blood urea of 65.90 mg/dL (reference value: 19.00-44.00 mg/dL) and elevated creatinine of 7.25 mg/dL (reference value: 1.4 mg/dL).

Objective examination findings showed extraoral examination revealing bilateral leg swelling, yellowish facial appearance, and pale inner eyelids. Intraoral examination showed multiple irregular hyperpigmentation lesions with 2-5mm diameter, brownish coloration on upper and lower inner labial mucosa, bilateral buccal mucosa, and tongue, consistent with uremic hyperpigmentation. The patient's tongue showed linear longitudinal grooves on the dorsal tongue with branching patterns called fissured tongue.

Figure 1. Extraoral and intraoral lesions presenting as brownish macules on lips, labial mucosa, buccal mucosa, and tongue

The patient received the following medications for CKD and hypertension: sodium heparin injection, furosemide injection, omeprazole injection, famotidine, folic acid, clonidine, nifedipine extended-release, valsartan, spironolactone, nitroglycerin, and sodium bicarbonate. The management plan incorporated patient education addressing oral manifestations as possible sequelae of CKD and the associated anemia. The patient was educated to consistently consume foods high in folic acid to help overcome anemia, maintain healthy eating patterns, regularly brush teeth and clean the tongue to maintain oral hygiene.

Case 2

A 48-year-old female patient was hospitalized in the Internal Medicine Department of Prof. Dr. Margono Soekarjo Regional Public Hospital, Purwokerto, Central Java. The patient reported of progressively brownish lips and tongue discomfort over several weeks. She had received no prior treatment for her complaints and had no similar family disease history. The patient had stage 5 CKD and routinely underwent hemodialysis twice weekly.

Objective examination findings showed extraoral examination revealing mild swelling of both legs and abdomen. Intraoral findings included brown macules on upper and lower labial surfaces diagnosed as oral hyperpigmentation. Additionally, grooved lesions on the tongue extending from around the second molar to the incisor teeth, same color as surrounding tissue, smooth texture, bilateral, located on lateral tongue, and linear longitudinal lesions between 1/3-2/3 anterior tongue in the midline area, shallow base, same color as surrounding tissue, single, branching, diagnosed as crenated tongue and fissured tongue. Non-scrapable, asymptomatic white-yellow plaques were noted on the posterior dorsal tongue, diagnosed as coated tongue.

Figure 2. Extraoral and intraoral lesions presenting as brownish macules on lips, labial commissures, and buccal mucosa.

Case management included providing health education regarding lesions found in the oral cavity as asymptomatic conditions commonly appearing in CKD patients, education on maintaining oral hygiene by regularly brushing teeth twice daily (morning

after breakfast and night before sleep), cleaning the tongue with sweeping motions from back to front, drinking adequate water, avoiding spicy foods, consuming balanced nutritious foods, and getting adequate rest.

RESULTS AND DISCUSSION

Results

Patients in both cases were CKD sufferers, with case 1 accompanied by hypertension and anemia. Patients were diagnosed with stage 5 CKD with GFR of 12.1 mL/min/1.73m² requiring routine hemodialysis treatment twice weekly. Case 1 patient was a 51-year-old male and case 2 patient was a 48-year-old female. Patients had no history of antibiotic consumption. Extraoral examination revealed swelling in body parts such as both legs and abdomen. Oral manifestations commonly found in CKD patients, especially in end-stage disease, include hyperpigmentation, pale mucosa (orofacial pallor), fissured tongue, and coated tongue. Patients in the cases noticed oral hyperpigmentation after several months of being diagnosed with CKD. Oral hyperpigmentation lesions in patients were multiple, irregularly shaped with approximately 2-5mm diameter, brownish colored on upper and lower inner labial mucosa and bilateral buccal mucosa. The case 1 patient experienced anemia with decreased Hb of 8.7 g/dL, visible in the patient's inner eyelids and pale tongue color.

The patient's medication regimen for CKD and hypertension included sodium heparin injection, furosemide injection, omeprazole injection, famotidine, folic acid, clonidine, nifedipine extended-release, valsartan, spironolactone, nitroglycerin, and sodium bicarbonate. Management of oral manifestations in CKD patients involved explaining that oral complaints are side effects of the disease and treatment provided. Patients were educated to maintain adequate folate intake, maintain healthy eating patterns, regularly brush teeth and clean the tongue to maintain oral hygiene, and use non-alcoholic antiseptic mouthwash.

Due to facility limitations, tissue biopsy was not performed. Hyperpigmentation diagnosis was established based on anamnesis, clinical examination, and exclusion of other causes.

