

Oral Complications Associated with Idiopathic Medullary Aplasia: Case Report

Marcel Clercq, DMD, MSc; Mélanie Gagné-Tremblay, DMD

Contact Author

Dr. Clercq

Email: marcel.clercq@chuq.qc.ca



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.

For citation purposes, the electronic version is the definitive version of this article: www.cda-adc.ca/jcda/vol-74/issue-4/373.html

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^{1,2} in the absence of problems of cell maturation and malignant or fibrotic medullary invasion.^{3,4}

Worldwide, the annual incidence of medullary aplasia is 2 cases per million population.^{2,4-7} 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.^{2,4-7}

On rare occasions, medullary aplasia may present as a complication of hepatic grafting,⁸ or it may appear in patients with an immunologic disorder such as systemic lupus erythematosus.⁹ The disease has also been associated with pregnancy, although

no causal link has been demonstrated.¹⁰ For about one-third of acquired cases, the disease occurs secondary to toxic exposure to ionizing radiation or certain chemicals or pharmaceuticals^{1,2,5,11-13} 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.^{5,6,11,12,14-17} In the context of acquired disease, autoimmune mechanisms are more likely than direct viral action on the hematopoietic stem cells. Other infectious agents more rarely associated with the development of aplastic anemia have been mentioned in the literature, including the *Rubella virus* (a paramyxovirus), the *Mumps virus* (another paramyxovirus), the varicella-zoster virus (also known as *Human herpesvirus 3*) and the *Influenza A virus*. Contrary to what is commonly accepted, some authors have linked medullary aplasia to the hepatitis A, B, C and G viruses.^{5,18,19} For the other 70% of acquired cases, the disease

Chemicals and medications most frequently associated with medullary aplasia^{5,13}

- Benzene
- Other organic solvents
- Insecticides derived from petroleum and organochlorine products
- Gold salts
- Chloramphenicol
- Colchicine
- Sulphonamides
- Penicillamine
- Phenylbutazone
- Quinacrine
- Cimetidine
- Carbamazepine

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 com-

patible donor is available. In this setting, the recovery rate is 70%–90%.^{7,28-32} 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 $50 \times 10^9/L$. 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 antibrachial 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.³³ In its acute or chronic form, GVHD can affect a variety of organs, particularly the skin, the liver and the gastrointestinal tract.³³⁻³⁶ 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

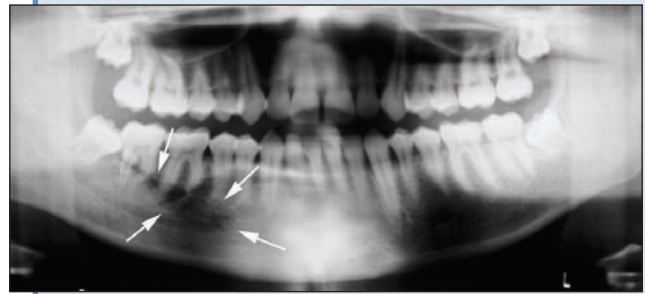


Figure 1: Osseous lesion of the right mandible, associated with ischemic osteonecrosis arising from a large hematoma.

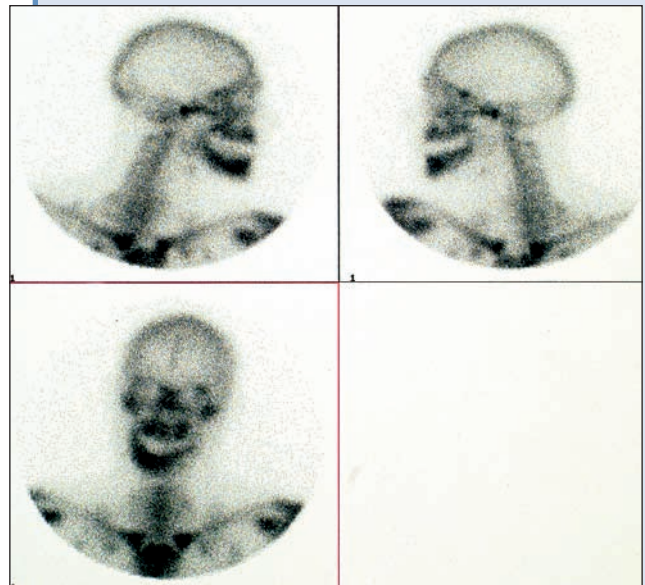


Figure 2: Contrast-enhanced bone scan (obtained after administration of ^{99m}Tc-methyl diphosphonate) shows asymmetric uptake of the contrast agent: the concentration is greater at the horizontal ramus of the right inferior maxilla, the site of the ischemic osteonecrosis.



Figure 3: Panoramic radiograph after extraction of all teeth in the fourth quadrant, performed as part of the treatment for ischemic osteonecrosis.



Figure 4: Four osseointegrated implants in place.



Figure 5: Intraoral photograph of the implant abutments and ball attachment shows the antebrachial flap (forearm skin) and its hairiness.



Figure 6: Partial removable prosthesis and its attachments.



