Periodontal Management of a Patient Undergoing Liver Transplantation

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This case report describes the periodontal management of a patient with end-stage liver disease undergoing liver transplantation. In the first part of this article, all medical and dental findings are reported to elaborate adequate diagnoses. A patient-specific treatment plan was structured given the challenging periodontal and systemic scenarios. The second part describes the periodontal therapy delivered in close interaction with the referring physicians. Last, the article reviews current principles and protocols in managing these patients.
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Periodontitis, a chronic inflammatory disease initiated by dental plaque biofilm and perpetuated by a deregulated immune response, is considered one of the most important global oral health burdens. The World Health Organization (WHO) reported that severe periodontitis exists in 5% to 20% of adult populations worldwide.[1] Periodontal breakdown results in tooth mobility, pathologic migration, and eventually, tooth loss, thereby compromising chewing and speech functions, esthetics, psychologic well-being, and quality of life. A recent workshop reviewed the bidirectional association between periodontitis and systemic diseases and provided further evidence of periodontal disease as a health hazard.[2]

Inflammation is a key component of periodontal disease.[3] This suggests that periodontitis may have an impact on systemic health and insinuates efforts to reverse inflammatory periodontal disease may contribute to systemic health.

Based on the reported 2011 national data, 5,805 adult liver transplants are performed annually in the United States. For the organ recipients, these surgeries are expected to provide a 1-year survival of 88.2%.[4] Inflammation is widely recognized as playing a pivotal role in transplant rejection. In this respect, periodontitis seems to have

Table 1 List of current medications and laboratory data collected on the day of admission

Medication	Dosage	Class
Lamivudine 100 mg	1 tab daily	NRTI
Adefovir 10 mg	1 tab daily	NRTI
Aldactone 50 mg	1 tab daily	Diuretic
Furosemide 80 mg	1 tab daily	Diuretic
Lisinopril 10 mg	1 tab daily	ACE inhibitor
Nadolol 80 mg	1 tab daily	Beta-blocker
Lantus 100 unit/mL	10 units qam, 30 units qhs	Hypoglycemic
Novolog 100 unit/mL	20 units twice daily	Hypoglycemic
Lansoprazole 30 mg	1 tab daily	Proton pump inhibitor
Vitamin D3 5,000 unit	1 cap daily	Vitamins

Table 2 Laboratory data at initial situation

Component	Normal range	At initial situation
Platelet count (K/μL)	150–400	23 (low)
Mean platelet volume (FL)	6.00–11.00	13.70 (high)
International normalized ratio (INR)	0.9–1.2	1.4 (high)
Prothrombin time (PT) (sec)	9.6–13.3	15 (high)
Glucose (mg/dL)	70–100	241 (high)

serious implications in solid organ transplant deterioration and chronic rejection.[5] Therefore, management of transplant patients' dentition prior to the surgery is essential.[6] Maintenance of periodontal health following solid organ transplant is also critical in individuals medicated with immunosuppressive agents to avoid the occurrence of drug-induced gingival overgrowth.[7] The aim of this case report is to present the periodontal management of a patient with end-stage liver disease prior to liver transplantation.

Clinical presentation

A 49-year-old Bangladeshi man referred by NYU Langone Medical Center presented to the Department of Periodontology and Implant Dentistry of NYU College of Dentistry for dental clearance.

The patient was undergoing evaluation for liver transplant. He had no known allergies. His pretransplant diagnosis was cirrhosis secondary to chronic hepatitis B, maintained on lamivudine/adefovir with excellent virologic suppression. Complications of cirrhosis included portal hypertension, ascites (well controlled on stable doses of diuretics) and esophageal variceal bleeding. In addition, the patient presented with poorly controlled diabetes and osteoporosis and was overweight. Medications taken by the patient are reported in Table 1. Laboratory data are shown in Table 2.

On the day of admission, a noninvasive initial oral examination (without periodontal probing) revealed a setting of neglected dental care and deterioration of periodontal tissues (Fig 1).

General findings included intraoral halitosis, disharmonious gingival levels, edematous gingiva, spontaneous bleeding, multiple recessions and blunted papillae, pathologic tooth migration, and supra/subgingival plaque and calculus accumulation. A full-mouth series of radiographs was taken and showed generalized severe horizontal bone loss and supra/subgingival calculus accumulation (Fig 2).

