Case Report

Oral aspects and management of severe graft-vs-host disease in a young patient with ß-thalassemia: case report

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ß-Thalassemia is an inherited hematologic disorder commonly found in people from Mediterranean, Middle Eastern, and Southeast Asian countries as well as in blacks.[1,2] The disorder involves reduction or impairment of the synthesis of the ß-globin chain which leads to ineffective erythropoiesis, anemia, impaired physical growth and development, hypertrophy of the erythropoietic tissues in the medullary and extramedullary spaces, hepatosplenomegaly, and a characteristic facies.[2–4] The affected child has skull bossing, hypertrophy of the mandible and prominent malar eminences ("chipmunk facies"), retraction of the upper lip, protrusion of the anterior teeth, and various degrees of malocclusion. Several radiographic changes are observed in the jaws as a result of the expansion of the marrow spaces, including rarefaction of the alveolar bone and thinning of the cortical bone.[5,6] There are two types of ß-thalassemia: the heterozygous or ß-thalassemia minor (trait) and the homozygous or ß-thalassemia major. Patients with the major type may have serious complications such as recurrent infections, spontaneous fractures, hypersplenism, and leg ulcers.[4]

Treatment of thalassemia involves multiple blood transfusions to elevate the hematocrit. However, a primary complication caused by regular transfusions is iron overload, which may lead to damage to the myocardium, liver, spleen, pancreas, thyroid, parathyroid, and gastrointestinal (GI) mucosa.[4,5] Improvements in the efficacy of iron chelation with deferoxamine have increased the survival of well-managed patients into the third and fourth decades of life.[3] Splenectomy results in a modest reduction in transfusion frequency but increases the infection risks. Bone marrow transplantation (BMT) can cure thalassemia, especially in young patients who have not had severe organ damage due to iron overload.[3]

In children undergoing a BMT due to hematologic/oncologic conditions, therapies used to treat the baseline disease before considering the transplantation and the preparative transplant conditioning itself (chemotherapy with or without radiotherapy) can cause long-term effects. These effects may include neuroendocrine function disturbances, ophthalmologic problems, central nervous system dysfunction, secondary malignancies, and dental developmental abnormalities.[7–11] Graft-vs-host disease (GVHD) is one of the most significant complications of BMT and results from immunologically competent donor cells that react against histocompatibility antigens of the host.[12] Acute GVHD appears in the first 100 days post-transplant (median: 19 days)[13] while the chronic type develops between 3 and 12 months in 25–40% of long-term survivors.[14] GVHD can involve the skin, liver, GI tract, eyes, mucous membranes, and the mouth where xerostomia, mucosal atrophy, and lichenoid changes of the buccal and labial mucosa are frequently seen.[15,16]

The case of a young ß-thalassemia patient who received a BMT and subsequently developed severe chronic GVHD with serious oral complications is discussed.

Case report

Past medical history and chief complaint

A 6-year-old Saudi Arabian male was referred to the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle in September, 1994 for evaluation and treatment of severe chronic GVHD. The patient had been diagnosed with ß-thalassemia major at 6 weeks of age and had blood transfusions until 1 year of age, when he came to the US for an allogeneic transplant, preceded by a conditioning regimen of busulfan and cyclophosphamide. The donor was his mother, who was a complete human leukocyte antigen (HLA) match.

Despite having an adequate engraftment, he presented several post-transplant complications includ-

ing cytomegalovirus (CMV) infection, hypertension, and chronic GVHD diagnosed on day 82 post-transplant. He developed progressive dermal induration, dyspigmentation, and elevated serum liver enzymes. He returned to his home country where he received cyclosporine and prednisone for 5 years on an irregular schedule due to poor compliance to medical recommendations, which may also have contributed to the severity of his disease. The parents could not offer many details about the patient's status prior to the transplant.

All his primary teeth were removed under general anesthesia a few years earlier due to multiple extensive carious lesions. He was unable to take solid foods by mouth and subsisted on small amounts of liquids and pediatric liquid feedings. He had never used fluoride or antibacterial rinses.