Figure 7: Partial removable implant-supported prosthesis in the mouth.

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 osteo-blasts, an increase in collagen production and angiogen-esis 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 hemor-rhage, 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-geneic stem cell transplantation, may be associated with a variety of oral complications, such as mucositis, xero-stomia, 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 complica-tions 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 ♦

THE AUTHORS



Dr. Clercq maintains a practice dedicated to oncology at the Hôtel-Dieu de Québec hospital in Québec City. He is respon-sible for intraoral implant-supported rehabilitation at the hospital.



Dr. Gagné-Tremblay maintains a practice dedicated to onc-ology at the Hôtel-Dieu de Québec hospital in Québec City. She is responsible for the oral care of patients who have under-gone bone marrow transplantation at the hospital.

Correspondence to: Dr. Marcel Clercq, Médecine dentaire en oncologie, Hôpital L'Hôtel Dieu de Québec, 11, côte du Palais, Québec QC G1R 2J6.

The authors have no declared financial interests.

This article has been peer reviewed.

References

1. Pérusse R. Désordres systémiques: planification des soins dentaires. Sainte-Foy: Les presses de l'Université Laval; 1996. p. 14.
2. Young NS. Aplastic anaemia. *Lancet* 1995; 346(8969):228-32.
3. Young NS, Maciejewski J. The pathophysiology of acquired aplastic anemia. *N Engl J Med* 1997; 336(19):1365-72.
4. International agranulocytosis and aplastic anemia study. Incidence of aplastic anemia: the relevance of diagnostic criteria. *Blood* 1987; 70(6):1718-21.
5. Alter BP, Young NS. Bone marrow failure syndromes. In: Natan DG, Orking SM, editors Hematology of infancy and childhood. Philadelphia: W.B. Saunders; 1998. p. 237-76.
6. Mary JY, Baumelou E, Guiguet M. Epidemiology of aplastic anemia in France: a prospective multicentric study. The French Cooperative Group for Epidemiological Study of Aplastic Anemia. *Blood* 1990; 75(8):1646-53.
7. Brodsky RA, Jones RJ. Aplastic anaemia. *Lancet* 2005; 365(9471):1647-56.
8. Goss JA, Schiller GJ, Martin P, Seu P, Stribling R, Mc Diarmid SV, and others. Aplastic anemia complicating orthotopic liver transplantation. *Hepatology* 1997; 26(4):865-69.
9. Walport MJ, Hubbard WN, Hughes GR. Reversal of aplastic anaemia secondary to systemic lupus erythematosus by high-dose intravenous cyclophosphamide. *Br Med J (Clin Res Ed)* 1982; 285(6344):769-70.
10. Oosterkamp HM, Brand A, Kluin-Nelemans JC, Vandenbrouck JP. Pregnancy and severe aplastic anemia: causal relation or coincidence? *Br J Haematol* 1998; 103(2):315-6.
11. Young NS. Acquired aplastic anemia. *Ann Intern Med* 2002; 136(7):534-46.
12. Neville BW, Damm DD, Allen CM, Bouquet JE. Oral and maxillofacial pathology. Philadelphia : W.B. Saunders; 1995. p. 422.
13. Kaufman DW, Kelly JP, Levy M, Shapiro S. The drug etiology of agranu-locytosis and aplastic anemia. New York: Oxford University Press; 1991. 18: 1-49.
14. Nissen C. The pathophysiology of aplastic anemia. *Semin Hematol* 1991; 28(4):313-8.
15. Brown KE, Tisdale J, Barrett AJ, Dunbar CE, Young NS. Hepatitis-associ-ated aplastic anemia. *N Engl J Med* 1997; 336(15):1059-64.
16. Hibbs J, Frickofen N, Rosenfeld SJ, Feinstone SM, Kojima S, Bacigalupo A, and others. Aplastic anemia and viral hepatitis. Non-A, Non-B, Non-C? *JAMA* 1992; 267(15):2051-4.
17. Kurtzman G, Young N. Viruses and bone marrow failure. *Baillieres Clin Haematol* 1989; 2(1):51-67.
18. Paquette RL, Kuramoto K, Tran L, Sopher G, Nimer SD, Zeldis JB. Hepatitis C virus infection in aquired aplastic anemia. *Am J Hematol* 1998; 58(2):122-6.
19. Crespo J, de las Heras B, Rivero M, Lozano JL, Fabrega E, Pons-Romero F. Hepatitis G virus infection as a possible causative agent of community-acquired hepatitis and associated aplastic anaemia. *Postgrad Med J* 1999; 75(81):159-61.

