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CASE REPORT

Sickle Cell Beta Thalassemia: A Rare Entity

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ABSTRACT

Introduction: Haemoglobinopathies are the disorders which affect the structure of hemoglobin. Most common hemoglobinopathies are sickle cell disorders and thalassemia. Sickle cell disorders are genetic disorders characterized by the predominance of hemoglobin S whereas thalassemia is the disorder of hemoglobin synthesis with decreased production of globin chains of hemoglobin molecules.

Case report: We present a case of a rare hereditary disease in a 19-year-old female patient with both sickle cell and beta thalassemia traits along with the clinical, radiological manifestations, diagnosis, management, and dental considerations.

Conclusion: Oral physicians and oral pathologists should be vigilant enough to identify any hemoglobinopathy, with adequate radiological and hematological investigations, although it has a rare occurrence. If diagnosed, a multidisciplinary approach involving dental surgeon, and orthodontist is mandatory for these patients

Keywords: Beta-thalassemia, Genetic disorder, Hemoglobinopathies, Sickle cell disease.

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INTRODUCTION

Hemoglobinopathies are a group of genetic disorders of hemoglobin (Hb) in which there is abnormal production or structure of the hemoglobin molecule. Sickle cell disease is a generic term for a group of genetic disorders characterized by the predominance of Haemoglobin S (HbS). The disorders include sickle cell anemia, the sickle cell beta thalassemia syndromes and hemoglobinopathies in which HbS is in association with abnormal hemoglobin like sickle cell hemoglobin C disease (hemoglobin SC disease), sickle cell hemoglobin D disease (hemoglobin SD disease) and hemoglobin O_{Arab} disease.[1] Sickle cell beta thalassemia is a disorder in which both sickle beta-globin gene (β^S) and beta thalassemia gene are present.[2]

The sickle cell disorders are found in people of African, Mediterranean, Indian and Middle Eastern heritage.[3] The highest prevalence of hemoglobinopathies in India has been recorded in the Central Eastern area, especially in the state of Orissa (1–44%) followed by Madhya Pradesh (1–40%), Kerala (1–30%) and the least in Karnataka (1–8%).[4] The overall prevalence of sickle cell beta thalassemia in India is 0.02%.[5]

CASE REPORT

A 19-year-old female patient, a native of Orissa, reported to the Department of Oral Medicine with a chief complaint of forwardly placed upper front teeth since 7 years. Her medical history revealed that she is a sickle cell beta thalassemia patient diagnosed during her childhood, and had undergone multiple blood transfusions till the age of 18 years. No other family member except her youngest brother was affected with this disease, who expired at the age of 10 years. The patient gave a history of extraction of teeth in the lower left and right back tooth region 3 years back due to decay. On physical examination, the patient had a normal gait, and she was moderately built and nourished. Examination of the systems revealed hepatosplenomegaly, whereas CVS, CNS and respiratory system were normal.

On extra oral examination, pallor and yellowish discoloration of the skin over the face and yellowish tint of both the sclera were noted. Other findings included bimaxillary protrusion, lip incompetence and features of chipmunk facies like slanting of the eyes, frontal bossing, hypertelorism, saddle nose, increased malar prominence (Figs 1A and B). Intraorally, hard tissue examination revealed bilateral Class I canine relation with an overjet of 5mm, missing teeth 36 and 46 and discolored 42. On soft tissue examination, yellowish discoloration of the mucosa was noted over the gingiva, hard and soft palate, tongue, buccal mucosa, and floor of the mouth (Figs 2A and B). Thus, based on clinical examination, a provisional diagnosis of Angles class I malocclusion was given. Since the patient was a known case of sickle cell beta thalassemia, we proceeded with the radiological and hematological investigations before the treatment.

