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Amlodipine-induced gingival overgrowth in a child after liver transplant

André Guollo[a], Ana Paula Molina Vivas[a], Rodrigo Nascimento Lopes[a], Gilda Porta[b], Fábio Abreu Alves[a,c]

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ABSTRACT

Drug-induced gingival overgrowth (GO) has been associated with phenytoin, cyclosporine, and calcium channel blocker therapies. This study reports the case of an 11-year-old girl who was referred for evaluation of GO, which had occurred over the last 6 months. Her medical history included a liver transplant due to biliary atresia 3 years ago, immunosuppressive therapy, and hypertension, which is why she was started on a daily intake of amlodipine. The intraoral examination showed generalized GO, and the treatment consisted of a gingivectomy. Subsequently, amlodipine was replaced with captopril and oral hygiene instructions. There was no recurrence of GO after 28 months of follow-up. Although GO may be related to the chronic use of amlodipine, such an association is uncommon in pediatrics, and the treatment consists of the replacement of medication combined with a surgical approach and plaque control.

Keywords
Amlodipine; Gingival Overgrowth; Liver Transplantation

INTRODUCTION

Liver transplantation is the current treatment for end stage chronic liver disease and acute hepatic failure, even though it is a very demanding procedure. The most frequent indications are biliary atresia, fulminant liver failure, metabolic diseases, hepatic tumors, cirrhosis, and other cholestatic liver diseases. Liver-transplanted children have shown good overall patient/organ survival rates of 83.8/75.3% after 3 years, and 70.2/65.1% after 5 years of transplantation. This increase in survival time is mainly due to the improvement of surgical techniques, the management of complications, immunosuppressive medications, and multidisciplinary intervention.[1,2]

Liver transplant complications may be associated with the surgical procedure, infections, and immunosuppressive therapy. Tacrolimus, cyclosporine, and corticosteroids are most often used to prevent graft rejection.[3,4] Calcium-channel blockers, such as nifedipine and amlodipine, are usually recommended for the treatment of hypertension after liver transplantation,[5-8] since this complication represents a possible side effect associated with the immunosuppressive regimen.

In 1993, Ellis et al.[9] first reported gingival overgrowth (GO) associated with the chronic use of calcium channel blockers; since then, its

[a]Stomatology Department - A.C. Camargo Cancer Center, São Paulo/SP – Brazil.
[b]Department of Liver Transplantation - A.C. Camargo Cancer Center, São Paulo/SP – Brazil.
[c]Stomatology Department - Universidade de São Paulo, São Paulo/SP – Brazil.

prevalence has been reported in nearly 3% of patients. The enlargement of the gingiva may hamper the appropriate oral hygiene, predisposing tooth decay and periodontal infections, requiring rigorous plaque control, anti-hypertensive drug schedule replacement, and surgical correction for aesthetic purposes.[10,11]

Although a liver transplant is commonly associated with cardiovascular alterations and the use amlodipine is not infrequent, to date, only a single report has shown the involvement of GO in a young patient after solid organ transplantation.[12] The objective of this case study is to describe such an association in a child, and how this was managed.

CASE REPORT

An 11-year-old girl was referred to the Stomatology Department due to gingival enlargement. The patient reported slow and progressive growth of the gums over the last 6 months. Her medical history included a liver transplant to treat biliary atresia when she was 8 years old. Since then, she had been using tacrolimus (0.25 mg once a week) and prednisone (10 mg daily)—to avoid organ graft rejection—and amlodipine (10 mg/day) for blood pressure control.

Her dental history showed no particular treatment and she had regular visits to the dentist. The oral hygiene was proper and no dental caries was observed. However, many white spots were present in almost all teeth, which is consistent with enamel hypoplasia. In addition, an extensive fibrous GO in the anterior permanent teeth of both arches was observed. Such GO mainly affected the marginal gingiva, but also it affected the interdental papilla and covered the tooth crown 4 mm on average with standard color, without any inflammatory component. There was no bleeding during periodontal probing (Figure 1). The diagnostic suspicion was amlodipine-related GO. The treatment consisted of oral care instructions (the use of a soft brush at least three times a day and dental floss) and a gingivectomy.