20. Sauntharajah Y, Nakamura R, Nam JM, Robyn J, Loberiza F, Maciejewski JP, and others. HLA-DR15 (DR2) is overrepresented in myelodysplastic syndrome and aplastic anemia and predicts a response to immunosuppression in myelodysplastic syndrome. *Blood* 2002; 100(5):1570–4.
21. Shichishima T, Okamoto M, Ikeda K, Kaneshige T, Sugiyama H, Terasawa T, and others. HLA class II haplotype and quantitation of WT1 RNA in Japanese patients with paroxysmal nocturnal hemoglobinuria. *Blood* 2002; 100(1):22–8.
22. Zeng W, Maciejewski JP, Chen GH, Risitano AM, Kirby M, Kajigya S, and other. Selective reduction of natural killer T cells in the bone marrow of aplastic anaemia. *Br J Haematol* 2002; 119(3):803–9.
23. Torres HA, Bodey GP, Rolston KV, Kantarjian HM, Raad II, Kontoyiannis DP. Infections in patients with aplastic anemia: experience at a tertiary care cancer center. *Cancer* 2003; 98(1):86–93.
24. Brennan MT, Sankar V, Baccaglini L, Pillemer SR, Kingman A, Nunez O, and others. Oral manifestations in patients with aplastic anemia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; 92(5):503–8.
25. Sepulveda E, Rojas Castro J. Signs of medullar aplasia in the oral cavity: report of case. *ASDC J Dent Child* 2001; 68(1):70–2.
26. Sepulveda E, Brethauer U, Rojas J, Le Fort P. Oral manifestations of aplastic anemia in children. *J Am Dent Assoc* 2006; 137(4):474–8.
27. Luker J, Scully C, Oakhill A. Gingival swelling as a manifestation of aplastic anemia. *Oral Surg Oral Med Oral Pathol* 1991; 71(1):55–6.
28. Ball SE. The modern management of severe aplastic anaemia. *Br J Haematol* 2000; 110(1):41–53.
29. Gillio AP, Boulad F, Small TN, Kerman NA, Reyes B, Childs BH, and others. Comparison of long-term outcome of children with severe aplastic anemia treated with immunosuppression versus bone marrow transplantation. *Biol Blood Marrow Transplant* 1997; 3(1):18–24.
30. Passweg JR, Socié G, Hinterberger W, Bacigalupo A, Biggs JC, Camitta BM, and others. Bone marrow transplantation for severe aplastic anemia: has outcome improved? *Blood* 1997; 90(2):858–64.
31. Bacigalupo A, Hows J, Gluckman E, Nissen C, Marsh J, Van Lint MT, and others. Bone marrow transplantation (BMT) versus immunosuppression for the treatment of severe aplastic anaemia (SAA): a report of the EBMT SAA working party. *Br J Haematol* 1988; 70(2):177–82.
32. Speck B. Allogeneic bone marrow transplantation for severe aplastic anemia. *Semin Hematol* 1991; 28(4):319–21.
33. Clercq M, Gagné-Tremblay M. Greffe de moelle osseuse et cellules souches hématopoïétiques chez l'adulte : implications et complications bucco-dentaires. *J Dent Québec* 2004; 41:317–28.
34. Schiller GJ. Hematology/oncology clinics of North America: Hematopoietic Stem Cell Therapy. Philadelphia: W.B. Saunders; 1999. p. 889–986.
35. Vignes S, Farge D. Mécanismes et expression clinique de la GVH. Service de médecine interne, Hôpital Saint- Louis, Paris. Available: www.medicalistes.org/spip/article133.html.
36. Arai S, Vogelsang GB. Management of graft-versus-host-disease. *Blood Rev* 2000; 14(4):190–204.
37. Marx RE, Johnson RP. Studies in the radiobiology of osteoradionecrosis and their clinical significance. *Oral Surg Oral Med Oral Pathol* 1987; 64(4):379–90.
38. Marsh JC, Zomas A, Hows JM, Chapple M, Gordon-Smith EC. Avascular necrosis after treatment of aplastic anaemia with antilymphocyte globulin and high-dose methylprednisolone. *Br J Haematol* 1993; 84(4):731–5.
39. Greensberg MS, Cohen SG, McKittrick JC, Cassileth PA. The oral flora as a source of septicemia in patients with acute leukemia. *Oral Surg Oral Med Oral Pathol* 1982; 53(1):32–6.
40. Woo SB, Matin K. Off-site evaluation program for prospective bone marrow transplant recipients. *J Am Dent Assoc* 1997; 128(2):189–93.
41. Meurman JH, Pyrhonen S, Teerenhovi L, Lindqvist C. Oral sources of septicemia in patients with malignancies. *Oral Oncol* 1997; 33(6):389–97.
42. Barker GJ. Current practices in the oral management of the patient undergoing chemotherapy or bone marrow transplantation. *Support Care Cancer* 1999; 7(1):17–20.
43. Jones JE, Coates TD, Poland C. Dental management of idiopathic aplastic anemia: report of a case. *Pediatr Dent* 1981; 3(3):267–70.
44. Valdez IH, Patton LL. Aplastic anemia: current concepts and dental management. *Spec Care Dent* 1990; 10(6):185–9.
45. Yalman N, Sepet E, Aren G, Mete Z, Külekçi G, Anak S. The effect of bone marrow transplantation on systemic and oral health in Fanconi's aplastic anemia. *J Clin Pediatr Dent* 2001; 25(4):329–32.