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Dental Management of a Kidney Transplant Patient

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Dental Management of a Kidney Transplant Patient

LEARNING OBJECTIVES
After participating in this CE activity, the individual will learn:
• The reasons and the process regarding dentists performing a pretreatment dental/oral evaluation of patients scheduled for kidney transplant.
• The etiology and management issues related to drug-induced gingival overgrowth (DIGO).

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INTRODUCTION
De Rossi and Glick\(^1\) reported in 1996 that the number of Americans living with end stage renal disease (ESRD) is increasing. ESRD patients are typically placed on dialysis therapy. There have been steady yearly increases in the number of ESRD patients requiring dialysis. Therefore, more and more dentists will need to acquire the knowledge and training in order to treat these patients. These patients tend to have advanced dental disease and a number of comorbid conditions such as hypertension and diabetes (which also happen to be the most common causes of ESRD).\(^2\) The function of the kidneys is to filter out and remove wastes and poisons from the circulatory system. The destruction of the nephrons results in the loss of filtering capacity, and such damage can happen quickly, although most kidney diseases tend to be slowly progressive. Slowly progressive kidney disease tends to be silent in that symptoms may not be evident until 80% or 90% of the nephrons in both kidneys are destroyed. Previous to the utilization of dialysis therapy, ESRD tended to result in death, as kidney function is essential. Dialysis therapy allows mechanical kidney functions to be performed in patients without viable kidney function. The dialysis procedures are usually performed 3 times a week and each session takes several hours. Furthermore, the patient is tethered to the dialysis equipment and is heparinized during the procedure.\(^1-5\)

Fortunately, kidney organ transplant procedures have proven relatively successful in allowing patients to reattain renal function, discontinue renal dialysis, and attain a better quality of life.\(^3\) However, transplant patients have an increased risk of death compared to age-matched controls and a prognosis similar to patients with a cancer diagnosis. Graft rejections occur secondary to allograft nephropathy, and such conditions as cardiac disease, malignancy, and infection are often lethal in this patient population. Immunosuppressive drug regimens are designed to
decrease the incidence of acute allograft rejection with aggressive induction therapy, and afterwards, maintenance requires powerful but somewhat toxic drug regimens. Furthermore, maintenance therapies include expensive prophylactic protocols against bacterial, fungal, and viral infections. Despite emerging discoveries, the 20-year survival rate of kidney transplant patients has not improved very much during the past 30 years.6,7

Before performing renal transplantation, it is important to control ongoing infections. As dental infections are relatively common, and particularly so with regard to renal dialysis patients, a pretransplant dental evaluation is helpful in providing information to the transplant team regarding oral and dental infections so that necessary dental therapies can be accomplished previous to the transplantation procedure.2,8,9 Thus, the importance of a prekidney transplant dental evaluation is emphasized.

Drug-induced gingival overgrowth/enlargement (DIGO) is a relatively common condition secondary mainly to anticonvulsant drugs such as phenytoin, calcium channel blocking agents (CCBA), antihypertensive drugs such as nifedipine and amlodipine, and the immunosuppressive drug cyclosporine. Other antiseizure inducing drugs include sodium valproate, valproic acid, phenobarbital, and primidone, and other CCBA-inducing drugs include diltiazem, verapamil, and nitrendipine. DIGO was previously known as drug-induced gingival hyperplasia although the condition is neither hyperplastic nor hypertrophic, but rather due to an increased deposition of connective tissue (glycosaminoglycans/interstitial ground substance). Therefore, the descriptive terms of overgrowth or enlargement rather than hyperplasia are more accurate. The histopathology of DIGO is noted for acanthosis and elongated rete pegs.10-12

This article reports a case in which an ESRD patient scheduled for a kidney transplant presented with DIGO, and discusses how dentists can evaluate and manage these patients.

CASE REPORT
A 25-year-old male presented to an oral medicine clinician referred by a hospital-based kidney transplant team for a pretransplant oral/dental evaluation. The chief complaint was, “Work-up for a kidney transplant.” The medical diagnosis was kidney failure secondary to hypertension. Current treatment for hypertension consisted of nifedipine and clonidine. The patient was presently being treated with dialysis therapy 3 times a week and was scheduled for a kidney transplant procedure with a donation from a relative with matching human leukocyte antigens compatibility. The patient reported no known drug allergies. The family medical history was not significant. The patient’s physicians had prescribed amoxicillin for the patient’s dental infection. The patient reported pain of the left mandibular area which was particularly painful when eating and chewing. The patient reported that his gums bled when flossing. There was no lymphadenopathy noted on palpation.