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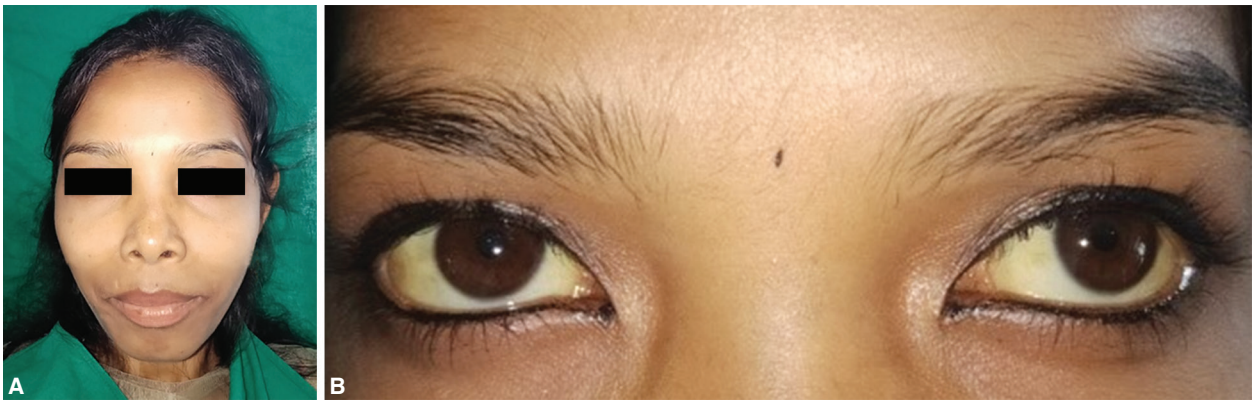
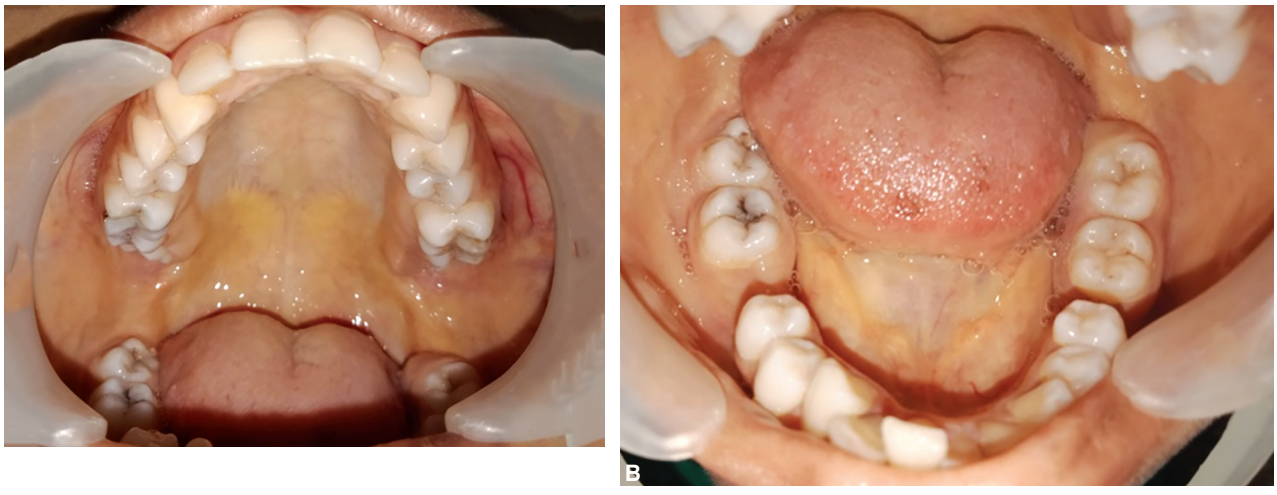
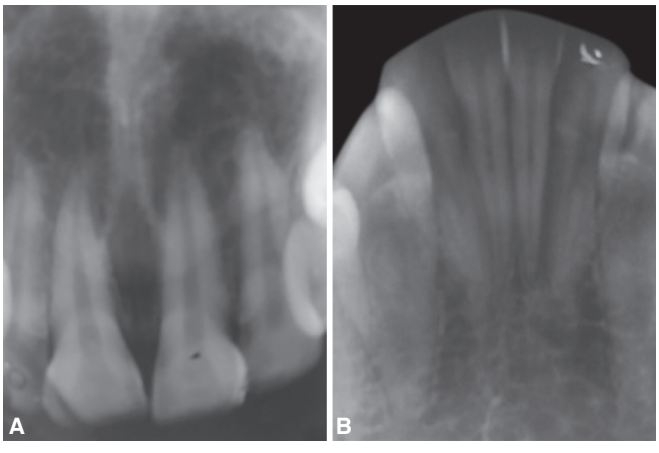