Antibiotic prophylaxis consisting of 2 g amoxicillin was given orally 1 hour prior to each dental appointment. The patient was recalled the following day for periodontal charting.

According to the most recent classification of periodontal diseases,[8] the diagnoses elaborated were generalized severe chronic periodontal disease and secondary occlusal trauma. Short-term (< 5 years) and long-term (> 5 years) prognoses were formulated based on the classification proposed by Kwok and Caton.[9] In brief, third and second molars were nonmaintainable due to marked tooth mobility, severe bone loss, and Class III furcation involvement.

Fig 1 *Clinical views of initial situation.* (a) *Lateral, right.* (b) *Front.* (c) *Lateral, left.* (d) *Occusal, maxilla.* (e) *Occlusal, mandible.*

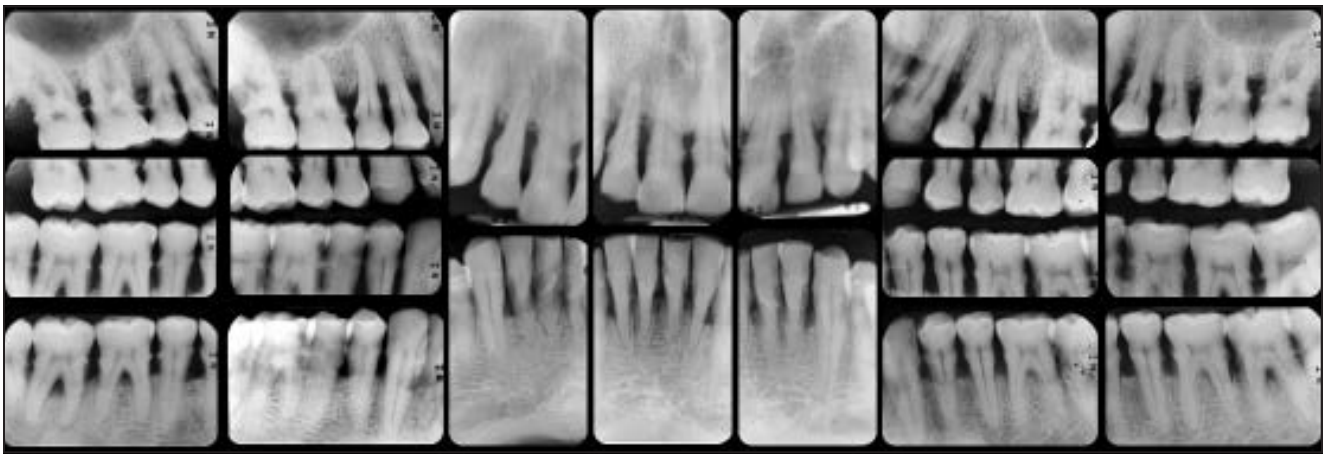

Fig 2 *Full-mouth series of radiographs on the day of admission.*

Based on these considerations, treatment goals included the following:

- Informing the patient about the risk factors
- Advising on lifestyle modifications (diet and exercise)
- Diabetes control and possibly improved glycemic control
- Long-term conservation of the teeth
- Reduction of the gingivitis (bleeding on probing < 25%) and plaque accumulation (Plaque Index < 10%)
- Absence of residual pockets
- Elimination of open furcations in multirooted teeth
- Gingival anatomy that facilitates professional periodontal maintenance
- A harmonious occlusal scheme to decrease tooth mobility and provide chewing comfort
- Prevention of drug-induced gingival overgrowth following liver transplant

Fig 3 *Clinical views after initial therapy.* (a) *Lateral, right.* (b) *Front.* (c) *Lateral, left.* (d) *Occusal, maxilla.* (e) *Occlusal, mandible.*

Case management

Motivational session

The patient was informed about the risk factors for periodontal disease. Instructions were given on how to use dental floss and interdental brush in open contact areas, followed by recommendations for frequency and time spent per brushing. Dietary and exercise instructions were also provided.

Medical consultation

The current status of the patient's health and immune system and the degree of organ dysfunction was discussed with his transplant physician following the initial examination. Glycated hemoglobin (HbA1c) levels were monitored periodically during the active periodontal treatment.