Intraoral evaluation revealed generalized bulbous fibrotic overgrowth of the gingiva papillae consistent with DIGO (Figure 1). Clinically and radiographically (panoramic and bitewing radiographs were exposed), it was revealed that the mandibular right first molar and the mandibular left third molar were missing. The mandibular left second molar was severely decayed with an evident periapical radiolucency of the mesial root (Figure 2). The maxillary right first and second molars were noted for deep occlusal caries, and the maxillary left first and second molars were noted for occlusal caries. The mandibular right first molar was noted for deep occlusal-buccal caries, and the mandibular right third molar was noted for occlusal-buccal caries. The bone level appeared to be adequate. Probing depths were insignificant with bleeding upon probing.

Listed diagnoses included: ESRD, DIGO secondary to nifedipine drug therapy and gingivitis, a periapical abscess.
of a nonrestorable tooth (No. 18), and dental caries. The proposed treatment plan noted: (1) suggestion to physicians to discontinue nifedipine therapy with the substitution of another antihypertensive drug not within the CCBA category; (2) extraction of tooth No. 18; (3) oral hygiene instruction; (4) dental prophylaxis; (5) removal of caries and sedative restorations for teeth Nos. 2, 3, and 31; and (6) after completion of the kidney transplant and when the patient was medically stable, consider treatment of DIGO, and restorative and prosthetic dental procedures as necessary. Furthermore, it was noted that the utilization of tetracycline was to be avoided.

**DISCUSSION**

The concept of a presystemic therapy dental evaluation was initiated at approximately age 50 years and became accepted practice approximately 20 years ago with regard to dental evaluations previous to radiation therapy for head and neck cancers. In view of infection concerns, some kidney transplant hospital centers are embracing this concept of performing a dental evaluation prior to initiating kidney transplant procedures. There is the potential for exposure of distant anatomical sites from oral cavity bacteria. As the kidneys account for approximately 20% of the cardiac output, renal exposure to such bacteremias with regard to a transplanted kidney would tend to be substantial. Dental therapy directed at reducing oral and dental infections would tend to decrease such exposure. However, in treating dental infections, it is important for the dental clinician to avoid the use of tetracycline, as such antibiotics have the potential to rapidly cause further kidney damage. Furthermore, completing dental procedures such as extraction and initial scaling and dental prophylaxis procedures previous to the kidney transplant would avoid exposing the newly transplanted kidney to more severe bacteremias. The emphasis upon oral hygiene procedures would tend to aid oral and dental health and in decreasing bacteremia secondary to oral bacterial carriage.

With regard to the presented case, it was most important to eliminate the major sources of oral infection first, which included the abscessed nonrestorable tooth (the mandibular second molar) and the generalized gingivitis. An extraction procedure and a dental prophylaxis along with oral hygiene instruction were therefore sequenced as the beginning procedures. After these procedures were accomplished, the kidney transplant team would schedule the transplant procedure. Although it could be considered beneficial to also complete the caries removal and sedative restorations on those teeth with deep caries infections previous to the transplant, it is possible that one or both of these teeth could result in another tooth abscess, which would then involve either extraction or endodontic procedures and further bacteremic exposure. The remaining restorative, prosthetic, and periodontal therapies could be reasonably accomplished after the transplant.

The treatment of the DIGO condition is more complex. DIGO is problematic for 2 reasons: the appearance and increased difficulty with oral hygiene procedures. The bulbous fibrotic gingival papillae protrude over the surface of the teeth and make cleansing difficult. The diagnosis is usually accomplished through the history and the clinical appearance, although a biopsy procedure may be utilized to rule out any ambiguity. The differential diagnosis consists of hereditary gingivostomatosis, leukemic infiltrate, and granulomatous
conditions such as tuberculosis, sarcoidosis, Crohn's disease, and orofacial granulomatosis. However, DIGO is much more commonplace compared to other conditions noted within the differential diagnosis. Furthermore, the medical histories and clinical presentations would tend to rule out a definitive necessity for biopsy in most instances. Current therapies for DIGO include discontinuation and decreasing the dosage of the inducing drug, attention to oral hygiene including antiplaque rinses, surgical treatment (both scalpel and laser), topical folate therapy, and azithromycin therapy.

