Periodontal Attachment Loss in Children with Amegakaryocytic Purpura: Case Reports of Two Male Siblings

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Abstract

Aims: To report the periodontal condition of two siblings (ages 2 and 4) diagnosed with congenital Amegakaryocytic Purpura (AP), who underwent allogeneic hematopoietic stem cell transplant (HSCT) and developed graft-versus-host disease (GVHD) with oral manifestations.

Methods: Clinical history was obtained through physical examination and medical records. Patients received clinical and microbiological assessment at 2 months post-HSCT, when they started to show signs and symptoms of GVHD and were monitored at 8/15-months post-transplant. They were treated by means of prophylaxis and oral hygiene instruction. Two supragingival biofilm samples were collected from each patient and analyzed by Checkerboard DNA-DNA hybridization.

Results: Patients developed severe periodontal clinical attachment loss (CAL) in deciduous dentition associated with recession of the periodontal tissues. They also presented GVHD lesions in the oral mucosa, lips and tongue. Caries lesions, gingivitis, and heavy biofilm deposits were identified. The microbiological profile of biofilm samples presented high levels and proportions of periodontal pathogens, such as *Aggregatibacter actinomycetemcomitans*.

Conclusions: The cases presented suggested that severe periodontal CAL in children with AP may be an atypical manifestation associated with AP and/or GVHD, which may be aggravated by the presence of a dysbiotic biofilm containing periodontal pathogens, especially *A. actinomycetemcomitans*.

Keywords. Hematologic Diseases, Periodontal Diseases, Stem Cell Transplantation

Introduction

Amegakaryocytic Purpura, also known as Amegakaryocytic Thrombocytopenia is a rare autosomal hereditary disease that causes bone marrow aplasia and may occur in two forms: congenital or acquired. Amegakaryocytic Purpura is characterized by thrombocytopenia and decreased or absent bone marrow megakaryocytes (Geddis, 2009; Newman *et al.,* 2017). Hematopoietic stem cell transplant (HSCT) is the only predictable treatment, and when performed early may increase patient's survival rates. If the disease is not properly treated, the prognosis is poor and the survival rate is low (Al-Qahtani, 2010; Piccin *et al.,* 2018).

Graft-versus-host disease (GVHD) is one of the most serious complications affecting patients undergoing allogeneic HSCT and is a major cause of morbidity and mortality after transplants (Piccin *et al.,* 2018; Qiu *et al.,* 2018). GVHD can present in two forms, acute and chronic, according to their clinical manifestations. It is a reaction that occurs when donor-derived T-lymphocytes are activated after recognizing the transplant recipient's

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tissues. Thus, the higher the degree of histocompatibility between donor and recipient the lower the chance of developing GVHD. However, the disease may occur even in cases with high donor-recipient histocompatibility (Piccin *et al.,* 2018; Kato, 2018) and the number of patients who develop GVHD seems to be increasing worldwide (Piccin *et al.,* 2018).

Both HSCT and GVHD may lead to oral problems, but clinical attachment loss is not among the reported conditions associated with these disorders (Haverman *et al.,* 2014; Motta *et al.,* 2018). GVHD can affect multiple organs, such as skin, oral and ocular mucosa, intestines, and lungs (Piccin *et al.,* 2018; Qiu *et al.,* 2018; Haverman *et al.,* 2014). The most common oral signs and symptoms of GVHD are hyperkeratotic plaques, erythema and ulcerations, pain and difficulty to eat. In patients undergoing HSCT, oral manifestations such as lichenoid and ulcerative lesions on the mucosa are normally associated with patient's immunosuppression (Majorna *et al.,* 2000; Haverman *et al.,* 2014).

Periodontitis is an infectious-inflammatory condition associated with a dysbiotic biofilm and a susceptible host (Haffajee and Socransky, 1994; Teles *et al.,* 2013). Periodontitis may affect systemically healthy or compromised adults, but in children they are normally associated with systemic diseases (Prud'homme *et al.,* 2018; Hilgers *et al.,* 2004; Suzuki *et al.,* 2003). Certain systemic disorders may affect the prevalence or the course of periodontitis by decreasing host-defenses or by leading to an over express of host-modulators (Miranda *et al.,* 2020). In addition, in certain cases, periodontal attachment loss may be a consequence or an oral manifestation of a systemic condition (Albandar *et al.,* 2018). Improving the knowledge related to these associations would allow early diagnosis and may prevent attachment and tooth loss in childhood.

This report describes two young children who have had Amegakaryocytic Purpura, underwent hematopoietic stem cell transplant, developed GVHD and severe periodontal clinical attachment loss without pocket formation. We hypothesized that this atypical CAL could be due to, or worsened by, Amegakaryocytic Purpura or GVHD.

