OPEN ACCESS

Saudi Journal of Oral and Dental Research
Abbreviated Key Title: Saudi J Oral Dent Res
ISSN 2518-1300 (Print) | ISSN 2518-1297 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Case Report **Pediatric Dentistry**

Continuing Challenges and Current Issues of Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Case Report

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DOI: 10.36348/sjodr.2023.v08i01.003 | **Received:** 28.11.2022 | **Accepted:** 02.01.2023 | **Published:** 08.01.2023

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Abstract

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy, accounting for nearly 75% of all newly diagnosed leukemias and 25% of all malignancies in childhood. The Philadelphia chromosome-positive Ph^+ is a rare subtype of ALL, considered one of its poorest subgroups, and accounts for 3-5% of pediatric ALL. Dentists should acquire some background information about leukemia and its oral manifestations for better dental care. Commonly reported oral manifestations include regional lymphadenopathy, mucous membrane petechiae and ecchymoses, gingival bleeding, gingival hypertrophy, pallor, and non-specific ulcerations. In this case report, we aim to raise awareness among dentists and discuss the orthodontic management of a pediatric patient with Ph^+ ALL. The patient was cleared by her treating physician, and treatment was done in the dental chair. Treatment included restorations of all carious teeth, reinforcement of oral hygiene, a series of removable appliances to correct the anterior cross-bite, and in-office bleaching.

Keywords: Acute Lymphoblastic Leukemia - Philadelphia-Positive chromosome - Pediatric - Dentistry - Orthodontic treatment.

INTRODUCTION

Leukemia is a hematopoietic malignancy where abnormal leukoblast cells proliferate in the bone marrow and disseminate into the blood, replacing tissues and other organs of the body (Dean, 2021). According to the Saudi Cancer Registry (2016), leukemia is the leading cancer among Saudi children, accounting for 30.4% of all malignancies in childhood (Cancer incidence report, 2016). Acute lymphocytic leukemia (ALL) is the most common pediatric malignancy and accounts for nearly 75% of all newly diagnosed leukemia and 25% of all malignancies in childhood (Valéra *et al*., 2015). The etiology of ALL is largely unknown, with its peak age of occurrence among children being between the ages of 3-5 years, with its occurrence being more frequent among boys (1.2:1) (Lowal *et al*., 2015). Paleness, tiredness, weakness, enlarged lymph nodes, recurrent minor infections or poor healing of minor cuts, and excessive bruising or bleeding are all reported signs and symptoms of leukemia (Valéra *et al*., 2015).

ALL can be further defined by its subtype based on the chromosome translocations and interstitial rearrangements that cause dysregulated oncogene expression (Fielding, 2015). Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ ALL) is defined by the translocation that produces BCR-ABL1, a constitutively active tyrosine kinase. BCR-ABL1 fusion subtype is present in 3% to 5% of pediatric ALL (Fielding, 2015; Bernt and Hunger, 2014). Ph^+ ALL has been regarded as one of the poorest-risk subgroups of ALL among children and adolescents, demonstrating a 20–30% 5-year event-free survival (EFS) rate using chemotherapy alone (Schultz *et al*., 2007). Revolutionized treatment outcomes are seen with the introduction of imatinib combined with chemotherapy, with a 3-year EFS of 88–11%, suggesting that this combination may be used as the initial treatment for people with Ph+ ALL (Schultz *et al*., 2009).

Oral manifestations of leukemia are reported in 29% of pediatric patients (Dean, 2021). Commonly reported oral manifestations include regional lymphadenopathy, mucous membrane petechiae and

ecchymoses, gingival bleeding, gingival hypertrophy, pallor, and non-specific ulcerations (Dean, 2021).

In this case report, we present a school-aged pediatric patient with Ph^+ ALL who is undergoing dental treatment, including restorative and orthodontic management. Many Ph^+ ALL cases have been reported. However, no cases discussing the dental management of this rare subgroup were found in the literature. Therefore, we aim to raise awareness about PH+ ALL among dentists and discuss the orthodontic management of the developing dentition and orofacial growth in children.