Partially based upon a successful folate efficacy study reported by Drew et al, Brown et al presented a multifactorial hypothetical mechanism model in 1992. This hypothesis is based upon several issues: (1) bacterial plaque tends to cause inflammation of the gingiva which initiates an increase in connective tissue growth, (2) DIGO is due to increased connective tissue buildup and not due to hyperplasia, (3) all of the inducing drugs affect cation function, (4) folate transport is dependent upon both energy dependent ion channel transport and passive diffusion pathways, (5) collagenase activation is a multistep process affected by matrix metalloproteins (MMPs), and (6) DIGO appears to be secondary to the failure of catabolism to break down the buildup of increased connective tissue within the gingiva. The following cascade of events was hypothesized: the inducing drug decreases gingival cellular uptake of folic acid (folic acid is necessary for the addition of carbon molecules necessary for the conversion of purines to pyrimidines base-pairs), the synthesis of a particular MMP (MMP 1, 2, 8, 9, or 13) is decreased, which results in the inability to activate sufficient collagenase, resulting in decreased efficiency in catabolism, resulting in overgrowth.

Seymour et al also favored a similar multifactorial hypothetic model which included many of the same concerns (although excluding folic acid concerns) but tended to focus more upon genetic issues. Gómez et al, Tokgöz et al, and Ramalho et al all reported the efficacy of azithromycin therapy in the treatment of DIGO. Kim et al proposed that azathioprine improves DIGO symptoms by interfering with collagen accumulation by activating MMP 2.

With the above in mind, the treatment of a patient with DIGO undergoing a kidney transplant is a complicated matter. As the patient in this case presented with DIGO secondary to nifedipine, it would seem reasonable that this patient would have a predilection toward DIGO secondary to cyclosporin. Possibly, kidney transplantation with tacrolimus immunosuppression is another possible consideration. Tacrolimus is a relatively new immunosuppressive drug, which although implicated as a DIGO inducing drug, may be less of a problem compared to cyclosporin. However, it would be reasonable to treat the patient’s DIGO condition sometime after the transplant, and then determine the treatment strategy. Available treatment strategies consist of topical folate therapy, systemic azithromycin therapy, chlorhexidine therapy, and periodontal surgery either with laser or scalpel. Kara et al compared oral improvement of gingival overgrowth in 60 adolescent subjects. The subjects received oral hygiene instructions, scaling, surgical therapy, and periodontal maintenance therapy. Although they noted statistically significant improvement with regard to all therapies, treatment of DIGO surgical (scalpel) therapy was the most successful and was the treatment of choice. Mavrogiannis et al reported that DIGO is a common clinical problem that usually requires surgical intervention. They agree that nonsurgical therapies are helpful and may reduce the rate of recurrence, and should be the first-line therapies. However, they reported that surgical therapy is usually the most reliable option and scalpel gingivectomy remains the treatment of choice.

However, laser-assisted surgical treatment is preferred by many because of improved hemostasis during surgery, optimal final gingival tissue positioning and tissue architecture, and a possible sterilization effect of laser on granulomatous tissue and bacterial colonization within periodontal pockets and gingival sulci. Various soft-tissue lasers such as diodes and Nd:YAG may be accommodated for fibrotic tissue noted for some DIGO cases, and generally, choices of wavelength can be adjusted dependent upon individual tissue characteristics. Mavrogiannis et al reported that after 6 months’ follow-up, there was significantly less recurrence of DIGO. They concluded that although DIGO can be managed by a variety of techniques, laser excision resulted in a reduced rate of recurrence.

According the 2002 American Academy of Periodontology Academy Report, laser therapy is considered superior to
scalpel use in conventional soft-tissue removal for several reasons. Laser therapy has less bleeding, less discomfort (possibly due to cauterizing soft tissue, forming a protein coagulum that acts as a dressing, and closing off the sensory nerve endings), and may require less local anesthesia, less healing time, and less scar tissue. However, Cobb concluded that scalpel surgery requires less time and effort when compared to laser surgery. Furthermore, the tissues in conventional surgery are not subjected to irradiation.