Figs 1A and B: (A) Extraoral photograph depicting the facial features; (B) Icterus in both eyes



Figs 2A and B: (A) Yellowish discoloration on the palate and buccal mucosa; (B) Yellowish discoloration in the floor of mouth



Figs 3A and B: (A) Intraoral periapical radiograph of maxillary anterior region; (B) Intraoral periapical radiograph of mandibular anterior region

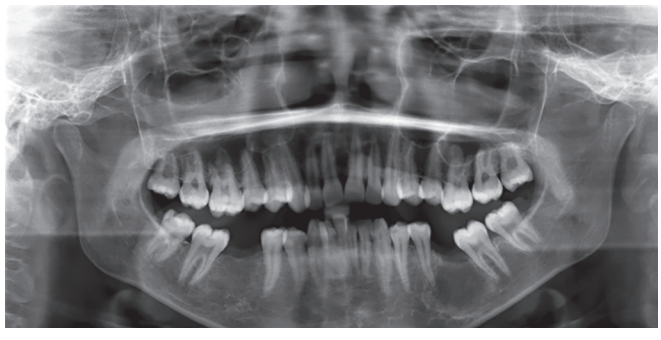


Fig. 4: Panoramic radiograph showing enlarged marrow spaces and residual cyst irt missing 36

On radiographic investigations, intraoral periapical radiographs of the maxillary and mandibular anterior region (Figs 3A and B) and panoramic view showed the presence of enlarged marrow spaces, large and coarse trabeculae. There was also the presence of missing teeth 36 and 46 with a well-defined unilocular radiolucency in the missing tooth 36 region extending from the distal of 35 to mesial of 37 suggestive of residual cyst in relation to missing 36 region (Fig. 4). Lateral skull radiograph showed increased diploic space (Fig. 5). Lateral cephalogram showed maxillary and mandibular prognathism, frontal bossing, and lip incompetence (Fig. 6).

The centrifuged blood of the patient showed more plasma proportion than formed elements and the color was yellowish brown (Fig. 7) The complete hemogram showed hemoglobin of 7.5 gm/dl. Hematocrit value was 37.5% and had a lower MCV, MCH values 45 fl and 15 pg respectively, MCHC value = 333g/dL and a low Mentzer index of 9. Blood investigations revealed RBC count 5 million/cu.mm, normal WBC counts (6600cells/cu.mm) with neutrophil count 74%, ESR (5mm/hour)

