Clinical Practice

Oral Complications Associated with Idiopathic Medullary Aplasia: Case Report

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ABSTRACT

This article describes a patient who experienced serious oral sequelae after severe oral hemorrhage associated with medullary aplasia. These complications required medical, surgical and prosthetic treatments necessitating dental expertise in the hospital setting.

Medullary aplasia is a rare hematologic disorder characterized by pancytopenia (i.e., anemia, leukopenia and thrombocytopenia) occurring in association with hypocellularity or acellularity of the bone marrow in the absence of problems of cell maturation and malignant or fibrotic medullary invasion.

Worldwide, the annual incidence of medullary aplasia is 2 cases per million population. The condition may be congenital or acquired. The rare congenital form (mainly associated with Fanconi anemia or congenital dyskeratosis) occurs in children between 2 and 5 years of age, whereas the age distribution of the more common acquired form has 2 peaks, one among adolescents and young adults (15–25 years of age) and the other among adults over 60 years of age.

On rare occasions, medullary aplasia may present as a complication of hepatic grafting, or it may appear in patients with an immunologic disorder such as systemic lupus erythematous. The disease has also been associated with pregnancy, although no causal link has been demonstrated. For about one-third of acquired cases, the disease occurs secondary to toxic exposure to ionizing radiation or certain chemicals or pharmaceuticals or after a viral infection, principally involving Human parvovirus B19. Epstein–Barr virus (EBV), HIV and certain unidentified viruses responsible for hepatitis have also been implicated, although their roles have not been clearly defined; neither hepatitis A, B, C and G are involved.

Contrary to what is commonly accepted, some authors have linked medullary aplasia to the hepatitis A, B, C and G viruses. For the other 70% of acquired cases, the disease...
is idiopathic (of unknown origin). Even so, numerous observations suggest the existence of immunologic mechanisms causing the release of cytokines, which activate T lymphocytes to suppress and destroy hematopoietic stem cells.2,3,5,20–22

Clinical Signs and Symptoms

The characteristic pancytopenia of medullary aplasia leads to a clinical pattern of anemia combined with asthenia, progressive dyspnea and pallor. The leukopenia allows the development of febrile infections, which constitute the primary cause of death among patients with aplasia.23 In the mouth, such infections usually present in the form of erythematous candidiasis, fungal angular cheilitis, herpetic lesions and multiple ulcerations.24–26

The hemorrhagic diathesis associated with thrombocytopenia manifests as a hemorrhagic syndrome characterized by petechiae and mucosal ecchymosis, spontaneous gingival bleeding, hematomas, epistaxis and menorrhagia.1,7,12,24–26 Gingival hyperplasia has also occurred in association with medullary aplasia.24,25,27

Treatments and Prognosis

To manage the clinical symptoms and prevent serious complications, broad-spectrum antibiotics are administered and blood values are stabilized through transfusions of red blood cells, leukocytes and platelet concentrate.1,5,7

In a minority of patients with less severe aplasia, the problem may resolve spontaneously. More often, progression of the disease leads to a requirement for immunosuppressive therapy (in the form of antilymphocyte globulin and cyclosporine), accompanied by corticosteroid therapy, possibly in combination with hematopoietic stimulation via granulocyte colony-stimulating factor and granulocyte–macrophage colony-stimulating factor.28 If there is no response to immunosuppressive therapy, hematopoietic stem-cell transplantation currently constitutes the best option for a patient under 30 years of age, if a compatible donor is available. In this setting, the recovery rate is 70%–90%.2,28–32 Age and disease severity are the most important prognostic factors, with mortality approaching 50% among patients over 40 years of age.

Case Report

A 16-year-old student, who took part in a few sports activities during a 3-week period of weakness accompanied by expectoration, presented with mucosal and cutaneous ecchymoses and petechiae, without spontaneous bleeding or adenopathy. The patient had a history of chickenpox and had undergone tonsillectomy at a young age. He had no known allergies, did not take any medications and did not use alcohol or tobacco. Given this clinical presentation, the patient underwent a medical examination. Laboratory tests revealed pancytopenia, requiring administration of a few units of platelet concentrate. The preliminary diagnosis was acute leukemia or postinfection medullary aplasia. The patient was admitted to the hematology unit and underwent bone marrow biopsy, which confirmed the diagnosis of idiopathic medullary aplasia.