Present illness and physical examination

At the time of admission to the FHCRC, the disease involved the skin, GI tract, eyes, and oral cavity. He exhibited failure to thrive with a weight of 13.2 kg (as a comparison, in a 26-month-old child, that would be 50th percentile) and was very short for his age. Physical examination revealed scleroderma, vitiligo, alopecia, premature hair whitening (Figure 1), dystrophic nails (Figure 2), speech problems, severe penoscrotal hypospadias, occular sicca syndrome with narrowing of eye opening, photophobia, and vision loss. Hand radiographs showed the distal radial epiphysis and the epiphyseal plate at the proximal phalanges to be consistent with a bone age of approximately 6 years. However, the development of the carpal bones indicated an age of approximately 3-and-a-half years. He had had no immunizations, had been off medications for about a year, and had no known drug allergies. Surgical history was significant for urethral stricture dilation and bilateral cataracts removal.

A skin biopsy was positive for active GVHD. Only a few small patches of normal skin could be observed on his entire body; scaling was seen in many areas. There were multiple healed lesions with profound scarring and extensive contractures. He was unable to stand completely erect although no major deformity of the spine or orthopedic abnormalities were evident. Joint contractures were most remarkable in the elbows, shoulder, and neck.

Oral and radiographic examination

The patient's mandibular range of motion was very compromised and he was unable to protrude it. Scarring and scleroderma-like changes were seen in the perioral region (Figure 3) with a resultant microstomia (Figure 4) making eating and oral hygiene extremely difficult. His interincisal opening was about 10 mm. He only complained of pain when oral hygiene was attempted around the posterior teeth. A panoramic radiograph (Figure 5) revealed extensive caries on all four permanent first molars, with associated periapical radiolucencies. Intraoral examination revealed crowding, malocclusion, and gingivitis, and purulent exudate was observed coming from the molar areas. Despite a negative history of trauma, his mandibular left central incisor was fractured at the cervical level. The oral soft tissues were very dry.

Treatment

Due to the microstomia, muscle atrophy, and his general medical condition, we were not able to remove his carious permanent first molars immediately. The patient was placed on broad spectrum antibiotics to treat his suspected dental abscesses. An intensive oral hygiene regimen was started using a small one-tuft toothbrush to gain access to the posterior area of the mouth, neutral sodium fluoride gel, and normal saline rinses combined with 0.12% chlorhexidine. Because of its high alcohol content (11.6%), the chlorhexidine was diluted to avoid further drying and burning of the oral tissues. He was also placed on daily rinses of dexamethasone (0.1 mg/mL, Roxane Laboratories, Inc.) for 4 weeks, resulting in general improvement of the soft tissues. Both the patient and his mother were carefully instructed in oral hygiene techniques and closely monitored.

Fig 1. Whitening of hair.

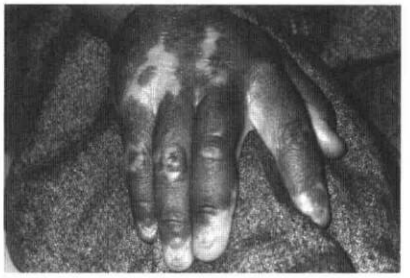


Fig 2. Distrophic nails and vitiligo.

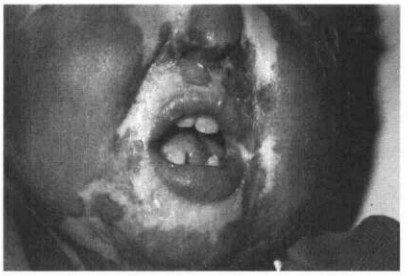
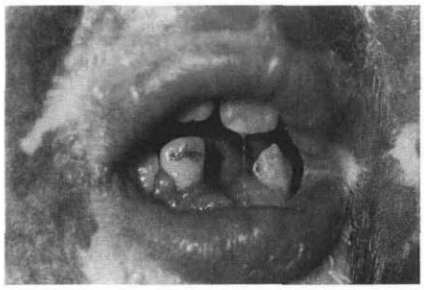
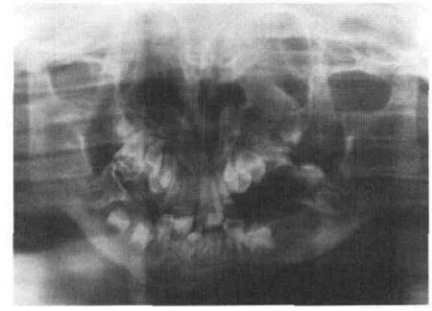


Fig 3. Scarring and scleroderma-like changes in the perioral region.