The consensus regarding the 2 surgical therapies is that when there is an excess of gingival enlargement, it may be more advantageous to remove the bulk of gingival excess with a scalpel. Scalpel therapy allows greater tactile sensitivity necessary to correct the gingival discrepancy and reduces the operating time significantly. Because of the difficulty in recontouring fibrotic tissues, the laser takes significantly more time. However, the laser has the advantage of greater recontouring control. Therefore, the scalpel is advocated for the initial tissue reduction and the laser has an advantage in obtaining tissue hemostasis, decreased patient discomfort, and final tissue recontouring.

CONCLUSION

Patients scheduled for a kidney transplant may benefit from a pretherapy dental evaluation. The side effect of DIGO presents challenges with regard to various dental therapeutic strategies in patients scheduled for kidney transplantation.

REFERENCES


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POST EXAMINATION QUESTIONS

1. Which of the following drugs should be avoided for patients with end stage renal disease (ESRD)?
   a. Penicillin.
   b. Erythromycin.
   c. Tetracycline.
   d. Metronidazole.

2. The main function of the kidneys is ____________.
   a. To monitor water and salt balance.
   b. To filter out and remove wastes and poisons from the circulatory system.
   c. To provide red blood cells for distribution of oxygen.
   d. To buffer the circulatory pH.

3. Slowly progressive kidney disease tends to be silent and symptoms do not tend to occur until ____________ of the nephrons in both kidneys are destroyed.
   a. 20% to 30%.
   b. 40% to 50%.
   c. 50% to 60%.
   d. 80% to 90%.

4. In describing the prognosis of kidney transplant patients, which of the below statements is the most accurate?
   a. Kidney transplant patients have similar life spans compared to other patients.
   b. Maintenance therapies such a prophylaxis are entirely unnecessary for kidney transplant patients.
   c. Graft rejection is unheard of with regard to kidney transplantation.
   d. Despite emerging discoveries, the 20-year survival rate of kidney transplant patients has not improved much during the past 30 years.

5. Which of the drug categories below is NOT substantially involved with DIGO?
   a. Calcium channel blocking agents.
   b. Antibiotics.
   c. Cyclosporin (and other calcineurin inhibitors).
   d. Phenytoin (and other anticonvulsants).

6. DIGO is due to ____________.
   a. Increased accumulation of connective tissue.
   b. Hypertrophy.
   c. Hyperplasia.
   d. Edema.
7. Studies have confirmed that such drug therapy/therapies as ________ have been helpful in the treatment of DIGO.
   a. Folic acid therapy only.
   b. Tetracycline therapy only.
   c. Azithromycin therapy only.
   d. Both folic acid and azithromycin therapies.

8. The histopathologic appearance of drug-induced gingival enlargement is noted for ______.
   a. Lymphocytic infiltration.
   b. Fibrosis.
   c. Acanthosis and elongated rete pegs.
   d. Necrosis.

9. Renal transplant medical centers are beginning to utilize ________.
   a. Pretreatment/surgical dental evaluations.
   c. Full-mouth dental extractions.
   d. Antibiotic prophylaxis protocols for ESRD patients.

10. Pretreatment dental evaluation was first utilized regarding ________ patients.
    a. Chronic obstructive pulmonary disease.
    b. Head and neck radiology oncology.
    c. Crohn's disease.
    d. Sjögren's syndrome.

11. Which of the following is NOT a first-line dental therapy for patients scheduled for a kidney transplant surgical procedure?
    a. Periodontal services.
    b. Homecare instruction.
    c. Prosthodontic therapy.
    d. Emergency dental therapy.

12. The main issue(s) with regard to gingival overgrowth is/are ________.
    a. Pain.
    b. Appearance and difficulty of oral hygiene.
    c. Increased incidence of periodontal disease.
    d. Increased caries incidence.

13. The diagnosis of DIGO/enlargement is usually attained through ________.
    a. Histopathology.
    b. DNA evaluation.
    c. History and clinical appearance.
    d. Plaque analysis.

14. The differential diagnosis of DIGO does NOT include which of the below?
    a. Hereditary gingival fibromatosis.
    b. Orofacial granulomatosis.
    c. Leukemic infiltrate.
    d. Ludwig's angina.

15. With regard to collagenase activation, which chemical or drug appears to be involved?
    a. Folic acid.
    b. Azithromycin.
    c. Purines.
    d. Matrix metalloproteins.

16. With regard to immunosuppression drugs for kidney transplantation, which immunosuppressant may be substituted for cyclosporine in the future?
    a. Tacrolimus.
    b. Azithromycin.
    c. Azathioprine.
    d. Amphotericin B.
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