Technical Note

Distraction Osteogenesis After Stem Cell Transplantation: A Pioneer Approach

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Abstract

Allogeneic hematopoietic stem cell transplantation (HSCT) is an established therapy and is without alternative for certain groups of patients. Successful HSCT induces both long-lasting remission and tolerance without the need for further immunosuppression. In this case, cellular repair and regenerative processes work in a physiologic manner allowing elective surgical procedures, such as the interdisciplinary correction of dentofacial anomalies. Here, we report the successful management of transverse maxillary deficiency by transpalatal distraction and subsequent orthodontic treatment in a 12-year-old boy who underwent HSCT for high-risk acute lymphoblastic leukemia at 5 years of age.

Keywords: Dentofacial anomaly, stem cell transplantation, transpalatal distraction, transverse maxillary deficiency

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is an established therapy and is without alternative for certain groups of patients. Even in some forms of high-risk pediatric acute lymphoblastic leukemia, remission rates >80% can be achieved with allogeneic HSCT by taking advantage of the graft-versus-leukemia effect.[1] If remission without recurrence persists for >4 years, patients have a relapse risk of <1%.[2] Typical side effects of such a treatment include impairment of growth, hormonal dysregulation, secondary malignancies, and graft-versus-host reactions.[3] Specific osteotoxic effects can be caused by the initial hematological pathology or myeloablative conditioning including total body irradiation or may be steroid related during immunosuppressive graft-versus-host therapy.[4,5] Despite this, successful allogeneic HSCT, especially in childhood, implies induction of tolerance, which usually allows the patient to stop immunosuppression within the 1st-year posttransplant. Therefore, it is presumed that cellular repair and regeneration processes recover to work in a physiologic manner.[6]

Compared with lifesaving hemato-oncologic therapy, the interdisciplinary orthodontic-orthognathic correction of patients affected by dentofacial anomalies has an elective character due to functional and psychosocial indications.[7,8] Due to an increasing number of pediatric patients become long-term survivors following HSCT[9] and the fact that radio- and/or chemotherapy may be a trigger for dentofacial anomalies,[10,11] it is likely that there will be an increasing number of patients affected by such anomalies. To date, there have been no reports regarding the interdisciplinary correction of dentofacial anomalies in patients who previously underwent HSCT.

Case Report

We report the combined correction of a transversal maxillary deficiency by transpalatal distraction and subsequent orthodontic treatment in a 12-year-old boy who underwent

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allogeneic HSCT 7 years earlier for acute lymphoblastic leukemia. The initial diagnosis was made in September 2006. After intensive remission-induction chemotherapy, bone marrow transplantation from his human leukocyte antigen-identical brother was performed in the first remission in March 2007. Myeloablative therapy consisted of total body irradiation (12 Gy total dose), followed by intravenous (i.v.) administration of etoposide (VP-16; 60 mg/kg). In December 2008, the patient developed limited chronic graft-versus-host disease (GvHD; skin only), which resolved with prednisone and azathioprine. In December 2009, immunosuppression was terminated. Thereafter, hematological follow-up was uneventful with persistent remission and complete donor chimerism.

In 2014, 7 years after HSCT, the patient was referred by his orthodontist to correct the transverse maxillary deficiency (TMD) with crowding and malposition of both upper incisors in a skeletal Class II situation. Whether the occlusal situation was a result of the preceding oncologic therapy, impairing further maxillary growth is discussed [Figure 1a and b].

At that time, from a hematological point of view, there was no contraindication for combined correction of the present TMD and malocclusion with most of the relevant blood parameters within the normal range. Subsequently, in July 2015, a piezosurgery-assisted subtotal Le Fort I osteotomy modified according to Betts and Scully was performed[12] and a transpalatal distraction device was inserted (Surgitec "All-in-One," size 2.5, Surgitec, Leuven, Belgium) under general anesthesia and with perioperative i.v. administration of penicillin G. The device was activated intraoperatively up to 8 mm to control the widening [Figure 2a].

After 5 days of latency, activation of the device was performed for 12 days up to a diastema width of 14 mm [Figure 2b].