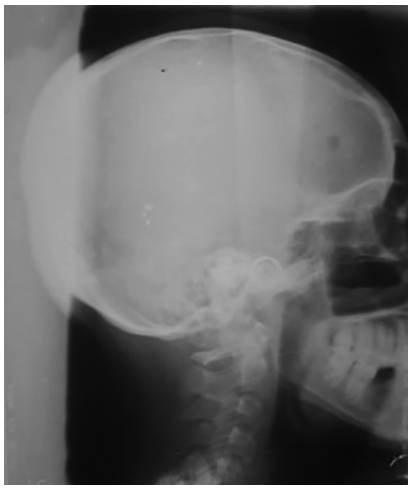


Fig. 5: Lateral skull radiograph showing increased diploic space

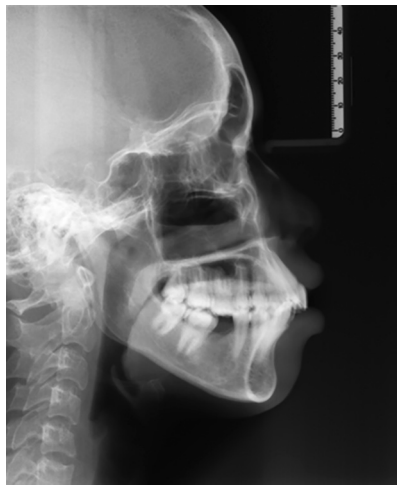


Fig. 6: Lateral cephalogram showing bimaxillary protrusion and lip incompetence

Fig. 7: The centrifuged blood with yellowish brown plasma

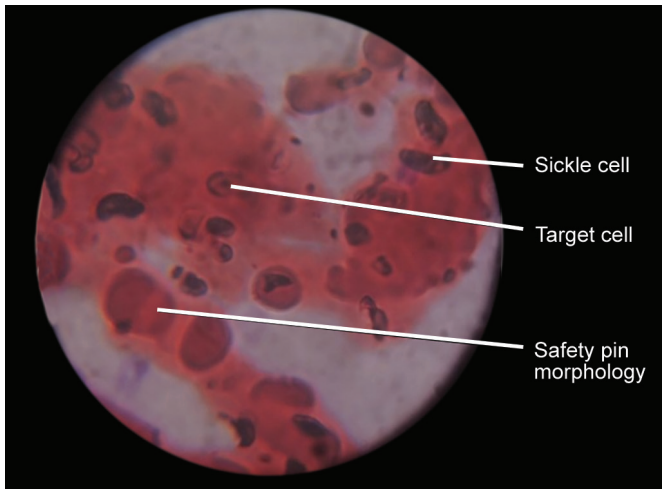


Fig. 8: Peripheral blood picture characterized by microcytic, hypochromic RBCs, with target cells and sickle cells

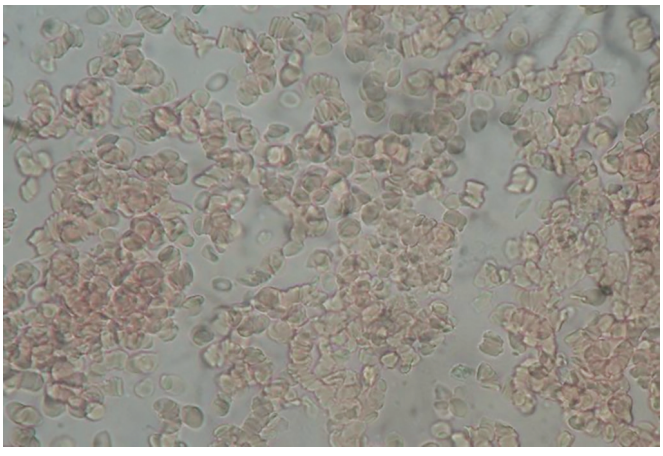


Fig. 9: The peripheral smear red blood cell showing sickling

and normal bleeding and clotting time of 3.30″ and 12 minutes, reticulocyte count of 10.5% and platelet count of 1.75 lakhs and normal blood sugar. Serum bilirubin was increased (22µmol/L). Peripheral blood smear with supravital staining (New methylene blue) showed RBC with hypochromia, microcytosis, poikilocytosis, and target cells. Most of the RBC showed safety pin morphology and sickling (Figs 8 and 9).

Thus the case presented with features of both sickle cell disease and beta thalassemia suggestive of sickle cell beta thalassemia, which has a unique presentation. The patient was referred for cyst enucleation and orthodontic treatment, and she was advised to take hematologist consent before the procedure.