CASE REPORT

History

A 12-year-old Saudi female diagnosed with a history of Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) presented to the dental clinic to evaluate the chief complaint of "I don't want to return back to school with the same bad-looking teeth" as she stopped attending school for one year due to medical treatment. The patient stated that she has had anterior cross-bite for years and that it bothers her aesthetically. Medical history revealed the patient was diagnosed with Ph+ ALL three years ago at the age of nine. The patient was not on active chemotherapy but was taking Dasatinib tablets of 50mg orally during dental treatment. Moreover, patient was hospitalized for intrathecal administration, Hickman line insertion, bone marrow aspiration, and allogeneic stem cell transplantation from her brother (Haploidentical). Dental history obtained indicated that the patient had no previous dental visits and was not under regular home dental care.

Clinical and radiograph examination

Extra-oral examination revealed a convex soft tissue profile, competent lips with white pigmentation around the lower lip (Fig 1). Intraoral examination revealed permanent dentition stage, poor oral hygiene causing plaque induced gingivitis, extrinsic yellow discoloration, multiple carious teeth, and deep fissures. Patient demonstrated a high caries risk according to Caries Risk Assessment Tool (CAT). Occlusal assessment shows a Class I molar and canine relationship, U-shaped maxillary and mandibular arch forms, and a cross-bite in the maxillary right central incisor and maxillary left lateral incisor. The overbite measured 30% and the overjet measured 2 mm, recorded at #21. The mandibular dental midline deviated 2 mm to the right from the facial midline. Panoramic views, right and left bitewings, upper standard occlusal radiographs (Fig 2), lateral cephalometric (Fig 3), and preoperative intraoral photographs (Fig 4) were taken. Radiographic evaluation revealed normal developing dentition, no missing teeth, and multiple occlusal caries.

Orthodontic Examination

A cephalometric investigation was carried out by means of the Steiner and Ricketts methods for basal classification. The patient showed a class II skeletal pattern due to a retrognathic mandible. The vertical skeletal pattern was hyper-divergent mandible (Fig 3). The space analysis showed a discrepancy of 5.5mm in the maxilla and 1mm in the mandible, indicating moderate crowding in the maxillary arch and mild mandibular crowding.

