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# Oral manifestations of aplastic anemia in children

Ester Sepúlveda, DDS; Ursula Brethauer, DDS; Jaime Rojas, MDS; Patricia Le Fort, MDS

**A**plastic anemia (AA) is a rare blood dyscrasia in which peripheral blood pancytopenia results from reduced or absent blood cell production in the bone marrow, and normal hematopoietic tissue in the bone marrow has been replaced by fatty marrow.<sup>1,2</sup> The estimated incidence of AA is two new cases per 1 million persons per year.<sup>3</sup> The disease is rare in children and the peak age of occurrence is between 3 and 5 years.<sup>4</sup> The disorder can be inherited, idiopathic or acquired; the causes include radiation therapy,<sup>5</sup> intake of drugs and chemicals,<sup>6-9</sup> viral infections,<sup>10-14</sup> thymoma,<sup>15</sup> pregnancy<sup>16,17</sup> and paroxysmal nocturnal hemoglobinuria.<sup>18</sup> However, the course, treatment and outcome are related more to the severity of the hematopoietic depression than to the cause.

## BACKGROUND

Severe AA is defined by two of three criteria: neutrophil count less than  $0.5 \times 10^9$  cells/liter (500 cells/cubic millimeter), platelet count less than  $20 \times 10^9$  cells/L (20,000 cells/mm<sup>3</sup>) and reticulocyte count less than 1 percent. When the reticulocyte count is less than  $0.2 \times 10^9$  cells/L (200 cells/mm<sup>3</sup>), the disease is characterized as very severe.<sup>19</sup> Hematopoietic progenitors of mature red and white blood cells and megakaryocytes are virtually absent.<sup>20</sup>

## ABSTRACT



**Background.** Few studies concerning oral manifestations of aplastic anemia (AA) in children have been reported. The purpose of the authors' study was to describe oral lesions in children with AA.

**Methods.** The authors conducted a retrospective review using medical records of children diagnosed with AA who were treated at the Pediatric Service of the Regional Hospital of Concepción, Chile, between March 1996 and May 2001. They recorded episodes of oral mucosal lesions and assessed platelet and neutrophil counts at the time the oral lesions appeared.

**Results.** Twelve children (nine boys and three girls) were diagnosed with AA. Their age range was 3 to 12 years (median age, 7 years). Nine subjects were receiving immunosuppressive therapy, and three received only supportive care. The most common oral manifestation of the disease was hemorrhage, which developed most often in patients with platelet counts less than  $25 \times 10^9$  cells/liter. The second and third most common oral manifestations were candidiasis and viral infection, respectively.

**Conclusions.** Children with AA frequently exhibit oral manifestations of the condition. Prevention, early diagnosis and proper treatment of oral complications are essential to diminish morbidity and avoid a possible fatal outcome.

**Clinical Implications.** Oral lesions can be the first manifestation of AA; consequently, dentists should be aware of these manifestations so that an early diagnosis of the disease can be made.

**Key Words.** Aplastic anemia; hemorrhage; candidiasis.

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TABLE

### Oral lesion episodes in 11 children with aplastic anemia during a five-year period.

ORAL LESION	NUMBER OF EPISODES
Hemorrhagic Episode	29
Candidiasis	10
Herpes Simplex	10
Herpangina	1
Varicella	1
Necrotizing Ulcerative Gingivitis	1
Pericoronitis	1
Gingival Hyperplasia	1
<b>TOTAL</b>	<b>54</b>