◀ Fig 4. Microstomia and perioral scarring.

▶ Fig 5. Panoramic radiograph showing extensive caries of first permanent molars, small conical crowns of upper second permanent molars, agenesis of the lower second permanent molars, and the lower left second premolar.



Intensive physical therapy and oral stimulation exercises improved mouth opening considerably after a few weeks. Extraction of the compromised teeth was successfully accomplished under general anesthesia by a team of oral surgeons 3 months after his hospital admission.

The patient is now back in his home country. The parents were instructed to continue the oral physical therapy exercises and the intensive oral hygiene. It was also recommended that the patient be established with a local pediatric dentist for regular recall examinations every 3 months. The patient will return to the FHCRC for yearly follow-up visits.

Discussion

BMT has become a common treatment for leukemias, aplastic anemia, lymphomas, and severe combined immunodeficiency diseases. It replaces diseased bone marrow or is a rescue therapy following administration of high dose chemotherapy or chemoradiotherapy in patients with solid tumors.[17] It has improved survival and reduced morbidity in thalassemia patients, especially if done before signs of iron overload appear.[3]

Careful monitoring of the changes seen in the oral tissues is of paramount importance. The preparatory conditioning for the transplant can induce several oral complications such as mucositis, xerostomia, secondary infections, ulcerations, pain, and bleeding. Acute GVHD can also appear if immunosuppressive prophylactic agents (for example, cyclosporine) are not given or given in a suboptimal dose.[15, 18, 19] Viral, fungal, and bacterial infections are the most significant life-threatening head and neck complications in the pretransplant conditioning period and in the first month after the procedure, though significant advances have been made in infection prophylaxis and treatment.[15] The oral cavity can be the first or only clinical site of CMV in early post-BMT phases, with extremely painful oral granulomatous ulcerations, covered by heavy pseudomembranes.[19]

Long-term oral and systemic effects of BMT complications have become more apparent as pediatric patients are surviving longer. According to Sanders,[7] these late effects can be related to the underlying disease (relapse), the preparative protocol (neuroendocrine dysfunction, ophthalmologic disturbances, dental developmental abnormalities, central nervous system dysfunction, secondary malignancies), and the transplant itself (engraftment problems, chronic GVHD, immune reconstitution).

GVHD is a major complication of allogeneic transplantation due to its significant morbidity and mortality.[13, 20–22] The disease is related to the degree of donor/host alloantigen disparity, the number of immunocompetent lymphocytes transplanted and, for acute GVHD, the effectiveness of the post-transplant immunosuppressive prophylaxis.[21] Chronic GVHD can progress directly from the acute form. According to a study of 145 patients, the main sites of the chronic form of the disease include the skin (in 79% of the cases), liver (73%), mouth (72%), eyes (47%), GI tract (16%), myofascial areas (11%), lungs (11%), and esophagus (6%).[23]

Typical dermal lesions begin as asymptomatic erythematous papules that progress in several weeks to a hyperpigmented desquamative dermatitis and persistent ulcerations which can involve the whole body.[24] Erythema, dyspigmentation, poikiloderma, and lichenoid changes are also observed which, if untreated, lead to progressive induration and sclerosis.[13] Our patient had severe active chronic GVHD with all of these features. He had joint contractures which led to a very limited range of motion in the neck, mandible, and upper and lower limbs. He presented a compromised gait and could not stand completely upright. He had localized alopecia and whitening of the hair which are also characteristic of chronic GVHD.[15, 24] The commonly described ophthalmologic complications associated with the disease, such as bilateral cataracts, photophobia, and keratoconjunctivitis sicca,[21] were also observed in our patient.