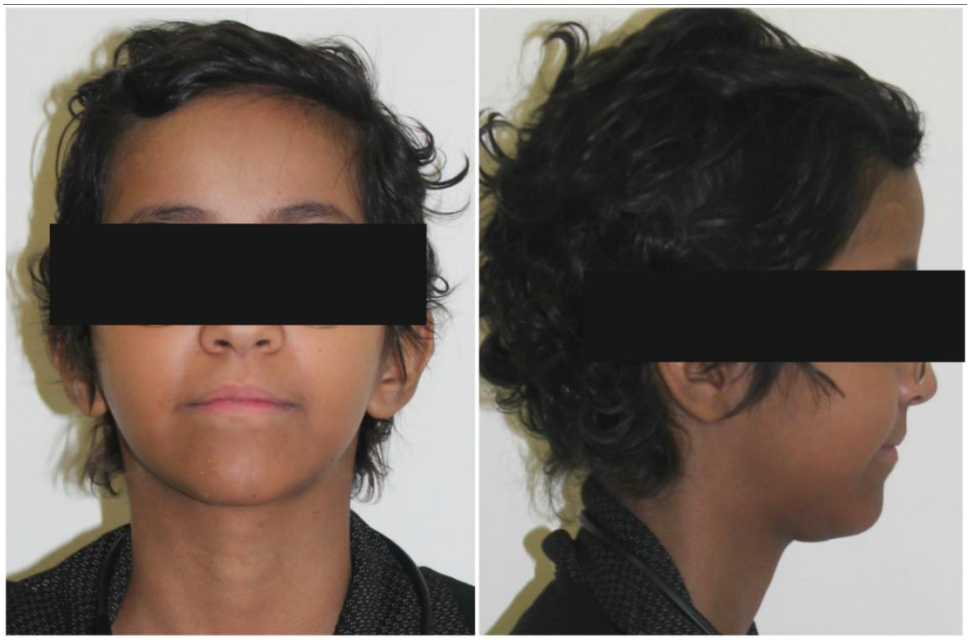


Fig 1: Preoperative extraoral photographs

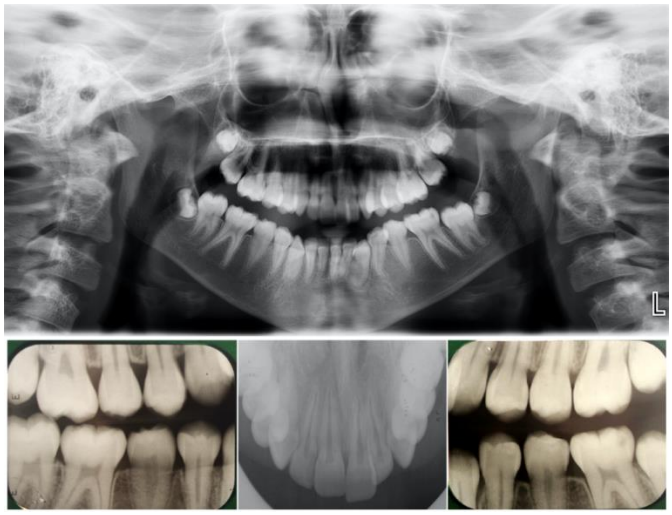
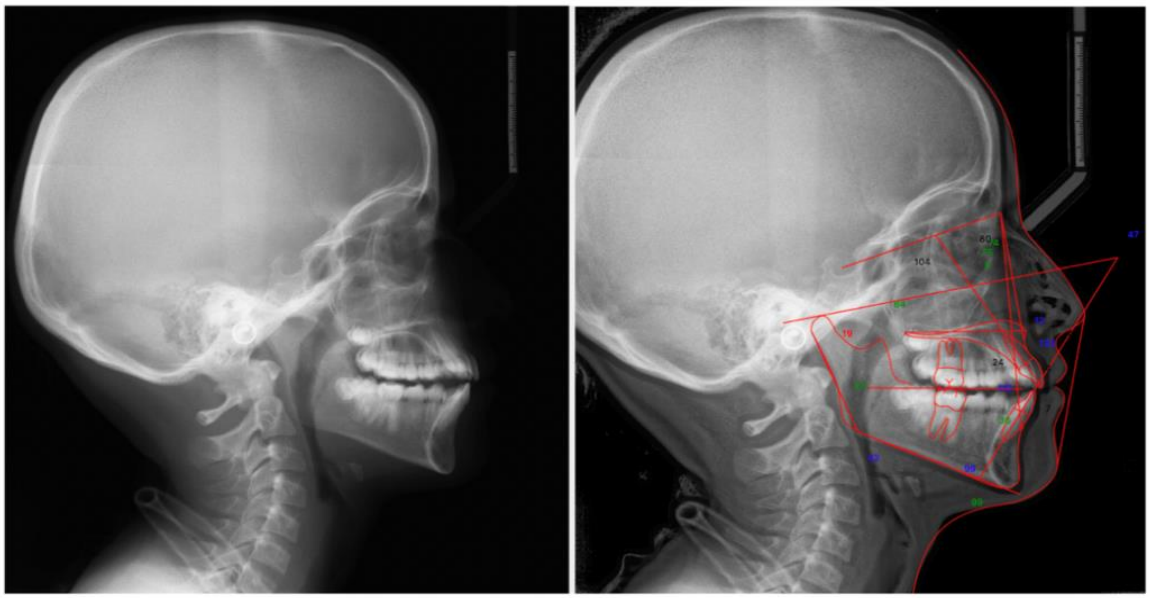