The surgery was performed under general anesthesia by two stomatologists after a preoperative work-up and an anesthetic evaluation. The internal bevel technique was used to remove all the gingival hyperplastic tissue, involving the anterior region of both dental arches. The patient received antibiotics (clindamycin) for a total of 7 days, and an analgesic (dipyrone) for 3 days. The postoperative period was uneventful, and she was discharged after 2 days of hospitalization. The histopathological features showed hyperkeratosis, acanthosis, and some long epithelial rete pegs. In addition, intense fibrosis of the connective tissue and an increase in the number of blood vessels with slight chronic perivascular inflammation were observed (Figure 2).

The amlodipine was replaced by captopril. After 28 months of follow-up, there was no GO recurrence (Figure 3).

DISCUSSION

Although the survival rate of pediatric patients who undergo liver transplantations has substantially increased due to the immunosuppressive therapy, these drugs always have been associated with many complications and side effects. In this context, GO had been described in children who had undergone kidney or liver transplants. It was also associated with the long-term use of cyclosporine, nifedipine, and amlodipine, and is similar to the well-known side effect of the anticonvulsant, such as phenytoin.[9,10,13,14] The case reported here showed an 11-year-old girl who developed GO after 30 months of amlodipine use.

Calcium channel blockers act directly on vascular smooth muscle, reducing systemic vascular resistance and improving renal blood flow, thereby reducing the systemic blood pressure.[15] Some studies[11,16,17] showed the incidence of GO ranging between 1.3%

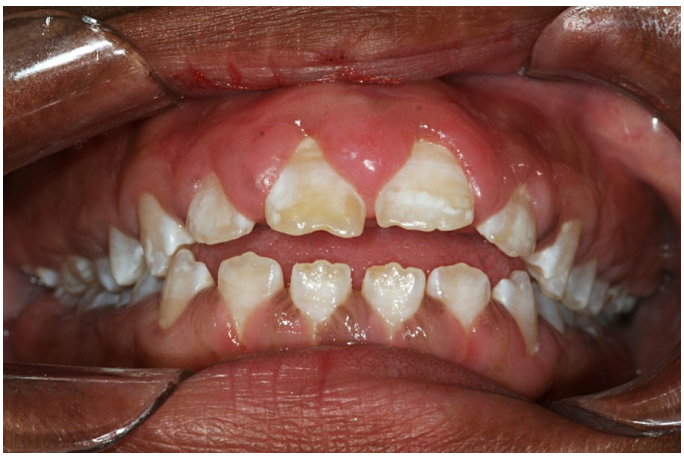

Figure 1. Intraoral examination showing GO in the anterior region of both arches.