Case report

This case report was approved by the research ethics committee from the Clinical Hospital Complex of the Federal University of Paraná (#18257019.3.0000.0096). Clinical medical history data were obtained from physical and electronic medical and dental records. The general dental condition, including intraoral mucosa, gingiva, teeth and oral hygiene was monitored two months after the transplant (when patients were diagnosed with GVHD) and followed up on for a period of 15 months.

Two male siblings aged two and four years old who were diagnosed with Amegakaryocytic Purpura were subjected to allogeneic HSCT. A stem cell haploidentical allograft was obtained from their mother. During the transplant period, the patients presented oral mucositis, which healed spontaneously after recovery of host-defense mechanisms. Approximately two months after transplantation they started to show many adverse symptoms including diarrhea, rash, respiratory desaturation, bronchospasm, dysphagia and weight loss. A diagnosis of GVHD was confirmed on the skin, lungs, oral and gastrointestinal mucosa. At this point, both children developed gingival recession and were referred to the Dental Clinic. Two supragingival biofilm samples were collected from each patient, from teeth presenting clinical attachment loss (CAL) and were analyzed for their content and proportions of 40 bacterial species by Checkerboard DNA-DNA hybridization technique (Socransky *et al*., 1994).

Clinical findings and treatment

At the dental clinic, the two patients were examined, and severe periodontal CAL was observed. No pockets were detected, the attachment loss was only due to severe gingival recession (Figure 1, a and b). They received prophylaxis and 9 months after the allogeneic haploidentical HSCT the patients still persisted with mouth GVHD as well as dental caries, extensive dental biofilm accumulation and gingivitis. Besides the severe periodontal CAL associated with generalized gingival recession, the two patients also had heavy biofilm accumulation and caries in many teeth. They received oral hygiene instruction (OHI), biofilm removal and restorations. They were asked to return to the clinic in a month, but they only returned 7 months later (Figure 1, c). At this time point, 9 months after the transplant, the two patients persisted with very poor dental condition, including heavy accumulation of dental biofilm and progression of CAL, which resulted in increased dental mobility. A follow-up panoramic radiograph was taken (Figure 2), another dental prophylaxis was performed as well as topical fluoride application, further restorations and extractions of other teeth. Additional appointments and OHI were performed up to 15 months post-transplant, but until the last follow-up session both children presented very poor oral status. Despite intensive care, lung disease caused respiratory failure and death of the older sibling at 15 months after HSCT.

Microbiological findings

Figures 3 and 4 present the microbiological composition of the patients' oral biofilms. Overall, the older sibling presented higher counts of all 40 bacterial species evaluated. Periodontal pathogens were detected in both patients, including *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans* and several species of the

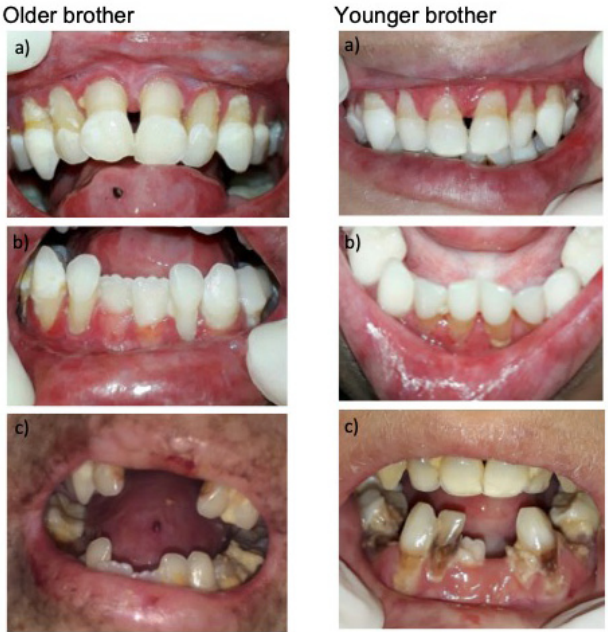

Figure 1. Oral condition of patients. First column has images of older brother and second column of younger brother. a and b are initial conditions and c, the final condition.