One week after the diagnosis had been established, a continuous 2-way central catheter was inserted to administer broad-spectrum antibiotics, red blood cells and platelet concentrate, with the goal of maintaining the platelet count as close as possible to 50 × 10^9/L. One week later (i.e., 2 weeks after the diagnosis), immunosuppressive therapy was started, consisting of antilymphocyte serum and cyclosporine in combination with low-dose glucocorticotherapy.

Another week later (i.e., 1 week after initiation of the immunosuppressive therapy), the patient, who still had aplasia causing thrombocytopenia and was also experiencing marginal gingivitis, took a turn for the worse. A small gingival hematoma developed between the premolars and the lower right molars. The hematoma was not associated with active hemorrhage or pain, but it quickly (within 6 days) evolved into a giant hematoma covering the cheek, the floor of the mouth and the right cervical region. Compression of the laryngopharyngeal pathways followed, presenting imminent risk of laryngeal obstruction; tracheotomy and intravenous hyperalimentation were initiated as supportive therapy. The tissue compression secondary to the hematoma led to ischemia of the floor of the mouth, the cheek area and the right hemimandibular area, which in turn caused mobility of teeth 43 to 48 without dental pain.

A new regimen of antibiotic and antifungal agents, as well as medullary granulocyte colony-stimulating factor, was ordered for the patient, who was febrile. Because there had been no recovery of medullary function, he was referred for hematopoietic stem cell transplantation from a related donor, his 13-year-old sister (human leukocyte antigen tissue compatibility 6/6).
Because the donor had active infectious mononucleosis at the time of the testing, she received antiviral therapy (acyclovir) for 1 week before bone marrow harvest; the same course of prophylaxis was given to the recipient for the entire period of immunosuppression, to avoid the risk of EBV-associated lymphoproliferative disorder.

Two weeks after the allogeneic graft, the first signs of medullary regeneration were observed, accompanied by gradual resorption of the oral hematoma. Thirty-one days after the transplant procedure, bone marrow biopsy showed cellularity of 25%, indicating good medullary recovery. The patient was afebrile and his clinical status was good, but his hemoglobin level could not be maintained above 70 g/L; therefore, 2 units of cytomegalovirus-negative irradiated red blood cells were administered. The intravenous hyperalimentation and antibiotic therapy were stopped, and the patient was discharged from hospital a little over 3 months after being admitted.

Late Oral Complications
About 5 months after the oral hemorrhagic event (i.e., 4 months after the medullary transplant), significant ischemic osteonecrosis of the floor of the mouth occurred, extending to the hemimandibular region and the right cheek (Figs. 1 and 2); this osteonecrosis was due to the compression caused by the hematoma. Treatment with clindamycin was started immediately, but extraction of all teeth in the fourth quadrant was required, along with sequestrectomy, ablation of the right submandibular gland and reconstruction using an antebrachial flap (Fig. 3); this work was performed by a surgical team with ENT and maxillofacial expertise. Five months after this intervention, dehiscence of the oral wound around the tongue and cheek was observed, along with a significant bone sequestrum; antibiotics were given and the same surgical team removed the sequestrum.

Late Medical Complications
Approximately 4 months after the sequestrectomy, chronic graft-versus-host disease (GVHD) developed, with skin and pulmonary symptoms, which were treated by immunosuppression (i.e., corticosteroids, tacrolimus) and exposure to ultraviolet radiation. GVHD, which develops after bone marrow or hematopoietic stem cell allograft, represents, in short, a reaction of the donor’s cells against the antigens of the recipient’s cells. In its acute or chronic form, GVHD can affect a variety of organs, particularly the skin, the liver and the gastrointestinal tract. The oral mucosa can also be affected in 25%–50% of cases of chronic GVHD, but this did not occur with this patient.