Oral pain and increasing dryness more than 100 days post-transplant are strongly suggestive of the

chronic form of GVHD.[15,21] In a study of 60 patients, Schubert et al.[13] described mucosal atrophy, erythema, lichenoid changes, xerostomia, and pain as the main oral manifestations of GVHD. The earliest change in the oral mucosa is a patchy erythema, followed by multiple, irregular, white-grayish, striated or reticular plaques consistent with oral lichen planus.[13,24] The mucosal surfaces become atrophic and dry, predisposing to trauma and infections.[17] Similarities between these manifestations and those of autoimmune diseases such as lichen planus, lupus erythematosus, scleroderma, benign mucous membrane pemphigoid, and Sjögren's syndrome have been reported.[15,24]

Our patient developed several oral complications of GVHD. He had a decreased mouth opening causing poor oral nutritional intake—probably complicated by xerostomia and a fibrotic tongue. He had used pediatric liquid feedings rich in carbohydrates for many years. Being unable to eat solid foods appeared to have contributed to atrophy of the masticatory muscles and some degree of trismus which, together with the perioral skin contractures, worsened his microstomia. All those factors contributed to poor oral hygiene and a high caries rate, requiring extraction of all his primary teeth.

Late dental abnormalities are related to the chemoradiation regimen and the child's age at the time it is administered. Pediatric patients treated with total body irradiation present more severe dental disturbances than those who receive chemotherapy only.[10,11] The developmental abnormalities are usually more significant in children younger than 5 years of age at the time of the transplant.[8–10,25] The most commonly reported problems are tooth agenesis, microdontia, atypical root and crown morphology, early apical closure, and hypocalcification.[8,9,25,26] The patient's panoramic radiograph (Fig 5) revealed maxillary second permanent molars with small conical crowns and no signs of development of the mandibular second molars. Agenesis of the mandibular left second premolar was noted.

Severe dental crowding and an anterior crossbite were evident. Dahllöf et al.[11] point out that craniofacial growth is severely affected, with the alveolar height reduced, most likely due to the dental developmental disturbances seen. It is also feasible that pituitary dysfunction interferes with craniofacial complex development, inducing retarded mandibular growth with skeletal disharmony between the jaws.[25]

An important concern for the dental treatment of these severely compromised patients is safety. Because of the intensive medical treatment they receive, these children may require special behavior management when dental procedures are attempted. Caretakers can be overprotective, interfering in the course of the dental visit and may not follow directions given for home or hospital care to avoid further stress to the child. They may also be so overwhelmed with the amount of medical information and issues presented to them that dental care becomes a low priority. Constant reassurance of the importance of oral care and frequent monitoring can help. Rapport with the medical and nursing staff also supports completion of dental/oral recommendations.

Positioning of the patient in the dental chair and/or on the surgical table is also important. Careful physical manipulation of the patient avoids skin breakdown which can potentially lead to discomfort, bleeding, and infection. Conscious sedation is not recommended because maintaining a patent airway and providing cardiopulmonary resuscitation are difficult, should a more serious situation arise due to the limited neck extension and mouth opening. The best way to manage this type of patient is in the operating room under general anesthesia.

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References

1. Hoffbrand HV, Lewis SM: Postgraduate Haematology, 3rd ed. Oxford: Heinemann Professional Publishing, pp 129–52, 1989.
2. Wainscoat JS: The Haemoglobinopathies. In Hematology—a pathophysiological approach, 2nd ed. Babior BM, Stossel TP, Eds. New York: Churchill Livingstone, pp 121–45, 1990.
3. Walters MC, Sullivan KM, O'Reilly RJ, Boulad F, Brockstein J, Blume K, Amylon M, Johnson FL, Lkemperer M, Graham-Pole J, Thomas ED: Bone marrow transplantation for thalassemia. The USA experience. Am J Pediatr Hematol Oncol 16:11–17, 1994.
4. Brody JI: Anemias caused by red blood cell destruction. In Internal Medicine for Dentistry. Rose LF, Kaye D, Eds. St. Louis: The CV Mosby Co, pp 294–95, 1990.
5. Van Dis ML, Langlais RP: The thalassemias: oral manifestations and complications. Oral Surg Oral Med Oral Pathol 62:229–33, 1986.
6. Hes J, van der Waal I, de Man K: Bimaxillary hyperplasia: the facial expression of homozygous ß-thalassemia. Oral Surg Oral Med Oral Pathol 69:185–90, 1990.