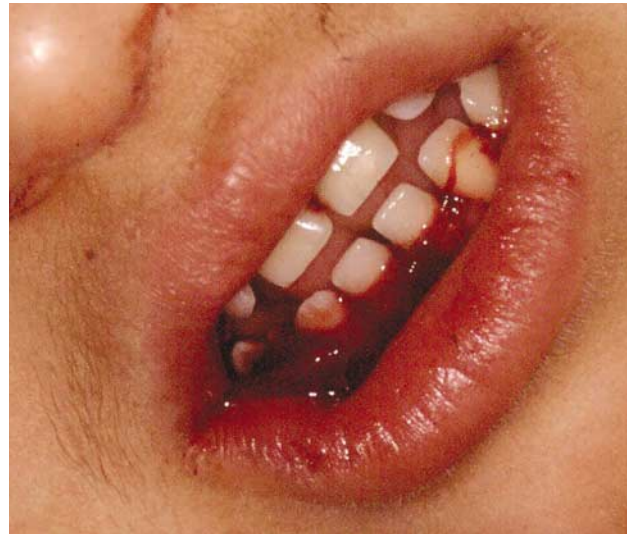
Bone marrow transplantation (BMT) and immunosuppressive therapy are the main therapeutic modalities used in pediatric patients. BMT is the treatment of choice for children with human leukocyte antigen-identical siblings, and immunosuppressive therapy is the treatment of choice for other children.<sup>21-23</sup> Immunosuppressive therapy can achieve a high response rate because of AA's immunitary nature in which bone marrow failure results from immunologically mediated, tissue-specific organ destruction.<sup>24</sup> However, this treatment increases the risk of morbidity in these patients.

Neutropenia, caused by the disorder itself and its treatment, leads to an increased susceptibility to infection, and thrombocytopenia leads to bruising and mucosal bleeding; both of these complications correspond to sepsis and hemorrhage, the main causes of death in these patients.<sup>25-27</sup> The oral cavity is a common site of these complications, and early diagnosis and treatment of oral lesions are important to diminish the risks of morbidity and mortality in patients with AA.

Our literature search revealed few studies concerning oral manifestations of AA in children. Therefore, we conducted a study to describe oral mucosal lesions in children with AA who were treated at the Pediatric Service of the Regional Hospital of Concepción, Chile.

#### SUBJECTS AND METHODS

One of us (E.S.) conducted a retrospective review using medical records of children previously diag-



**Figure 1.** Ten-year-old patient with spontaneous gingival bleeding.

nosed with AA and treated at the Pediatric Service of the Regional Hospital of Concepción, Chile, between March 1996 and May 2001. She collected information about patient age, sex and medical treatment. In addition, she recorded episodes of oral mucosal lesions that developed during the hospitalization and assessed platelet and absolute neutrophil counts (ANCs) at the time the oral lesions appeared.

One calibrated oral surgeon (E.S.) determined the clinical diagnoses of all children with oral lesions. She used cultures to confirm the diagnosis of candidal lesions and an enzyme-linked immunosorbent assay test for herpes simplex virus type 1 and 2 to confirm the diagnosis of herpetic lesions.

#### RESULTS

##### Patient and treatment characteristics.

Twelve children had been diagnosed with AA and received medical care and follow-up at the Pediatric Service of the Regional Hospital of Concepción during the study period. Subjects' age range was 3 to 12 years, and their median age at the time of hospitalization was 7 years. Nine (75 percent) of the 12 children were male and three (25 percent) were female. Nine subjects received immunosuppressive therapy consisting of anti-lymphocyte globulin, cyclosporine and corticosteroids, and three children received supportive care only, because they died before beginning immunosuppressive therapy.

##### Assessment of oral mucosal lesions.



**Figure 2.** Thirteen-year-old patient with erythematous candidiasis of the tongue.



**Figure 3.** Eleven-year-old patient with intraoral herpes simplex type 1 of the gingiva and hard palate.

Overall, we documented a total of 54 episodes of oral lesions in 11 children (Table). The median number of episodes per patient was 5.36 (range, one to 26).

**Hemorrhagic episodes.** We observed 29 hemorrhagic episodes in seven patients. Twenty-seven of these were classified as intraoral

petechiae (n = 8), ecchymoses (n = 8), hematomas (n = 7) and spontaneous bleeding of the gingiva (n = 4) (Figure 1). In addition, we observed two hemorrhages after tooth extractions. The first clinical manifestation of AA before diagnosis in three children were bleeding episodes in the oral cavity. Eleven hemorrhagic episodes occurred in patients with platelet counts less than  $10 \times 10^9$  cells/L (10,000 cells/mm<sup>3</sup>), 16 in patients with platelet counts greater than  $10 \times 10^9$  cells/L but less than  $25 \times 10^9$  cells/L (25,000 cells/mm<sup>3</sup>) and two in patients with platelet counts greater than  $25 \times 10^9$  cells/L (normal platelet counts are 220 to  $250 \times 10^9$  cells/L).