Fig 2: Preoperative panoramic view and intraoral radiograph



skeletal				
SNA	(deg)	80.1	82.0	-.6
SNB	(deg)	75.4	80.0	-1.5 *
ANB	(deg)	4.7	2.0	1.3 *
Wits Appraisal	(mm)	0.7	1.1	-.2
SNPog	(deg)	74.1	80.0	-1.7 *
Angle of Convexity	(deg)	11.8	.0	2.3 **
CRANIAL BASE A...	(deg)	136.1	130.0	1.0 *
vertical				
SN-palatal plane	(deg)	18.8	7.0	11.8 ***
GO-GN - SN (sn-...	(deg)	41.7	32.0	2.2 **
Md-palatal plane	(deg)	22.9	25.0	-.4
Y growth Axis an...	(deg)	64.3	59.4	1.4 *
jaw angle: Ar-Go...	(deg)	135.9	130.0	.8
face hight 1	(mm)			
face hight 2	(mm)			
face hight 3	(%)	100.0	79.0	
ANS-Me	(mm)	60.2		
N-Me	(mm)	104.2		
ANS-Me/N-Me	(%)	57.7	55.0	.9
dental				
Interincisor Angle	(deg)	115.1	130.0	-2.5 **
Mx 1 - SN	(deg)	104.1	104.0	.0
Mx 1 - PP	(deg)	122.9	110.0	2.1 **
Mx 1 - NA	(mm)	4.3	4.0	.1
Mx 1 - NA Angle	(deg)	23.9	22.0	.3
Md 1 - NB	(mm)	6.9	4.0	1.0
Md 1 - NB Angle	(deg)	36.3	25.0	1.9 *
Md 1 - APog	(mm)	4.2		
Md 1 - Md	(deg)	99.2	91.0	2.0 **

soft tissue				
Upper lip to E line	(mm)	-3.0	-4.0	
Lower Lip E-Plane	(mm)	-2.1	-2.0	-.1
Nasolabial Angle	(deg)	103.7	105.0	-.2
Subn. Perp.-uLip	(mm)	-0.1	3.0	-1.0 *
Subn. Perp.-lLip	(mm)	-2.8	1.0	-1.3 *
Subn. Perp.-Chin	(mm)	-10.9	-2.0	-3.0 **
Tweed				
IMPA	(deg)	99.2	90.0	1.5 *
FMIA	(deg)	47.4	65.0	-2.9 **
FMA	(deg)	33.4	25.0	1.4 *