Three weeks after the end of active distraction, orthodontic positioning leveling and aligning were initiated by fixed appliances using the straight wire technique (0.12–0.16 NiTi arches). Closure of the diastema was subsequently realized from the 12th week following termination of activation over the course of 3 months using orthodontic "power chains" and "figure-of-eight ligatures" [Figure 3a].

Three months following the termination of orthodontic therapy, the distraction device was removed under general anesthesia; during this procedure, the distraction zone was clinically inspected and distracted bone was harvested for histological evaluation in the same setting.

Overall consolidation time after the end of active distraction was 10 months. Clinically, physiologic processes were observed during all steps of therapy, as demonstrated in Figures 2b and 3a-c.

No impairments in wound healing, callus mineralization, or orthodontic dental movements were observed. There was no delayed wound healing following insertion and removal of the distraction device; no infective complication or problems with respect to bone stability during activation or the consolidation phase occurred. Orthodontic therapy was also uneventful, and correct alignment of the upper dental arch was achieved within the typical treatment

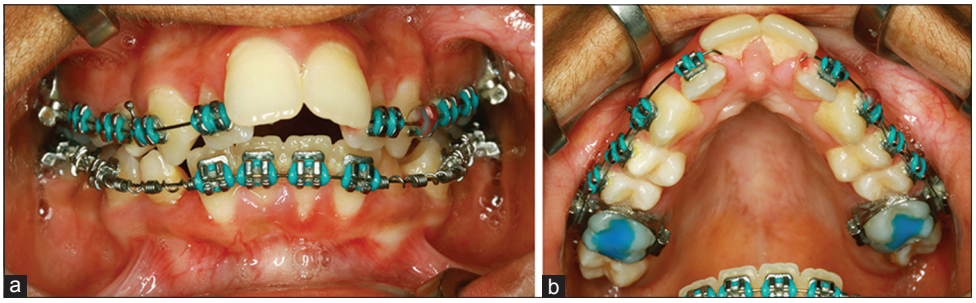

Figure 1: (a and b) Initial situation: skeletal Class II malocclusion with malposition of both upper incisors and increased risk for traumatic tooth loss

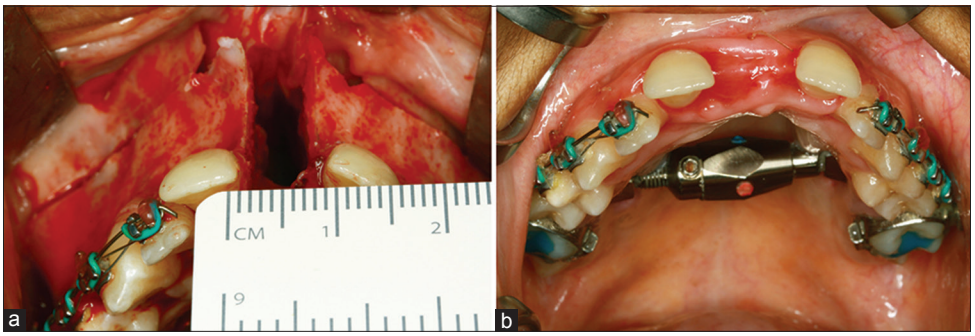

Figure 2: (a) Intraoperative view with inserted distraction device and testing of activation (8 mm). (b) Physiologic, clinical situation after the end of active distraction: 14 mm width of diastema

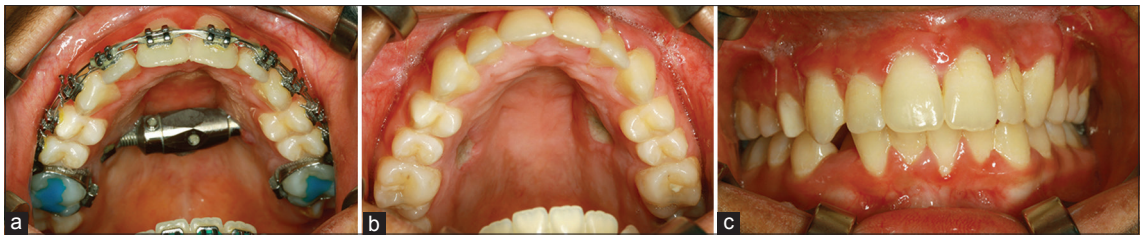

Figure 3: (a) Physiologic, clinical situation following orthodontic closure of the diastema 6 months after termination of the active distraction. (b and c) Clinical situation 5 days after device removal and 12 months after device insertion