Initial therapy

Due to the severe attachment loss and the abundant presence of subgingival calculus, four sessions of scaling and root planing (SRP) were necessary. Prior to SRP, blood pressure and random glycemic values were checked. The patient rinsed for 60 seconds with 0.12% chlorhexidine gluconate. In each session, subgingival debridement was performed under local anesthesia using mechanical instruments (ultrasonics, hand instruments, and polishing).

Re-evaluation

Approximately 6 weeks after completion of initial therapy, the patient was recalled for re-evaluation[10] (Fig 3). Overall, the periodontal tissues appeared to be in stable health. Measurements were made to evaluate periodontal status and effectiveness of therapy. Periodontal charting revealed an improvement in plaque scores and considerable reduction of bleeding on probing. As anticipated, recession of the gingival tissues occurred following nonsurgical therapy. Tooth mobility terminated in the anterior dentition, whereas teeth 17, 18, 46, and 47 did not improve. Intraoral halitosis disappeared.

Occlusal equilibration

Anterior teeth were subjected to occlusal adjustments in order to achieve a stable intercuspal position and develop a comfortable occlusion.

Extraction of nonmaintainable teeth

All four second molars and the two mandibular third molars were considered nonmaintainable due to the persistence of tooth mobility, severe attachment loss, and furcation involvement. Given the setting of chronic thrombocytopenia secondary to his liver disease, the patient received a single unit of prophylactic platelet transfusion prior to dental extraction to prevent excessive bleeding. On the first day of platelet transfusion, the patient was premedicated with acetaminophen 650 mg oral, diphenhydramine 25 mg oral, and hydrocortisone 50 mg IV. He received the same premedication at the second appointment, but after the transfusion hives and itching were noted and an additional 25 mg of diphenhydramine IV and hydrocortisone 50 mg IV were

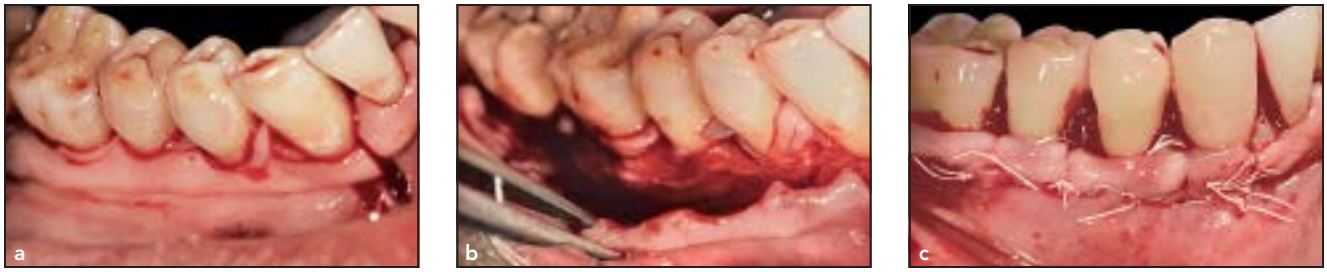

Fig 4 *Surgical pocket elimination of mandibular left posterior.* (a) *Submarginal incision.* (b) *Full-thickness flap elevation.* (c) *Flap sutured.*

administered with good effect and gradual resolution of hives.

Two sessions were necessary to extract the nonmaintainable teeth. Prior to surgery, blood pressure, platelet count, coagulation parameters, and glycemic values were checked. The patient rinsed for 60 seconds with 0.12% chlorhexidine gluconate. Teeth were extracted under local anesthesia. The alveoli were carefully curetted and rinsed with physiologic saline. Local hemostasis measures included the introduction of resorbable collagen sponges into the sockets. Extraction sites were sutured with 4.0 nonresorbable sutures. Bleeding ceased promptly with gauze and pressure and did not recur. Postoperative medications given were acetaminophen 650 mg oral tid as needed for pain and amoxicillin 500 mg oral tid for 7 days. One week after surgery, the sutures were removed. Undisturbed healing was observed during the follow-up visits.