Fig 3: Lateral Cephalometric radiograph and analysis

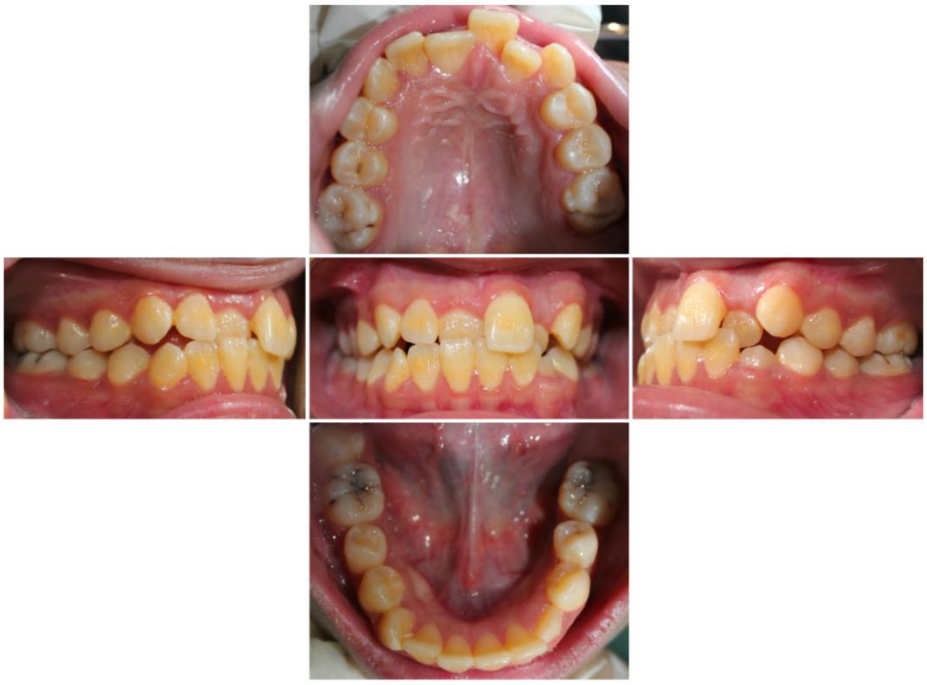


Fig 4: Preoperative intraoral photographs

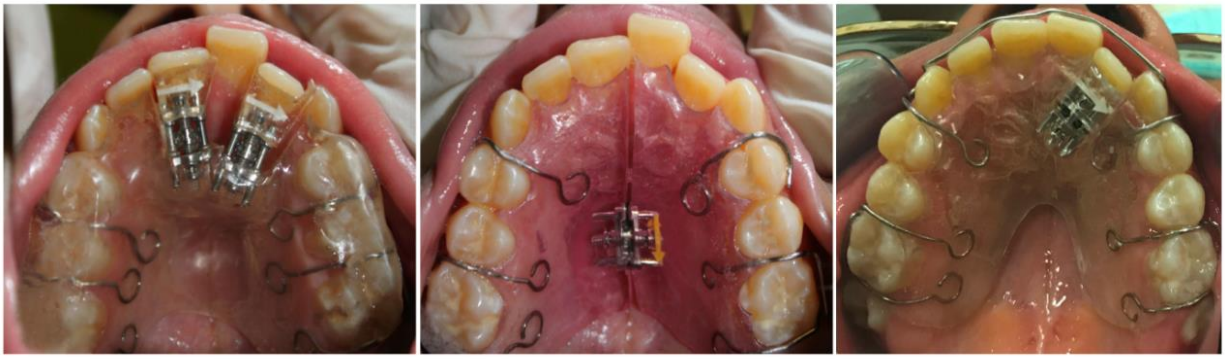
Treatment

After case assessment, the patient showed Frankel IV (++ve) behavior, and the decision to treat her in a regular clinical setting was made. A consultation with the patient's hematologist revealed that other than checking platelet and hemoglobin counts before treatment, no contraindications or special precautions were needed for dental treatment. Additionally, since the patient was not receiving active chemotherapy, there was no need to administer antibiotics either before or after any dental procedure. Informed consent was obtained from the patient's parents regarding the treatment and the sharing of the patient's medical history, radiographs, and intraoral photographs for educational purposes.

Treatment lasted for 5 months, starting with preventive and restorative treatment that included fissure sealants for teeth nos., 24, 25, 34, 44, and 45; preventive resin restorations for teeth nos. 15 and 35; class I composite restorations for teeth nos. 16, 36, 26, and 46, along with prevalent oral hygiene improvement. Regarding the orthodontic treatment, the main goal was to provide correct masticatory function and acceptable dental and facial aesthetics by correction of anterior crossbite and expansion of the upper arch. Orthodontic consultation was obtained, and the recommendation was to correct the anterior cross-bite and reduce the severity of malocclusion by interceptive orthodontic treatment using a series of upper removable appliances. The first removable appliance consisted of Adams' clasps on the first permanent molars, two anterior sagittal screws on teeth nos. 11 and 22 to align the teeth more labially, and a posterior bite plane to control the vertical component (Fig 5). The device had to be easy to use for the patient, as she was instructed to manually activate it once per day for three weeks and then wear it as a retainer for another week without activation until the second appliance was fabricated. The second removable appliance consisted of Adams' clasps on the first permanent molars, a midline transverse expansion screw, and a midline split in the baseplate (Fig 5). The patient was instructed to manually activate it once per day for two weeks and then wear it for another week as a retainer without activation until the third appliance is fabricated. The third removable appliance consisted of a single anterior sagittal screw on tooth no. 22, a labial bow, and Adams' clasps on the first permanent molars (Fig 5). A single unilateral expansion screw applies force to align the tooth more labially. The patient was instructed to manually activate the appliance once a day for three weeks, at which point there was an improvement and correction of the crossbite. A wrap-around retainer was constructed to be used as full-time retention except at mealtimes until the evaluation visit.