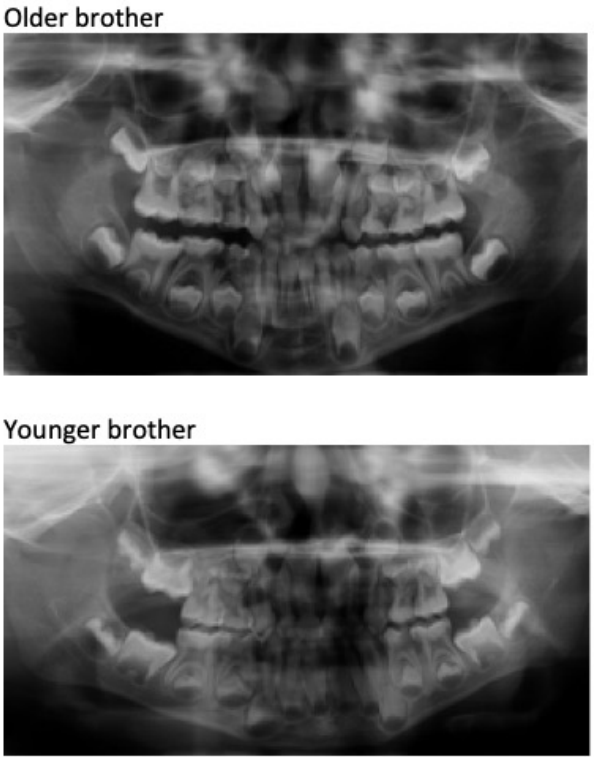

Figure 2. Radiographic images of both patients at the last follow up appointment.

orange complex, such as *Fusobacterium nucleatum ssp.* and *Prevotella nigrescens* (Figure 3). Both patients presented high proportions of orange complex species: 31% and 54.9% in the older and younger patient, respectively; and *A. actinomycetemcomitans* comprised 3.8% and 2.4%, respectively, of the 40 bacterial species evaluated. The host compatible *Actinomyces* species represented around 10% of the species evaluated (Figure 4).

Discussion

This manuscript reports the clinical cases of two male children aged two and four years old who were diagnosed with the same hematologic disease, Amegakaryocytic Purpura, underwent haploidentical allogeneic HSCT and developed GVHD accompanied by several oral alterations. Both patients had high amounts of biofilm, cavities, gingivitis and severe attachment loss, which led to the loss of several teeth. The biofilm samples of the two patients were heavily colonized by *A. actinomycetemcomitans* and other pathogens, such as *P. gingivalis* and species of the orange complex. An important finding was that *A. actinomycetemcomitans* comprised 3.8% and 2.4% of the 40 bacterial species evaluated in the older and younger sibling, respectively. Faveri *et al.*, (2009) have reported similar levels of this bacterium - around 3.9% - in young patients with localized aggressive periodontitis, while this species was present in very low proportions - around 0.5% - in periodontally healthy patients. These findings are interesting because *A. actinomycetemcomitans* is highly virulent and even low levels of this species, especially in the nonmature oral biofilm of very young subjects, may be associated with severe periodontal destruction (Bragd *et al.*, 1987, Rams *et al.*, 1997). Another important observation in this report relates to the proportions of bacterial species of the orange complex. According to Socransky and Haffajee (2005), this group of microorganisms favors, or enables, the establishment of the red complex pathogens. Faveri *et al.*, (2009) showed approximately 27% of orange complex species in healthy young individuals and 25% in individuals with localized aggressive periodontitis. In the present study, these species comprised 31% and 55% of the species evaluated in the older and younger sibling, respectively (Figure 4). In addition, both patients had very low proportions of the host compatible *Actinomyces* species. Taken together, these microbiological data indicate a high degree of dysbiosis on the biofilm samples of both patients.

Pain, dry mouth and oral sensitivity hampered the establishment of a good oral hygiene in these patients, and their high levels of biofilm was clearly a challenge. A better oral hygiene could have favored a healthier oral environment, decreasing the chances of developing caries lesions, gingivitis and periodontitis, and could have afforded a better quality of life for these children (Depalo *et al.,* 2015, Takahashi *et al.,* 2018).

Some hypothesis could be raised to explain the severe loss of periodontal attachment observed in these patients. One could speculate that the severe periodontal recession observed could be an unreported form of oral GVHD occurring in this group of immunocompromised patients. In this case, the dysbiotic biofilm could function as a secondary cause that would potentiate the process of periodontal breakdown. Alternatively,