Surgical pocket elimination

Residual pockets following initial therapy were eliminated by surgical means (Fig 4). Given the setting of chronic thrombocytopenia, the patient received a single unit of prophylactic platelet transfusion before this intervention as well. Premedication included acetaminophen 650 mg oral, diphenhydramine 25 mg oral, and hydrocortisone 100 mg IV. Only one hive was noted just as the patient was being discharged, at which point diphenhydramine 25 mg oral was administered with good effect. Prior to surgery, blood pressure, platelet count, coagulation parameters, and glycemic values were checked. The patient rinsed for 60 seconds with 0.12% chlorhexidine gluconate. The surgical site was infiltrated by a local anesthetic. The primary scalloped incision of the apically positioned flap was intrasulcular or at various distances from the gingival margin on the buccal and lingual aspects. The probing depth and the width of keratinized tissue dictated the design and position of this incision. A full-thickness flap was reflected, granulation tissue was removed, and the roots were planed using curettes. When indicated, the alveolar bone was modified to obtain positive architecture. In the maxillary posterior sextants, the palatal flap was thinned and scalloped to adapt precisely to the anticipated osseous profile. Flaps were sutured with 4.0 nonresorbable sutures. Hemostasis was achieved following surgery. Postoperative medications included acetaminophen 650 mg oral tid as needed for pain and amoxicillin 500 mg oral tid for 7 days. Two weeks after surgery, the sutures were removed. No bleeding complications occurred. Undisturbed healing was observed after flap surgery.

Supportive periodontal therapy

The patient was enrolled in a 3-month periodontal maintenance regimen due to his high-risk profile, which included an update of medical and dental histories, examination of extra- and intraoral soft tissues, dental examination, radiographic review, and evaluation of the patient's oral hygiene performance.

Clinical outcome

Gingival response to surgical pocket elimination was remarkable.

Fig 5 *Clinical views 12 months after surgery.* (a) *Lateral, right.* (b) *Front.* (c) *Lateral, left.* (d) *Occusal, maxilla.* (e) *Occlusal, mandible.*

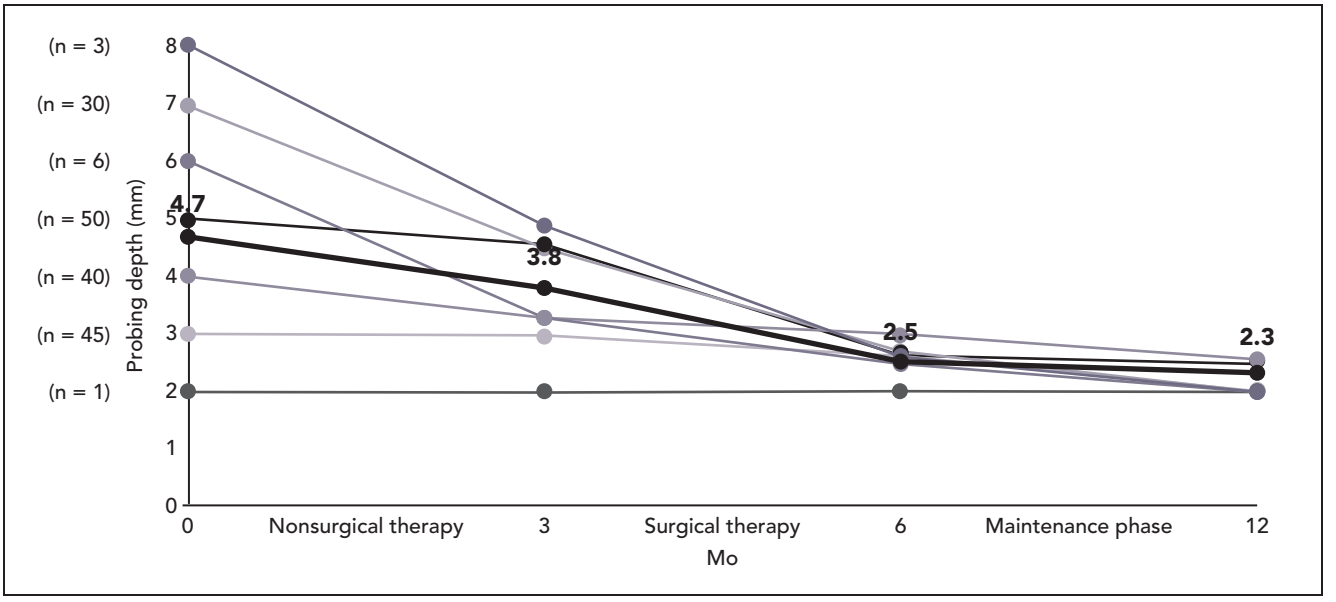

Fig 6 *Mean pocket depths at different times. The mean overall full-mouth pocket depth at each time is indicated in bold. n = number of sites.*

Clinically healthy gingiva was appreciated after completion of the surgical phase and was maintained for over 12 months (Figs 5 and 6). There was a considerable reduction in all clinical parameters over time (Table 3). Tooth mobility disappeared. Supra- and subgingival calculus was not detected clinically or radiographically (Fig 7). A stable occlusion with acceptable phonation was established. Splinting teeth was avoided as no further migration or further increasing mobility of individual teeth was noted. At this stage, the patient was periodontally cleared and ready for liver transplant.