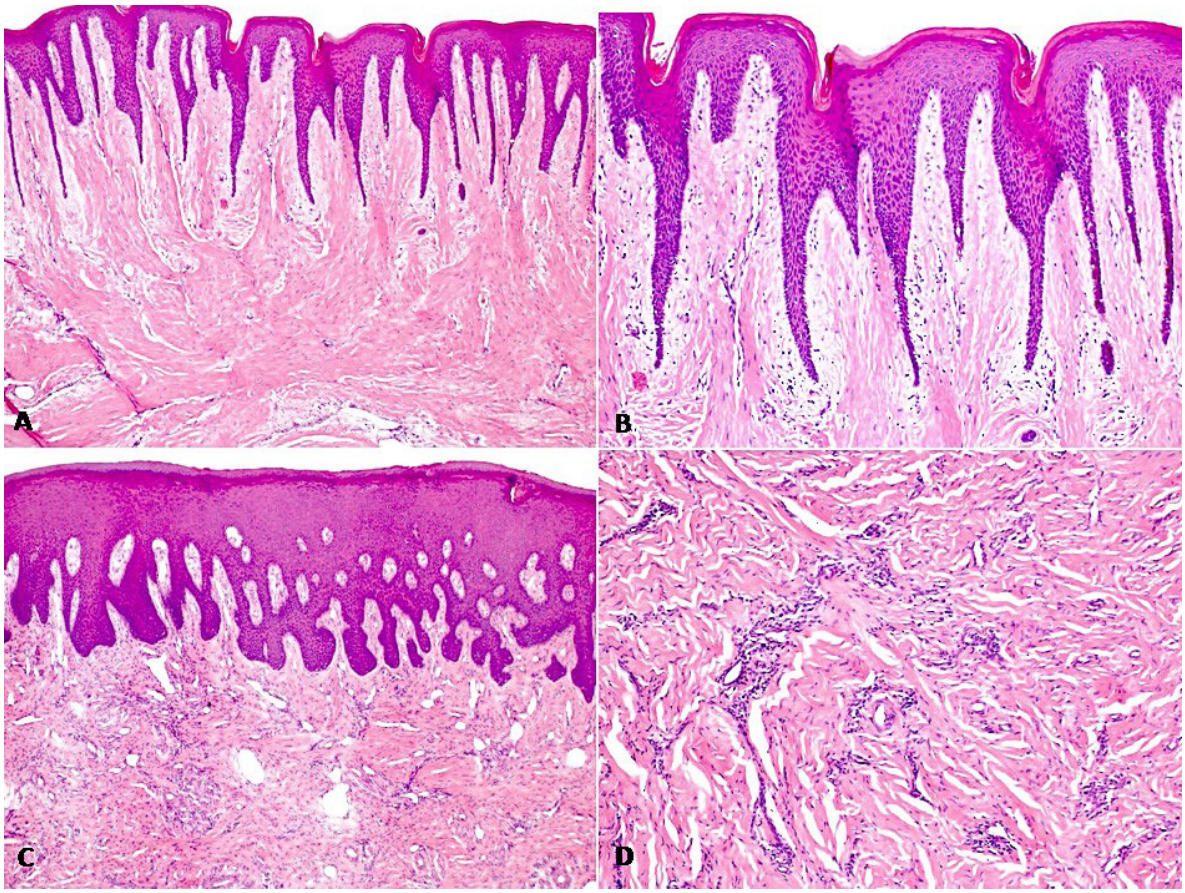

Figure 2. Photomicrography of the gingiva showing the histopathological features of the amlodipine-related GO. **A** - Slight hyperkeratosis, acanthosis, and **B** - long epithelial rete pegs; **C** - Intense fibrosis of the connective tissue, and **D** - an increased number of capillaries with slight chronic perivascular inflammation (H&E, 150X).