Discussion

Chronic kidney disease (CKD) is a condition of acute or chronic decline in kidney function. This condition has diverse pathophysiological process etiologies where kidneys cannot recover, so the body's ability to maintain metabolic, fluid, and electrolyte balance experiences decline or failure resulting in uremic conditions (Ministry of Health RI, 2018). CKD symptoms appear gradually, initially showing no clear symptoms. Complaints are felt when kidney function has declined severely and is difficult to treat (Kacaribu et al., 2018). In Indonesia, causes of CKD include hypertensive kidney disease (34%), diabetic nephropathy (27%), primary glomerulopathy (14%), obstructive nephropathy (8%), chronic pyelonephritis/PNC (6%), uric acid nephropathy (2%), lupus/SLE nephropathy (1%), polycystic kidney (1%), others (6%), and unknown (1%). The most common cause is hypertensive kidney disease at 34% (Aisara et al., 2018). CKD patients with hypertension are associated with excessive sodium storage resulting in hypervolemia. Hypervolemia can occur due to impaired sodium secretion and water excretion in urine, leading to increased blood pressure (Covic et al., 2017; Prasetya et al., 2023).

According to Prasetya et al.'s (2023) research, the majority of CKD patients were male at 76%, while females were 24%. This can occur due to male lifestyles that trigger CKD such as excessive protein consumption, salt consumption, energy drink consumption, and smoking. Nicotine content in cigarettes can release catecholamines causing increased heart rate and blood pressure, thus accelerating kidney function decline (Rachmaini, 2022; Prasetya et al., 2023). The highest age group in CKD patients was ≥50 years at 82%, followed by 36-50 years at 12% and 20-35 years at 6%. Increasing age is one of the CKD risk factors that can reduce kidney nephron mass and kidney physiology, disrupting the excretion process of metabolic waste products (Prasetya et al., 2023).

CKD can be classified into 5 stages based on glomerular filtration rate (GFR) values, which represent the level of plasma filtration by glomeruli per unit time as an indicator of kidney function. Normal GFR is 120-130 mL/min/1.73m². This is influenced by body weight, age, and patient gender. GFR can be calculated using the Cockcroft-Gault formula as follows:

GFR (mL/min/1.73m²) = (140-age) x body weight ÷ (72 x plasma creatinine).

CKD stage 1 shows mild kidney function decline with normal or decreased GFR at 90mL/min/1.73m² (Isro'in and Mas'Udah, 2020). Stage 2 with GFR 60-89 mL/min/1.73m² shows mild kidney function decline. Stage 3 with GFR 30-59 mL/min/1.73m² shows moderate kidney function decline. Stage 4 with GFR 15-29 mL/min/1.73m² shows severe kidney function decline. Stage 5 with GFR ≤15 mL/min/1.73m² requires kidney transplantation.

Body system function is disrupted in CKD patients because kidneys cannot function normally. Fluid accumulation occurs due to uncontrolled fluid intake, causing edema in body parts such as feet, face, abdominal cavity, hands, lungs, and others. This can also cause increased blood pressure and increased cardiac workload, potentially causing cardiac rhythm disturbances. Consequently, CKD patients require kidney replacement therapy, namely hemodialysis (Saragih and Sri, 2024). Patient non-compliance with hemodialysis will impact the accumulation of various harmful substances from blood metabolism in the body, causing body-wide pain and potentially death. However, complications can also arise from the hemodialysis process, requiring multidisciplinary cooperation including dentists to handle patients comprehensively. The principle is that CKD causes several systemic changes in patients, one of which is in the oral cavity (Nadiyah et al., 2024). Oral manifestations that appear may be caused by uremic syndrome, which is a complex of symptoms affecting the biochemical system balance of the body such as polyuria, metabolic acidosis, uremia, and others. Additionally, uremia affects the hematology of CKD patients who often experience bleeding or anemia. Oral manifestations appearing in CKD patients are often associated with declining kidney performance, consumption of certain medications, and hemodialysis processes (Kacaribu et al., 2018).

Uremic hyperpigmentation is an asymptomatic condition that frequently appears and ranks third as an oral lesion manifestation in CKD patients (Mahay et al., 2024). These lesions are often found in lip areas and oral mucosa. Clinical appearance presents as brownish macules with approximately 4-10 mm diameter, consistent with hyperpigmentation descriptions by Oyetola et al. (2015). High frequency of hyperpigmentation in CKD patients can also be influenced by medication use for disease

treatment such as antimalarials (quinacrine, chloroquine, hydroxychloroquine) that can stimulate melanin secretion. Genetic factors, especially black skin race and hot climate related to constant melanocyte exposure to sunlight can also accelerate hyperpigmentation (Costantinides et al., 2018).