Recall appointments were scheduled at 3 months and 6 months. At the 3-month recall, the patient presented with stable occlusion, showed satisfaction with the treatment result, and had improved oral hygiene with little plaque deposits, intact restorations, and no new carious lesions. The patient was instructed to continue wearing the wrap-around retainer at all times except when eating. The second re-call visit was after 9 months, as the patient did not show up for the 6-month re-call appointment. Intraoral photographs and radiographs (Fig 6) were taken. The patient presented in good health, and all medication was stopped by her primary care physician. The patient had no complaints about previous restorations, with stable occlusion, small plaque deposits, and intact restorations. Oral hygiene reinforcement, diet counseling, oral prophylaxis, and

topical fluoride application (APF, 1.23%) were performed.



First appliance: Removable appliance incorporating 2 anterior sagittal screws with bite plane

Second appliance: Removable appliance with transverse midline screw

Third appliance: Removable appliance with single anterior sagittal screw and labial bow

Fig 5: Upper removable appliances photographs

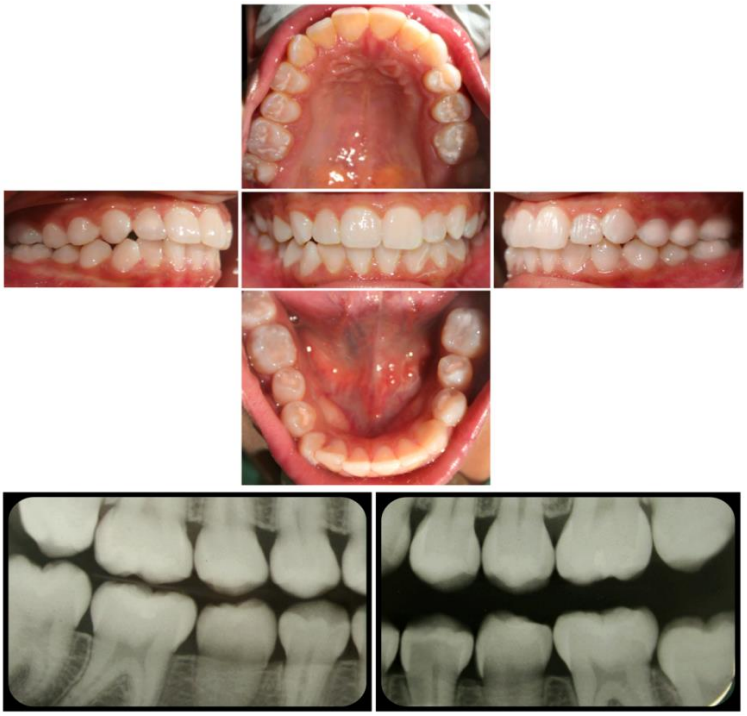


Fig 6: Recall intraoral photographs and radiographs at 9 months

Treatment Result

Restorative treatment was completed, and traumatic occlusion was eliminated by correction of the crossbite, leading to a reduced malocclusion and reduced orthodontic treatment need (orthodontic treatment need index). Extrinsic yellow discoloration was eliminated, providing better stability and functional and aesthetic results. The patient also demonstrated improved oral hygiene performance and achieved healthy soft tissues during the course of treatment. Therefore, the patient was judged to have a very good prognosis by continuing to demonstrate a low caries rate.