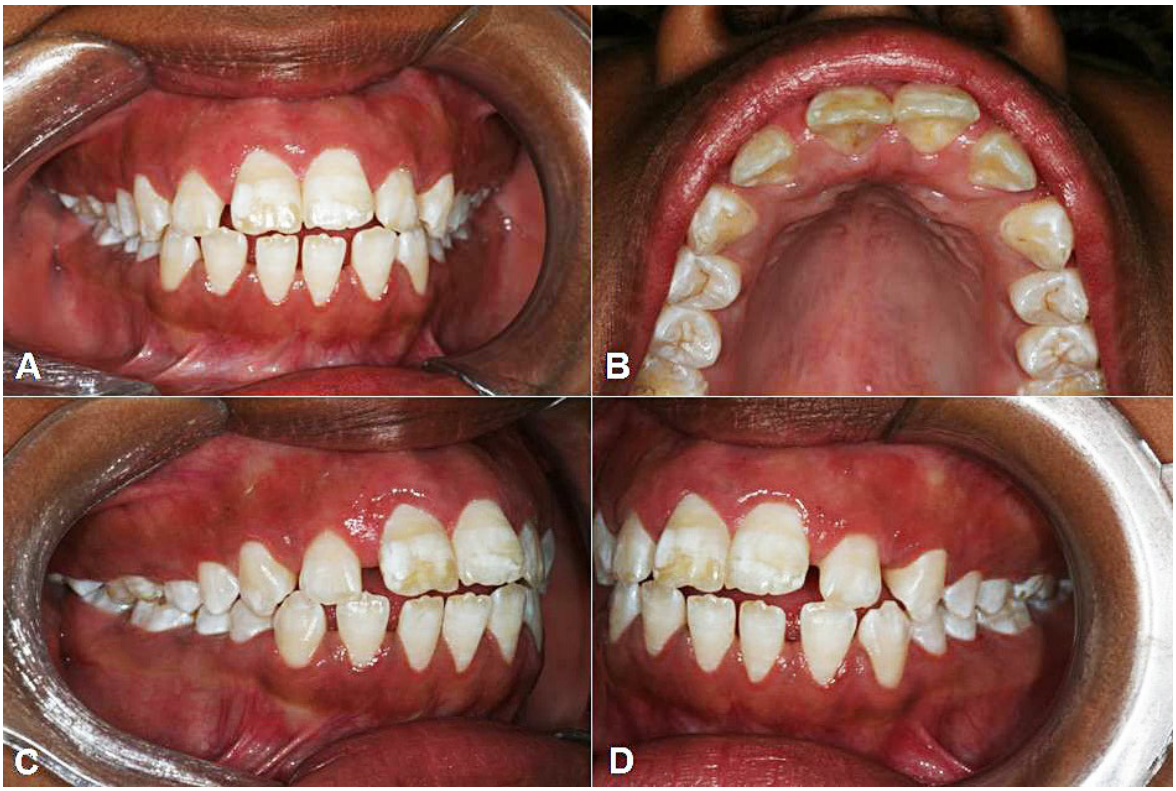

Figure 3. Intraoral examination after 28 months of follow-up, with no recurrence of gingival overgrowth. **A** - Anterior view; **B** - Occlusal view; **C** - Right side view; and **D** - Left side view.

and 3.4% in hypertensive adults using amlodipine for at least 3 months. These drugs also have been used for hypertension control in post-liver transplantation patients. Interestingly, a higher frequency of GO was observed in patients simultaneously taking cyclosporine and calcium channel blockers (46.7%) compared to patients taking tacrolimus and calcium channel blockers (8.3%).[18] Based on the study of Shiboski et al.,[19] tacrolimus was not related to GO, and, similar to his findings, in our institution, none of the children who underwent liver transplantation who were treated with tacrolimus presented GO.[13] Furthermore, neither James et al.[20] nor Greenberg et al.[21] found any association between the use of tacrolimus and GO in renal transplant patients. However, Cezário et al.[22] and Paixao et al.[23] related an association rate of 7.25% and 8.3%, respectively. In our case, the diagnosis of amlodipine-induced GO was established.

The pathogenesis of GO related to medications still remains unclear. However, a hypothesis involving anti-convulsants, calcineurin inhibitors, and calcium channel blockers has recently been described in a review[14] that states that the cation flux reduces the folic acid active transport in gingival fibroblasts, causing the reduction of cellular folate uptake. The matrix metalloproteinase metabolism is changed, which impairs the collagenase activation and results in the increase of collagen synthesis. In addition, the presence of inflammation caused by bacterial plaque also induces connective tissue production.[14]

Poor hygiene, local inflammation, and bleeding also may be associated with GO. The anterior region is the most affected by GO, and the local factor, such as bacterial plaque, may exacerbate such cases, increasing susceptibility to oral infections, dental caries, and periodontal diseases.[9,10,24] Similarly, the present patient was affected by GO in the anterior region of both arches, especially in the interdental papillae, without local factors, such as the presence of plaque and/or gingival bleeding.

The treatment of this condition is the replacement of the "guilty drug," which, in our case, was the amlodipine combined with removal of bacterial plaque if present. For aesthetic reasons, surgical intervention is recommended. The classic surgical approach of the internal bevel may be used in a gingivectomy.[10,24] This technique is based on the principle of excising the tissue that is extended with a scalpel blade tilted at an angle of 45 degrees in relation to the teeth, also contouring the papillae. Afterwards, interpapillary suturing must be performed to maintain the papillary position. The patient in this case report was successfully treated with the change of amlodipine to captopril and by undergoing a gingivectomy.

CONCLUSION

The present case illustrates the diagnosis and management of GO associated with the use of amlodipine. In addition, children who have undergone a solid-organ transplant should have periodic follow-up with dentists due to oral side effects related to immunosuppressive therapy and other drugs, such as amlodipine.

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Correspondence
Fabio Abreu Alves
Stomatology Department - A.C. Carmago Cancer Center
Rua Professor Antônio Prudente, 211 – São Paulo/SP – Brazil
CEP: 01509-900
Phone: +55 (11) 2189-5129 / +55 (11) 2189-5133
falves@accamargo.org.br