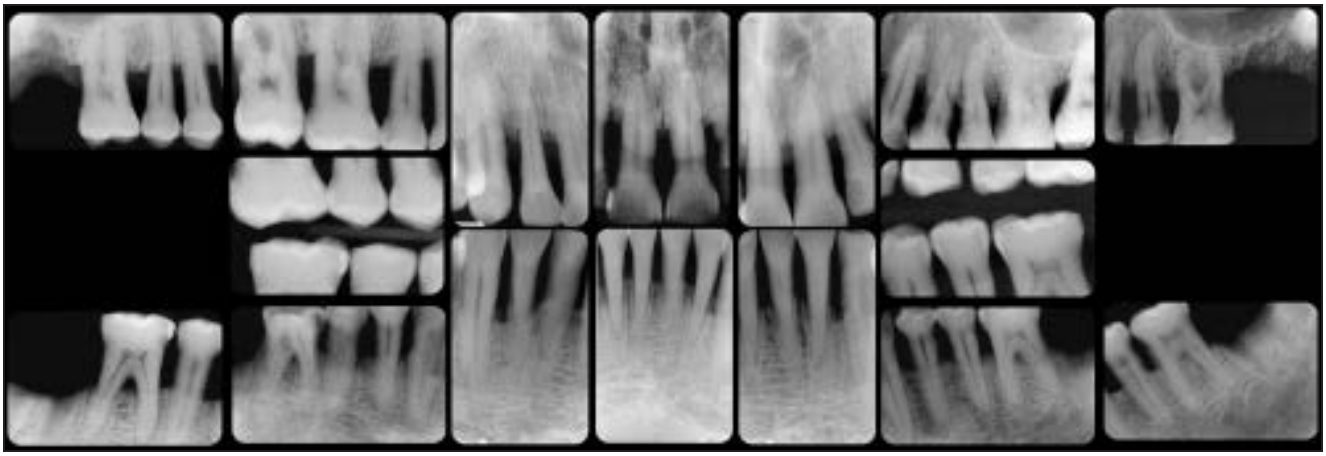

Fig 7 *Full-mouth series of radiographs 6 months after surgery.*

Despite the effectiveness of the periodontal therapy, a reduction in HbA1c levels was not observed after nonsurgical and surgical therapy (Table 4).

Table 3 **Mean clinical parameters at different times**

	Baseline	3 mo	6 mo	12 mo
Probing depth (mm)	4.7	3.8	2.5	2.5
Clinical attachment level (mm)	5.8	6.1	5.9	5.9
Plaque accumulation (%)	100	36	29	29
Bleeding on probing (%)	100	51	11	11

The data for each parameter, measured at 6 sites per tooth at all teeth, was averaged within the patient's dentition at each time.

Table 4 **HbA1c levels at different time points**

	Baseline	3 mo	6 mo	12 mo
HbA1c levels (%)	9.2	13.8	10.3	8.8

Discussion

Periodontium and liver disease

Viral hepatitis and alcohol-induced liver disease are common causes of cirrhosis in the liver transplant population.[11]

In the early 1960s, a greater prevalence of periodontal disease was found in patients with liver cirrhosis among hospitalized individuals.[12] These epidemiologic data suggested a possible relationship between this life-threatening condition and periodontal disease.