**Candidiasis.** We documented candidiasis episodes in five patients. We observed intraoral erythematous candidiasis (n = 6) (Figure 2) and commissural fungal cheilitis (n = 4). Five episodes occurred when the ANC was greater than  $1 \times 10^9$  cells/L (1,000 cells/mm<sup>3</sup>) and five occurred when the ANC was less than  $1 \times 10^9$  cells/L.

A total of 12 viral lesions developed in nine patients, including labial (n = 5) and intraoral (n = 5) herpes simplex (Figure 3) herpangina (n = 1) and varicella-zoster (n = 1). In 10 cases of viral infection, the ANC was less than  $1 \times 10^9$  cells/L, and in two cases, it was greater than  $1 \times 10^9$  cells/L.

## DISCUSSION

Similar to the results of a previous study conducted in adults with AA,<sup>28</sup> we found that hemorrhagic episodes were the most common oral manifestation in patients. These results differ from those found in immunosuppressed children with other diseases, such as leukemia, lymphomas and other malignancies.<sup>29-31</sup> The most frequent oral lesions observed in those patients were nonspecific ulcers, mucositis and candidiasis.<sup>29-31</sup> In addition, Leggot and colleagues<sup>32</sup> found that candidiasis was the most common oral disease affecting patients with immunodeficiencies such as HIV infection.

As stated above, there are two main approaches to treating patients with AA: BMT and immunosuppressive therapy.<sup>22,33,34</sup> No patients in our study group received BMT treatment; all patients received pharmacological therapy, resulting in a homogeneous population. Although immunosuppressive therapy has been shown to be effective in improving bone marrow function in most patients with AA, it commonly induces defects in host defense (pancytopenia)

that contribute to the underlying disease.<sup>35,36</sup>

We must point out that 11 (92 percent) of 12 children in our study experienced at least one episode of oral infection (fungal, viral or bacterial) during the study period. The mouth is a port of entry for early infections in these patients that can complicate general conditions and even be life-threatening.<sup>37,38</sup> In fact, three patients in our study died of bacterial sepsis before beginning immunosuppressive therapy.

Although fungal and viral infections usually are associated with absolute lymphocyte count, we did not assess this in our study. Further investigations are needed to determine the relationship between absolute lymphocyte count and infection in patients with AA.

The first clinical manifestation of AA before diagnosis was an oral hemorrhagic episode in three (25 percent) of 12 children. One of these cases has been reported elsewhere.<sup>39</sup> This illustrates the importance of conducting a rigorous clinical evaluation of a patient with unexplained or persistent bleeding in the oral cavity.

Eighteen (62 percent) of 29 hemorrhagic episodes observed in our study occurred in subjects with platelet counts greater than  $10 \times 10^9$  cells/L, while only 11 (38 percent) occurred in subjects with platelet counts less than  $10 \times 10^9$  cells/L. This might have resulted because the latter group received prophylactic platelet transfusions and a soft diet to avoid hemorrhage. Children with platelet counts of more than  $10 \times 10^9$  cells/L did not receive prophylactic platelet support or a soft diet.

Gingival hyperplasia was rare (only one case), although most of the children (nine [75 percent] of 12) were being treated with cyclosporine, which is known to induce this type of pathology.<sup>40,41</sup> A possible explanation for this is that at the time of the oral examination during the hospital stay, some patients had been receiving cyclosporine treatment for only a short period.

One limitation of this study is the small sample size, resulting from the low incidence of AA in children.

## CONCLUSION

Children with AA frequently have oral lesions associated with their systemic condition and therapy. Hemorrhagic episodes were the most commonly observed oral manifestation of the disease in this study, especially in patients whose platelet counts were less than  $25 \times 10^9$  cells/L.

Further investigations are needed to assess the prevalence of these oral manifestations in children with AA, as well as to evaluate their severity and the possible related fatal outcome. ■

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