DISCUSSION

The hemoglobinopathies are genetic disorders characterized by the production of structurally defective hemoglobin (Hb), and in thalassemia, there is reduction in rate of production of normal Hb due to absent or decreased synthesis of one or more types alpha(α) or beta (β) of globin polypeptide chains.[2] Sickle cell disorders (SCD) and β-thalassemia are autosomal recessive inherited disorders affecting the structure and synthesis of Hb.[1]

SCD result from the polymerization of HbS in red blood cells (RBCs) into the characteristic sickle shape under hypoxic conditions, which results in the occlusion of blood vessels.[6] SCD results when one β-globin

gene mutation includes the sickle cell mutation and the second β-globin includes a gene mutation in the β-globin gene such as mutations associated with HbC, Hb β-thalassemia, HbD, and HbO_{Arab}.[7]

The main hemoglobinopathies causing sickle cell disorder (SCD) include:[1]

- Sickle cell anemia (HbSS),
- Sickle cell β-thalassemia ($S\beta^0$ thal, $S\beta^+$ thal)
- Sickle hemoglobin C disease (HbSC)
- Sickle hemoglobin D disease (HbSD)
- Sickle hemoglobin E disease (HbSE),
- Other rare sickle-cell disorders.

Sickle cell beta-thalassemia affected individuals have a sickle beta-globin gene (β^S) and a gene for beta thalassemia; and is classified into two: one characterised by the complete absence of Hb-A due to the presence of a β^0 thalassemia gene ($S\beta^0$ thalassemia) and the other Hb-A levels of 10–30% due to β^+ gene ($S\beta^+$ thalassemia).[2]

Clinical Features

The two cardinal pathophysiologic features of sickle cell disorders include chronic hemolytic anemia and vaso-occlusion.[3] Other features include painful crises, acute chest syndrome, the hand-foot syndrome, aseptic necrosis of bone, and hepatosplenomegaly.[2] Pallor and yellowish discoloration of the skin is noted due to reduced Hb levels.

The characteristic facial feature is the *Chipmunk facies* or *rodent facies*, characterized by malar prominence, frontal bossing, saddle nose, and hypertelorism. Skeletal class II malocclusion is found due to maxillary protru-

Table 1: Diagnostic criteria

	Findings
History, Clinical features	• Chipmunk facies or rodent facies • Hepatosplenomegaly • Mucosal pallor • Yellowish discoloration of skin and mucosa • Tooth discoloration
Radiological features	• Enlarged marrow spaces due to chronic anemia • Large and coarse trabeculae • Thinned cortex of the mandible • Short and spiky roots, taurodontism • Widening of diploic spaces and thinning of the outer table • Hair-on-end appearance • Thickened frontal bone • Small maxillary sinuses • Faint inferior dental canal
Laboratory investigations	• Anemia- Hb level In β^0 type is 6–9 g/dL and in β^+ is 10–11g/dL • MCV, MCH -greatly reduced • Reticulocytosis • Serum bilirubin moderately increased(17-34 μmol/l)
Peripheral blood smear	• Hypochromia, • Target cells (Prominent granular cytoplasmic inclusion bodies, which represent aggregate of alpha chains and demonstrated by methyl violet staining in the cytoplasm and the normoblast and reticulocytes) • Basophilic stippling, • Microcytosis • Red cell fragments. • Anisopoikilocytosis with increased polychromasia, • Nucleated RBC, • Sickle cells • Oval cells
Haemoglobin solubility test	• Detects the presence of HbS. The basis of this test is the insolubility of reduced HbS in concentrated phosphate buffer, resulting in turbidity.
Indices to differentiate between thalassemia and iron deficiency anemia (IDA)[11,12]	**Mentzer index (MI)** = $\frac{\text{MCV}}{\text{RBC count (millions/μL)}}$ (MI< 13, suspect β-thalassemia, MI >13, suspect IDA). **Matos and Carvalho Index (MCI)** = (1.91 × RBC) + (0.44 × MCHC)2 • MCI <23.85 can be an IDA patient • MCI >23.85 is a thalassemia carrier
Definitive diagnosis	• Hemoglobin Electrophoresis (shows HbS with an elevation of HbF) • High paper liquid chromatography • Isoelectric focusing • Mass spectrometry or DNA testing

Table 2: Comparison of the types of sickle cell beta-thalassemia ($S\beta^0$ thalassemia and of $S\beta^+$ thalassemia)