Conflicting evidence exists on the effect of liver cirrhosis on periodontal disease. A case-control study indicated that the worsening of periodontal condition was associated with increasing neglect of the teeth and aggravation of liver cirrhosis.[13] Moreover, greater pocketing, bone loss, and attachment loss were observed in cirrhotic patients compared with healthy controls in a cross-sectional study.[14,15]

In contrast, other authors found that severity and duration of cirrhosis had no influence on periodontal disease.[16] It could only be speculated that elevated levels of serum cytokines secondary to liver dysfunction[17] might be associated with altered immune responses found in periodontitis.[18]

Evidence has emerged that untreated oral infections may exacerbate liver disease.[19] In a recent survey, several transplantation centers in the United States experienced cancellation or postponement of a transplant, or even episodes of sepsis after transplantation, due to the presence of active dental infections.[20]

Another important consideration is that the patient presented with two potential conditions that could affect salivary flow, which were

poor glycemic control and the use of diuretic agents for ascites.[21,22] Yet he never complained of oral dryness and no signs were observed of hyposalivation at initial examination or during the periodontal therapy. In a study to assess dental heath status of cirrhotic patients, the reduction and lack of saliva was found in more than half of the examined population.[23] Xerostomia may pose a problem to liver transplant candidates as decreased salivary secretion promotes plaque accumulation and increases the risk of gingival inflammation.[24]

Periodontium and liver transplant

The host responds to periodontal infections with an array of events involving both innate and adaptive immunity. Proinflammatory cytokines, particularly interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α), are released locally in the inflamed periodontal tissues[25,26] and may contribute to systemic inflammation.[27] IL-6 is currently regarded as a biomarker of systemic inflammation, which has been shown to be a reliable diagnostic indicator of renal transplant rejection.[28] Since inflammation has been identified as a key factor in destruction of the transplanted organ, there has been an interest in confirming the association between transplant rejection and periodontitis.

In this regard, a recent clinical study substantiated the theory that elevated levels of IL-6 accumulated in diseased periodontium might spill over into the circulation, inducing solid organ deterioration in transplant subjects.[5]

Periodontium and immunosuppressive therapy

Organ transplant patients are immunosuppressed due to the drugs taken to reduce the chance of organ rejection. One recognized side effect of the long-term administration of such antirejection medications is an increased connective tissue production in the periodontium, resulting in gingival enlargement. The pathogenesis of drug-induced gingival growth is thought to be multifactorial and presently is not well understood.[29] It seems that a combination of drug therapy, plaque-induced inflammation, susceptibility to gingival fibroblasts, and related genetic factors may all play important roles in the development of this condition.[30] The patient was subjected to intense interventions to improve oral hygiene and periodontal health. These measures were necessary to minimize the future risk of drug-induced gingival overgrowth.

Drug administration in patients with cirrhosis

There are some concerns about prescribing medications used in dentistry for individuals with end-stage liver disease because hepatic drug metabolism is impaired. The innate immune system is also defective, resulting in an increase of transient bacteremia caused by infections.[31] Given this scenario, there is not enough evidence that supports and defines the administration of antibiotic prophylaxis prior to invasive dental procedures; therefore, the present authors preferred to rely on the regimen for the prevention of infective endocarditis provided by the most recent guidelines.[32] For the management of this case, amoxicillin is the medication of choice as the major route of elimination for this antibiotic is via the kidney. As a general rule, in a setting of hepatic dysfunction drugs that are concentrated or eliminated by the liver should be strictly avoided.

Pain management in patients with cirrhosis is a difficult clinical challenge for the dentist due to the lack of evidence-based guidelines and potential fatal adverse effects from analgesics.[33] In patients with end-stage liver disease, nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided because increased risk of renal failure and the use of opiates should be restricted to prevent encephalopathy.[33] It is important to dismiss the misconception that acetaminophen should be strictly avoided in patients with liver dysfunction. Although this analgesic is the most common cause of fulminant hepatic failure in the United States, recent recommendations allow for patients with cirrhosis, provided that it is given at reduced dosage (maximum 2 to 3 g per day) and concomitant alcohol consumption is avoided.[34]

For the management of this case, a dose of acetaminophen 650 mg was used to treat postoperative pain following periodontal therapy

and tooth extraction, at maximum daily dose of 1 capsule every 8 hours for short-term use. This safe dosage of 1,950 mg per day provided effective pain control.