DISCUSSION

The Ph+ chromosome was first discovered by Nowell and Hungerford in 1960 in chronic myeloid leukemia patients, gaining its name from the presence of the Philadelphia (Ph) chromosome, named after the city it was initially described in (Nowell and Hungerford, 1960). This subtype results from a reciprocal translocation between the ABL-1 oncogene on chromosome 9 and a breakpoint cluster region (BCR) on chromosome 22, which results in a fusion gene, BCR-ABL1 (Fielding, 2015). Ph+ALL is rare among pediatric patients, accounting for 3-5% of pediatric ALL (Bernt and Hunger, 2014). With the discovery of TKIs and their combination with standard chemotherapy, 88.11% 3-year EFS was seen with Ph+ ALL (Schultz *et al*., 2009). The clinical presentation is indistinguishable from ALL and its other cytogenetic abnormalities (Aricò *et al*., 2010). Patients diagnosed with this subtype show a more aggressive clinical

course and a risk of central nervous system involvement (Gleissner *et al*., 2002).

In the field of dentistry, it is essential to have a good understanding of oral complications, dental management, and treatment precautions for leukemic patients. The underlying cause for the oral manifestations in leukemic patients is due to thrombocytopenia, neutropenia, or compromised granulocyte function, or as a result of direct leukemic infiltration (Benson *et al*., 2007). Common oral presentations include regional lymphadenopathy, mucous membrane petechiae and ecchymosis, gingival bleeding and swelling, pallor, and non-specific ulcerations. Occasionally seen oral manifestations include dentalgia, jaw pain, loose teeth, extruded teeth, gangrenous stomatitis, cranial nerve palsies, and chin and lip paresthesia (Dean, 2021). Oral compilations seen during the treatment of ALL include mucositis, gingival bleeding, oral candidiasis, herpes simplex, xerostomia, and bacterial infections (Xavier and Hegde, 2010). Graft-versus-host disease oral complications may develop in patients undergoing bone marrow transplant and radiotherapy; these oral complications include erythema, erosion, ulceration of the mucosa, lichenoid changes, and xerostomia (Martin, 2015). A leukemic child may be at risk for dental caries from a dietary point of view due to either overindulgence in unhealthy snacks or consuming medications containing sucrose (eg, Nystatin, dietary supplements) (da Fonseca, 2004). The diminished SFR that favors plaque accumulation could also make ALL patients more susceptible to dental caries (Javed *et al*., 2012). Enamel hypoplasia, arrested teeth development, tooth anomalies and tooth maturity disturbance are some of the orofacial abnormalities seen in leukemic patients. Dental management for this patient group may include esthetic restorations, orthodontic management, and endodontic treatment (da Fonseca, 2004). Thorough knowledge of the primary oral manifestations of leukemia allows the dentist to sometimes be the first healthcare professional to discover acute leukemia among children (Lowal *et al*., 2015).

Newly diagnosed cases of leukemia in children should be referred to a pediatric dentist before starting cancer therapy. A detailed oral examination with radiographs before starting antineoplastic treatment is required (Martin, 2015). Radical dental treatment should be performed to remove any source of infection that could, later, complicate the treatment and cause systemic complications (Valéra *et al*., 2015). The pediatric dentist should be aware of the patient's diagnosis, any treatment the patient has received since the diagnosis, complications or relapses of treatment, hematological status, allergies, medications, and a review of the systems (Valéra *et al*., 2015). Antibiotic prophylaxis for these patients may be required as most patients have a central line used to obtain blood samples and administer chemotherapeutic agents, making them at risk for infective endocarditis (da Fonseca, 2004). Leukemic patients can be treated as normal patients during the remission phase with careful evaluation of blood investigations if invasive dental treatment is planned (Wei and Yiu, 1993). Parents must be educated about the importance of good oral hygiene practices and the importance of recall appointments to maintain good oral health (Bonnaure-Mallet *et al*., 1998).

CONCLUSION

This report presented a comprehensive treatment of a 12-years-old girl diagnosed with Ph+ ALL. It is important to consider the impact of the treatments on the developing dentition and on orofacial growth in children. It is critical to address the oral complications and the methods of prevention and treatment including orthodontic management. A prompt diagnosis of orofacial complications could lead to early intervention.

Conflict of Interest: None declared.

ACKNOWLEDGMENT

The authors would like to express their profound gratitude and appreciation to the patient's parents for their consent to participate in this case report.

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