In addition to the patient’s continuing antiviral and immunosuppressive therapy, he was taking prophylactic trimethoprim–sulfamethoxazole; however, nodular obliterating bronchiolitis, with infection as the suspected
cause, developed concurrent with the GVHD and was treated with corticosteroids and ciprofloxacin. The patient then exhibited symptoms of moderate renal failure, probably precipitated by dehydration and some diarrhea (problems that may have been related to the patient’s difficulty in feeding himself).

**Dental Rehabilitation**

Nearly 3 years after the onset of the medullary aplasia, the patient’s medical status had completely stabilized, and he was fitted with a conventional removable prosthesis to compensate for the loss of his right lower teeth. Unfortunately, he did not use the prosthesis as prescribed because of its poor performance; in particular, the bone loss resulting from the sequestrectomy and the tissue compressibility associated with the tissue graft led to a marked deficiency in support for and stability of the prosthesis. The patient indicated a desire to improve his masticatory function and was referred to us. We decided to develop an implant-supported prosthesis to ensure adequate support. Because of the ischemic damage that had already occurred, it was deemed appropriate to protect the patient with a series of hyperbaric oxygen treatments before and after the placement of 4 Brånemark osseointegrated implants (Fig. 4). The Marx protocol was used,\(^{37}\) which specifies 20 hyperbaric treatments before and 10 treatments after surgery. Four months after the dental implant surgery, the implant abutments were positioned, and creation of the prosthesis was initiated (Fig. 5). At the time of writing, 2 years after the prosthesis became functional, the patient’s masticatory function remained optimal (Figs. 6 and 7).

**Discussion**

The literature includes reports of avascular necrosis following immunosuppressant treatment with antilymphocyte globulin and methylprednisolone (glucocorticoid).\(^{38}\) However, the reported cases have principally involved the hip and shoulders, never (to the authors’ knowledge) the jaw. The necrosis arises when methylprednisolone is administered at high doses (5 mg/kg daily) at the beginning of therapy and is then progressively reduced over a period of 3 weeks. No cases of necrosis have been reported during treatment with low doses (1 mg/kg daily). In addition to antilymphocyte globulin, the patient described here was receiving less than 1 mg/kg daily...
methylprednisolone, which was progressively reduced to zero over 14 days. The health care team therefore ascribed the partial necrosis of the mandible exclusively to vascular compression resulting from the hematoma.

The development of necrotizing ischemia following hematoma and surgical reconstruction with an antebra-chial flap led the health care team to suspect vascular deficiency; the patient was therefore sent for hyperbaric oxygen therapy, intended to optimize osseointegration of the implants and other aspects of the healing process. During hyperbaric oxygen therapy, the patient breathes pure oxygen at a pressure of 2.4 atm in a closed chamber. The result is a proliferation of fibroblasts and osteoblasts, an increase in collagen production and angiogenesis arising from the increased tissular oxygen tension.37 The Marx protocol was developed for surgical treatment in irradiated bone, which was not the situation here; however, a parallel was established between reduced vascularization of irradiated tissues and the reduced vascularization in ischemic tissue in the patient described here.

Medullary aplasia is one of several medical conditions that render patients vulnerable to infections and hemorrhage, because of the leukopenia and thrombocytopenia associated with both the disease and its therapy. The oral cavity can be an entry point for bacteria, which may be associated with subsequent complications experienced by patients with immunosuppression and which can lead to septicemia and death.39–42 It is therefore essential that all sites of infection and all conditions that carry any risk of infection (e.g., caries, periodontal disease) be treated before initiation of immunosuppressive therapy; in addition, the patient must receive instructions for proper hygiene. In addition to potential problems related to infections, the treatment of medullary aplasia, notably allo-genic stem cell transplantation, may be associated with a variety of oral complications, such as mucositis, xerostomia, GVHD and secondary neoplasia, which must be treated and monitored by the dental team.34 The oral health of the patient in this case was excellent when he was admitted to hospital, with the exception of marginal gingivitis requiring at most some instructions for proper hygiene. As described here, it was primarily the consequences of hemorrhagic complications that necessitated the intervention of the hospital dental team.

Conclusions

This case emphasizes the importance of including dental professionals on multidisciplinary hospital teams treating immunocompromised patients. A variety of diseases and therapies have medical consequences that require consideration of oral health and recourse to dental expertise to ensure optimal quality of life for the patients.42–45

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