7. Sanders JE: Long-term effects of bone marrow transplantation. Pediatrician 18:76–81, 1991.
8. Dahllöf G, Barr M, Bolme P, Modeer T, Lonnqvist B, Ringden O, Heimdahl A: Disturbances in dental development after total body irradiation in bone marrow transplant recipients. Oral Surg Oral Med Oral Pathol 65:41–44, 1988.
9. Dahllöf G, Rozell B, Forsberg CM, Borgstrom B: Histologic changes in dental morphology induced by high dose chemotherapy and total body irradiation. Oral Surg Oral Med Oral Pathol 77:56–60, 1994.
10. Nasman M, Bjork O, Soderhall S, Ringden O, Dahllöf G: Disturbances in the oral cavity in pediatric long-term survivors after different forms of antineoplastic therapy. Pediatr Dent 16:217–23, 1994.
11. Dahllöf G, Forsberg CM, Rigden O, Bolme P, Borgstrom B, Nasman M, Heimdahl A, Modeer T: Facial growth and morphology in long-term survivors after bone marrow transplantation. Eur J Orthod 11:332–40, 1989.
12. Sullivan KM, Parkman R: The pathophysiology and treatment of graft-vs-host disease. Clin Haematol 12:775–89, 1983.
13. Schubert MM, Sullivan KM: Recognition, incidence and management of oral graft-versus-host disease. NCI Monogr 9:135–45, 1990.
14. Sullivan KM, Shulman HM, Storb R, Weiden PL, Witherspoon RP, McDonald GB, Schubert MM, Atkinson K, Thomas ED: Chronic graft-versus-host disease in 52 patients—Adverse natural courses and successful treatment with combination immunosuppression. Blood 57:267–76, 1981.
15. Schubert MM, Sullivan KM, Truelove EL: Head and neck complications of bone marrow transplantation. In Head and Neck Management of the Cancer Patient. Peterson DE, Elias EG, Sonis ST, Eds. Boston: Martinus Nijhoff Publications, pp 401–427, 1986.
16. Schubert MM, Sullivan KM, Morton TH, Izutsu KT, Peterson DE, Flournoy N, Truelove EL, Sale GE, Buckner CD, Storb R, et al.: Oral manifestations of chronic graft-versus-host disease. Arch Intern Med 144:1591–95, 1984.
17. Parkman R: Overview: bone marrow transplantation in the 1990s. Am J Pediatr Hematol Oncol 16:3–5, 1994.
18. Barker GJ, Barker BF, Gier RE: Oral management of the cancer patient—a guide for the health care professional, 4th ed. Kansas City: Biomedical Communications, University of Missouri School of Dentistry, 1992.
19. Schubert MM: Oral manifestations of viral infections in immunocompromised patients. Curr Opin Dent 1:384–97, 1991.
20. Kapoor N, Copelan EA, Klein J, Tutschka PJ: Graft-versus-host disease: effects on long term disease free survival in marrow transplantation for haematological malignancies. Bone Marrow Transplant 4:153–55, 1989.
21. Sullivan KM: Chronic graft-versus-host disease. Cancer Treat Res 50:79–98, 1990.
22. Sullivan KM, Agura E, Anasetti C, Appelbaum F, Badger C, Bearman S, Erickson K, Flowers M, Hansen J, Loughran T, et al.: Chronic graft-versus-host disease and other late complications of bone marrow transplantation. Semin Hematol 28:250–59, 1991.
23. Sullivan KM, Witherspoon RP, Storb R, Weiden P, Flournoy N, Dahlberg S, Deeg HJ, Sanders JE, Doney KC, Appelbaum FR, et al: Prednisone and azathioprine compared to prednisone and placebo for treatment of chronic graft-versus-host disease: prognostic influence of prolonged thrombocytopenia after allogeneic marrow transplantation. Blood 72:546–54, 1988.
24. Medina JE, Frame R, Toth B, Nguyen l, Luna MH: Head and neck manifestations of the chronic graft vs. host disease. Laryngoscope 94:1145–51, 1984.
25. Sonis AL, Tarbell N, Valachovic RW, Gelber R, Schwenn M, Sallan S: Dentofacial development in long-term survivors of acute lymphoblastic leukemia. A comparison of three treatment modalities. Cancer 66:2645–52, 1990.
26. Goho C: Chemoradiation therapy: effect on dental development. Pediatr Dent 15:6–12, 1993.