Several cases reporting oral hyperpigmentation manifestations in CKD patients include Zulkarnain's (2017) research on CKD patients undergoing hemodialysis where hyperpigmentation occurred in 81 people (84.4%) while 15 people (15.6%) did not experience extraoral or intraoral hyperpigmentation. Mahay's (2024) research reported that among 150 CKD patients, the most common oral lesions were coated tongue (51.3%), fissured tongue (36%), then oral melanin pigmentation (33.3%) (Mahay et al., 2024). The mechanism that occurs is possibly direct stimulation of the pituitary gland by damaged kidneys or metabolites retained in blood despite dialysis, resulting in different β-MSH plasma levels between CKD and non-CKD patients. Another hypothesis is that there is a factor normally produced by kidneys that inhibits β-MSH secretion from the pituitary gland. In chronic kidney failure, this factor production progressively decreases, causing the pituitary gland to release large amounts of β-MSH (Constantinides et al., 2018). However, many researchers believe this hypothesis is less acceptable because high β-MSH secretion is generally associated with high adrenocorticotropic hormone (ACTH) secretion, which has not been found in CKD patients. The currently accepted mechanism is that the main metabolism of β-MSH occurs in the kidneys. In damaged kidneys, this leads to metabolic failure and cannot be adequately dialyzed, causing increased plasma β-MSH in patients, resulting in excessive melanocyte stimulation appearing in oral epithelial basal cell layers and causing hyperpigmentation (Hussein et al., 2022).

Oral hyperpigmentation in CKD patients can be influenced by several types of medications consumed to treat CKD. Levofloxacin is an antibiotic that can be used effectively as an optimal choice for urinary tract infections and in CKD patients. 10-20% of cases show drug interactions from long-term consumption. In quinolone drugs, namely levofloxacin and pefloxacin, several cases have been reported to cause hyperpigmentation in CKD patients. The pathophysiology is due to iron oxide and hydroxide present in levofloxacin being excreted through kidneys while patients cannot metabolize optimally (Padmalatha et al., 2017). Patients in the cases had no history of long-term antibiotic consumption, so hyperpigmentation was not influenced by medications given, and hyperpigmentation was more likely caused by increased β-MSH due to kidney damage. Additionally, hemodialysis treatment can affect hyperpigmentation occurrence in CKD patients. Brownish skin and mucosa discoloration in patients indicates increased melatonin in response to higher oxidative stress from hemodialysis treatment. Among all, melatonin's most significant effect is as a specific reactive oxygen species (ROS) scavenger in skin and elsewhere. Bilirubin has also been identified as an ROS scavenger that correlates with kidney function (Becker et al., 2016). Diagnosis is established through detailed anamnesis about skin pigmentation history, objective evaluation, and histopathological biopsy or patch/skin prick tests can be performed if more directed toward drug allergies (Ridho et al., 2023).

Other oral manifestations frequently found in end-stage CKD patients include orofacial pallor, fissured tongue, and coated tongue. Orofacial pallor or pale mucosa is seen in most CKD patients (76.2%). Anemia causing the appearing pallor occurs due to kidney inability to produce erythropoietin, reduced red blood cells during dialysis sessions,

fragility, and nutritional status in patients (Hussein et al., 2022). Coated tongue is an asymptomatic condition caused by retention of desquamated epithelial cells and dead leukocytes on filiform papillae and by volatile sulfur compounds produced by anaerobic bacteria on tongue surfaces, found in half of the CKD patient population (Mahay et al., 2024). Contributing factors to this condition include low salivary flow, diet lacking water content, and poor oral hygiene in hemodialysis patients. Dry and cracked lips or tongue are seen in 36% of CKD patients. This can be caused by low salivary flow, certain medications, and overall poor health in dialysis patients (Jayanti et al., 2022). Additionally, macroglossia can also be found in CKD patients. Macroglossia is a condition where the tongue is larger than normal tongue size, so the tongue appears more prominent and tongue edges are outside the dental arch when the mouth is at rest. Pathophysiological analysis shows that macroglossia can be caused by excessive tissue growth or tissue infiltration. Macroglossia accompanied by dry tongue is often found in CKD patients. This decreased salivary flow is related to uremia from salivary glands in CKD patients (Ridho et al., 2023).

Management of CKD patients presenting with oral hyperpigmentation, fissured tongue, and coated tongue involved patient education, emphasizing that these lesions are asymptomatic manifestations of kidney disease, with ongoing monitoring and evaluation should symptoms subsequently develop (Nadiyah et al., 2024). Additional therapy that can be provided includes recommendations to consume healthy foods high in antioxidants, supplementation, vitamins, and non-alcoholic antiseptic mouthwash, maintaining patient oral hygiene such as tooth brushing, regular tongue cleaning, routine scaling treatment to clean plaque and calculus to minimize urease and ammonia amounts in the oral cavity (Abati et al., 2024).

CONCLUSION

Oral hyperpigmentation, coated tongue, and fissured tongue are common oral manifestations of CKD, particularly in end-stage (stage 5) patients undergoing hemodialysis. Recognition and management of these conditions are important for supporting overall patient well-being and improving quality of life.

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