Hemostasis and liver disease

In this patient, baseline laboratory values showed a thrombocytopenia with a platelet count of 23,000/mL. Also as expected, the INR and PT were slightly high (baseline values: 1.4 and 15 s). It should be taken into account that, unlike patients on anticoagulant therapy, even small deviations from the normal limits implies significant liver disease.[35]

These findings were concerning given the risk of persistent bleeding following invasive dental interventions. In this respect, some authors have reported several cases of hemorrhagic complications and impaired wound healing in patients with chronic liver disease undergoing surgical procedures.[36] In an experimental model, a significant delay on early healing events in extraction sockets was observed due to cirrhosis.[37]

To overcome the risk of excessive bleeding, clinicians order transfusions preoperatively, either platelets or blood products, in cirrhotic patients.[38,39] It is still unclear whether individuals with low platelet counts (< 50,000/mL) benefit from prophylactic transfusions to increase platelet counts before invasive or surgical procedures. A recent study concluded that it was difficult to determine a real benefit from transfusion prior to dental extraction in patients with thrombocytopenia secondary to hematologic malignancy. Nevertheless, patients with end-stage liver disease have varying deficits in both vitamin K–dependent and K-independent coagulation factors associated with low platelet count, therefore the complexity of hemostasis impairment is higher.[35]

In this case study, a complete blood count, platelet count, and coagulation parameters were obtained at baseline and prior to any invasive procedures. The patient was transfused with a single unit of platelets prior to tooth extraction and surgical pocket elimination. Allergic reactions in the absence of fever are often seen with platelet transfusion.[40] The patient manifested hives and itching at the end of the second and third transfusions. Mild allergic reactions are caused by soluble substances present in donor plasma and mediated by the Immunoglobulin E response and histamine release in recipients. Administration of antihistamine reagents such as diphenhydramine before platelet transfusion minimizes the frequency of allergic reactions. In this case, an additional dose of diphenhydramine 25 mg IV and hydrocortisone 50 mg IV led to resolution of hives. Finally, interventions were staged to minimize the surgical time and blood loss. This strategy showed no intraoperative bleeding complications.

Periodontal treatment and liver disease

Some authors consider the extraction of all natural teeth the most conservative approach in managing these patients.[41] Conceptually, this radical strategy would appear adequate to eliminate active dental inflammation and minimize the risk of reinfection. There is evidence that full-mouth extraction results in a significant reduction of all periodontopathogens,[42] which could lead to an attenuation of the inflammatory response. Nevertheless, the present authors believed maximum preservation and protection of natural teeth was the ideal approach for this case. All treatment goals were achieved: the patient's response to periodontal therapy was considerable and he demonstrated high compliance with maintenance schedules.

The patient was subjected to surgical pocket elimination to avoid disease recurrence and facilitate professional maintenance. A long-term conservation of the teeth is expected in this case, as shown by previous clinical studies.[43,44] Despite its effectiveness in improving all periodontal parameters, the periodontal therapy had no effect in controlling HbA1c levels at the 3- and 6-month follow-ups. This finding is consistent with a recent clinical trial[45] and likely related to his severe multiorgan impairment.

Alternatives to periodontal therapy were discussed with the patient and included full-mouth extraction and conventional complete dentures or oral rehabilitation with dental implants. The first option was excluded given the patient's desire to preserve his dentition (he expressed functional compliance and he was not particularly concerned

about esthetics). Concerning the second option, the patient was considered a poor candidate for implant therapy due to uncontrolled diabetes, which is a risk factor found to be associated with peri-implant disease.[46]

The duration of periodontal therapy offered to the patient was realistic with the national average median wait time to liver transplant (18.5 months in 2011[47]), as the priority was to complete the nonsurgical and surgical phases prior to organ transplant. In this regard, a recent guideline recommended that all dental treatment, except for emergencies, must be avoided for at least 3 and up to 6 months after organ transplantation, as well as in patients with organ rejection.[48]

Medical and dental standardization for liver transplant recipients

Dental management of transplant patients is essential: measures to improve oral health were associated with a reduction in mortality among pre- and postoperative liver transplant patients.[49] The literature presents various dental treatment strategies for the solid organ transplant patient.[6,11,50–52] Guidelines regarding the care of organ transplant patients were recently introduced in an attempt to standardize dental management and improve interaction between dentists and transplant physicians.[7]

Conclusions

Dentists and physicians should be more aware of the bidirectional nature of the relationship between oral heath and systemic conditions. Standardized protocols for pre- and post-transplantation dental care should be established and implemented in both transplant centers and dental offices. The positive outcome of this case shows how an adequate periodontal management can be extremely beneficial for a patient undergoing liver transplantation.

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