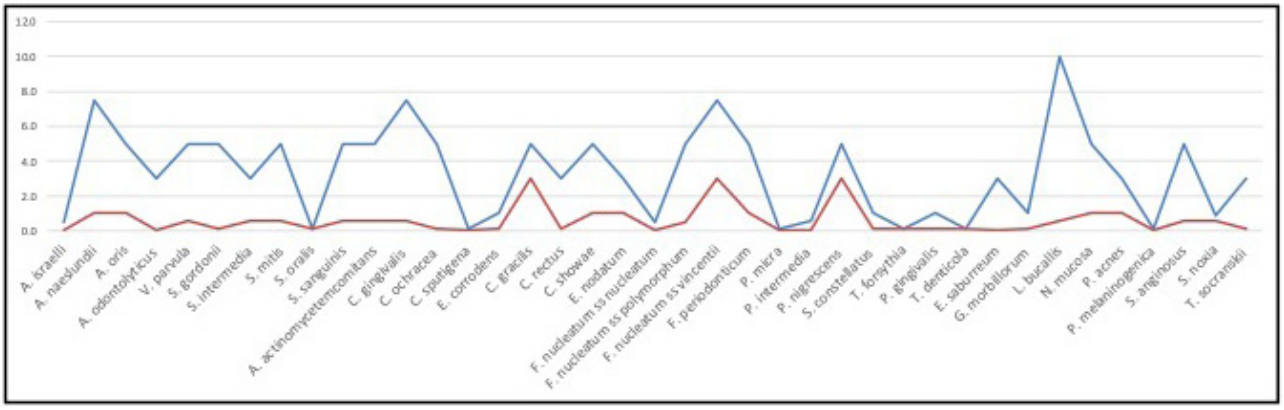

Figure 3. Mean counts (x10^5 cells) of the 40 bacterial species assessed in the dental biofilm samples of the two siblings. In blue the profile of patient 1 (older brother), and in red of patient 2 (younger).

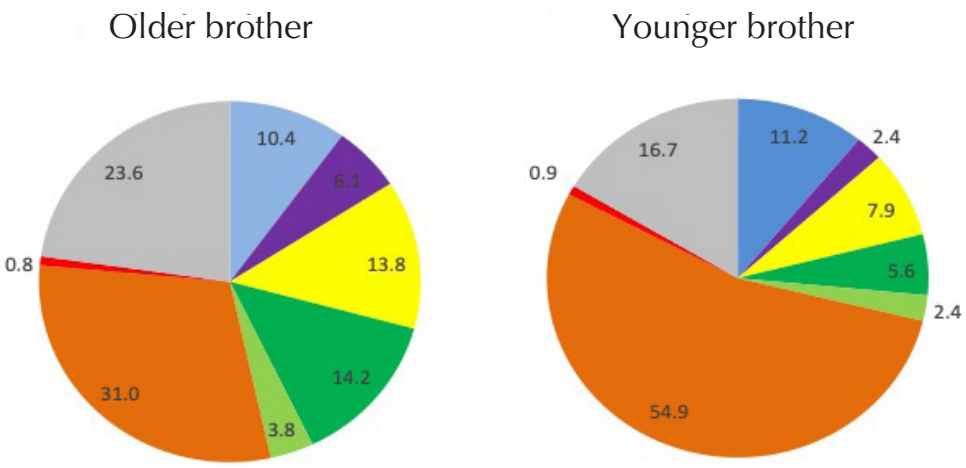

Figure 4. Mean proportions (%) of the microbial complexes. Color code: Red: red complex; Orange: orange complex; light green: Aggregatibacter actinomycetemcomitans; Dark green: green complex; Yellow: yellow complex; Purple: purple complex; Blue: Actinomyces sp.; Gray: bacterial species that do not fit into the other complexes (Socransky et al., 1998).

certain periodontal pathogens found in high levels in the biofilm of these patients, especially *A. actinomycetmcomitans*, could have started tissue destruction in these immunocompromised patients. However, the similarity between the periodontal phenotypes of both siblings presenting the same systemic conditions (Amegakaryocytic Purpura and GVHD) support the first hypothesis. In addition, these two cases are in agreement with a previously reported case of a child diagnosed with acute lymphocytic leukemia who also underwent HSCT. A few months after the transplant, the patient was diagnosed with oral and skin GVHD followed by a similar pattern of clinical attachment loss by means of periodontal recession observed in the cases we have reported here. The authors suggested that the patient's periodontal manifestations were an atypical manifestation of GVHD (Fonseca and Murdoch-Kinch, 2007). Microbiological analysis was not performed in that study. In addition to the similarities in the periodontal clinical manifestations between that case and those reported here, in both studies the patients were young children, diagnosed with hematological diseases, who underwent HSCT and developed GVHD before the identification of periodontal manifestations. Thus, the case reported by Fonseca and Murdoch-Kinch (2007) reinforces the hypothesis that periodontal destruction observed in these young patients could be an atypical manifestation of GVHD in the mouth.

The World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions considered that periodontitis may be a manifestation of different systemic diseases (Albandar *et al.,* 2018, Caton *et al.,* 2018). Possibly, in the future, Amegakaryocytic Purpura and/or GVHD could be included in the list of conditions with periodontal implications.

Conclusion

The cases presented in this manuscript suggested that severe periodontal attachment loss in children with Amegakaryocytic Purpura may be an atypical oral manifestation associated with this condition and/or GVHD, which may be aggravated by the presence of a dysbiotic biofilm containing high levels of certain periodontal pathogens, especially of *A. actinomycetmcomitans*.

Acknowledgments and conflict of interest

The authors present no conflict of interest. No funding source supported this work.

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