	Hematologic values				*Hemoglobin electrophoresis*				
Type	*Hb (g/dL)*	*Reticulocyte (%)*	*MCV (fl)*	*RBC Morphology*	*Interacting genes*	*HbS (%)*	*HbF (%)*	*HbA_2 (%)*	*HbA (%)*
$S\beta^0$ thalassemia	6-10	5-20	<80	Sickle cells, nucleated rbc, hypochromia microcytosis, anisocytosis, poikilocytosis, target cells	β^S and β^0 gene	70–90	5–30	4–8	0
$S\beta^+$ thalassemia	9-12	5-10	<75	No sickle cells, hypochromia, microcytosis, anisocytosis, poikilocytosis, target cells	β^S and β^+ gene	60-85	2-10	4-8	10-30

sion and mandibular atrophy.[8] The present case showed features such as icterus, yellowish discoloration of the skin, hepatosplenomegaly, bimaxillary protrusion, lip incompetence, saddle nose, malar prominence, frontal bossing and hypertelorism, all favoring the features of thalassemia.

Oral Manifestations

In affected individuals, decreased hemoglobin levels manifest as mucosal pallor and atrophic glossitis. Severe gingivitis is seen if a splenectomy is done. Iron deposits may lead to teeth discoloration and inflammation of salivary glands. High ferritin levels in blood lead to dark-colored gingiva.[8] Those affected are prone to high caries index with increased overjet and anterior open bite.[9] Our case showed findings such as mucosal pallor, yellowish discoloration of the oral mucosa, increased overjet, and tooth discoloration.

Diagnosis

Various features which help in diagnosis of the disease has been compiled and enumerated in Table 1.

Our case showed radiographic features such as enlarged marrow spaces, increased diploic space and maxillary protrusion. Laboratory investigations and peripheral blood smear revealed reduced hemoglobin count, reduced MCV,[10] reticulocytosis, increased serum bilirubin, RBC with anisocytosis and microcytosis, sickle cells, and target cells, and low Mentzer index.

The differences between the two types of sickle cell beta-thalassemia, $S\beta^0$ thalassemia and $S\beta^+$ thalassemia based on hematological findings and hemoglobin electrophoresis are described in Table 2.[2,3]

Management

Management of patients with sickle cell beta thalassemia primarily begins with education and psychosocial support, genetic counseling, followed by immediate treatment of acute complications of vaso-occlusive crisis by the supplemental oxygen therapy, correction of acidosis and aggressive treatment of associated infections. Prophylactic penicillin prophylaxis is used until 5 years of age.[7] Blood transfusions are indicated only during acute severe exacerbations of anemia, as during splenic crisis or aplastic crises. Chelation therapy can be administered with iron chelators such as deferoxamine, deferasirox, and deferiprone to reduce the iron overload after multiple blood transfusions. Bone marrow transplantation and gene therapy are definitive therapies to cure the disease.[8]

Dental Considerations

Factors precipitating stress, acidosis, and hypoxia should be avoided. Liver function, Hb level (should be >10 mg%) and coagulation tests should be done before any surgical procedure.[8] Any invasive procedure should be done under antibiotic prophylaxis and immediately after transfusion.[9] In less severe type, the orofacial defects and malocclusion can be treated surgically followed by an orthodontic correction. If the malocclusion is minimal, it can be corrected at an early stage by preventive and interceptive orthodontics with low forces.[8]

Drugs like aspirin, tetracycline, metronidazole, erythromycin estolate, and other hepatotoxic drugs should be avoided.[9] In cases who underwent splenectomy, administration of antiplatelet drugs requires monitoring of bleeding time and hematologist consultation.[8] Sedation should be used with caution in patients with thalassemia due to the risk of respiratory depression and the presence of chronic, potentially severe anemia.

CONCLUSION

Oral physicians and oral pathologists should be vigilant enough to identify any hemoglobinopathy, with adequate radiological and hematological investigations, although it has a rare occurrence. If diagnosed, a multidisciplinary approach involving dental surgeon, and orthodontist is mandatory for these patients.

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