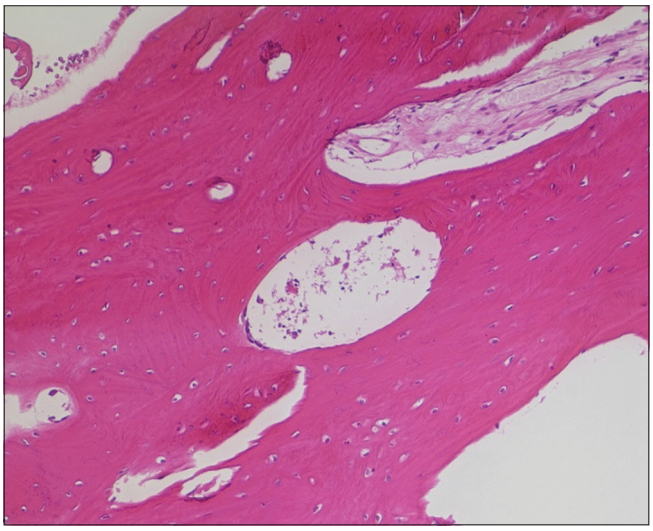

Figure 4: Histological specimen taken from the distraction zone during device removal demonstrating physiologic bone formation of mineralized bone with small, vital osteocytes and slight fibrosis in the medullary cavity (H and E; ×100)

time. Histological samples of the distraction zone showed a physiologic pattern of mineralized bone 12 months after device insertion [Figure 4].

Discussion

HSCT following successful initial treatment is regarded as the treatment of choice in forms of high-risk acute pediatric leukemia.[6] However, impairment of further growth may be one of the multiple side effects, which are caused by the primary neoplastic disorder or the subsequent therapy and can both affect bone metabolism.[13,14] Related bony pathology during childhood is complex and cannot be prevented by substitution. Monitoring of bone metabolism and the elimination of additional factors is recommended.[5]

The principle of distraction osteogenesis (DO) is an established therapy when skeletal deficiency is present. Almost 100 years after the first successful femoral callus distraction in humans by August Bier, the underlying physiology of DO is better understood.[15] A systematic description and development of the method for limb lengthening have been provided by Ilizarov, who was the first to describe the "tension-stress effect" and the required conditions: Metabolic activation and improved vascularization mediated by gradual traction.[16,17] Using this principle, not only bone but also the surrounding neurovascular and soft tissues can be expanded, thus comprehensively correcting the deficiency. Therefore, the term "distraction histiogenesis" might be more appropriate. Application of DO for the correction of craniofacial and dentofacial deformities was emphasized by McCarthy *et al.* in the late 1980s,[18] although the first comparable approaches were described significantly earlier by Wasmund and Rosenthal to correct dentofacial growth deficiency.[19]

On the molecular level, it has been hypothesized that gradual external tension initiates a complex cellular differentiation that is mediated by elements of the cytoskeleton ("mechanotransduction") and acts like an "*in vivo* bioreactor," although not all details are known.[20] According to observations made during the combined surgical-orthodontic treatment of our patient, DO and subsequent bone remodeling appear to work in the same way in patients who have already undergone successful allogeneic HSCT. Histological bony architecture and mineralization within the distraction zone showed a physiologic pattern 10 months after the end of active distraction [Figure 4]. Therefore, the principle of gradual expansion of bone and surrounding soft tissues appears to also be applicable for patients following HSCT, provided GvHD has resolved, and immune reconstitution has occurred.

Conclusions

With an individually adapted treatment approach, interdisciplinary surgical-orthodontic treatment of dentofacial anomalies is possible in patients who have previously undergone allogeneic HSCT. Clinical outcome of this patient-year after bone marrow transplantation was similar compared to healthy adolescent patients who received transpalatal DO and subsequent orthodontic treatment for the correction of a dentofacial anomaly. Therefore, the principle of gradual expansion of bone and surrounding soft tissues is also applicable to posttransplant patients at least in the absence of GvHD and immunosuppression. The management of dentofacial growth impairment by DO in this group of patients appears to be a viable approach.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names

and initials will not be published and due efforts will be made to conceal patient identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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