CASE REPORT

Co-occurrence of biphenotypic acute leukaemia, glucose 6-phosphate dehydrogenase deficiency and haemoglobin E trait in a single child

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SUMMARY

Acute leukaemias occur as the result of clonal expansion subsequent to transformation and arrest at a normal differentiation stage of haematopoietic precursors, which commit to a single lineage, such as myeloid or B-lymphoid or T-lymphoid cells. Biphenotypic acute leukaemia (BAL) constitutes a biologically different group of leukaemia arising from a precursor stem cell and co-expressing more than one lineage specific marker. The present report describes a child with unusual co-occurrence of biphenotypic (B-precursor cell and Myeloid) acute leukaemia, haemoglobin E trait and glucose 6-phosphate dehydrogenase (G6-PD) deficiency. To the best of our knowledge, this constellation of haematological conditions in a single child has never been described before.

BACKGROUND

Leukaemia is one of the most common causes of non-accidental death in children. This report describes a child with unusual co-occurrence of biphenotypic (B-precursor cell and myeloid) acute leukaemia, haemoglobin E (HbE) trait and glucose 6-phosphate dehydrogenase (G6-PD) deficiency. To the best of our knowledge, this constellation of haematological conditions in a single child has never been described before.

CASE PRESENTATION

A 3-year 6-month-old male child, born to non-consanguineous parents, was initially seen for a 4-day history of low-grade fever and progressive pallor for the past 3 months. There was no history of convulsion, loss of consciousness, joint pain, rash, abdominal pain and bleeding episodes. He had never received blood or blood product transfusion in the past. His medical history and family history for significant illness were non-contributory.

At presentation, he was extremely pale and febrile with stable vitals. Generalised lymphadenopathy was noted with the largest lymph nodes in the neck, axillae and inguinal regions measuring 1.5×2 cm, 1×1.5 cm and 1.5×1.5 cm, respectively. They were firm, mobile and non-tender. The liver and the spleen were palpable 3.5 and 2 cm below the right and the left costal margins, respectively. Other major systems were normal.

INVESTIGATIONS

Haematological examination revealed a predominantly normocytic normochromic smear with few hypochromic microcytes, tear drop cells and

occasional nucleated red blood cells; haemoglobin (Hb): 2.4 g/dL; haematocrit: 10.5%; mean corpuscular volume (MCV): 77 fL; mean corpuscular haemoglobin (MCH): 13.9 pg; MCH concentration (MCHC): 16.5 g/dL; reticulocytes: 2%; platelets: 31 000/mm³; total leucocyte count: 7000/mm³ (neutrophils: 25%, lymphocytes: 47%, monocytes: 2%, eosinophils: 3%); blast cells: 23%. The erythrocyte sedimentation rate and C reactive protein were 90 mm (first hour) and 1.80 mg/L, respectively. His quantitative serum G6-PD was 1.4 U/g Hb (reference range: 4.6–13.5 U/g Hb). Those of his mother and father were 3.1 U/g Hb (consistent with her G6-PD carrier status) and 8.9 U/g Hb (normal), respectively. Sickling test was negative. High performance liquid chromatography (HPLC) of Hb (Variant β Thalassemia Short Programme, BioRad) revealed HbF of 0.9%, HbA of 57.8% and HbA₂+HbE of 29.5%, consistent with the diagnosis of HbE trait. The HPLC of the mother's Hb done concurrently revealed HbE trait carrier status. The child's red cell distribution width and serum ferritin were 20.2% and 147.98 ng/mL (reference range: 30–274 ng/mL), respectively. Serum urea, creatinine, electrolytes, bilirubin, proteins and liver enzymes were normal. The chest radiograph was normal and the abdominal ultrasound confirmed the organomegaly. The bone marrow aspiration study revealed hypercellular marrow with depressed erythropoiesis, myelopoiesis and megakaryopoiesis. Blast cells with coarse nuclear chromatin, indistinct nucleoli and a scanty, deep basophilic cytoplasm constituted about 90% of the non-erythroid marrow nucleated cell population. Some of the cells showed block Periodic acid Schiff (PAS) stain positive granules. The blast cells were negative for myeloperoxidase and Sudan Black B stains.

The immunophenotyping using a CD45/SSC scatter plot showed a large population of cells with a low to intermediate side scatter and variable CD45 expression (dim to negative). On further analysis, the cells expressed the immunophenotypic findings that are depicted in [table 1](#). The fluorescent in situ hybridisation analysis for BCR-ABL fusion, MLL and TEL/AML 1 gene rearrangements and the conventional karyotype returned normal.

OUTCOME AND FOLLOW-UP

Parents were informed about the diagnosis, the subsequent course of management and the likely outcome. Unfortunately, despite extensive

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Table 1 The immunophenotypic profile of the patient

Immunophenotyping markers	CD 45	Positive (34%) (dim)
Myeloid markers	Cytoplasmic myeloperoxidase	Positive (52%)
	CD 117	Negative
	CD 13	Positive (41%)
	CD 14	Negative
	CD 15	Negative
	CD 33	Positive (26%)
B-Lymphoid markers	Cytoplasmic-CD 79a	Positive (98%)
	CD 19	Positive (99%)
	CD 10	Positive (99%)
	CD 19/CD 10 (coexpression)	Positive (99%)
	CD 20	Positive (23%)
T-Lymphoid markers	Cytoplasmic-CD 3	Negative
	Soluble-CD 3	Negative
	CD 5	Negative
	CD 7	negative
Non-lineage specific markers	CD 34	Positive (99%)
	HLA DR	Positive (56%)

CD, cluster of differentiation; HLA, human leucocytic antigen.

motivation, they refused treatment for their child and denied further hospital stay.

DISCUSSION

Acute leukaemias occur as a result of clonal expansion subsequent to transformation and arrest at a normal differentiation stage of haematopoietic precursors, which commit to a single lineage, such as myeloid or B-lymphoid or T-lymphoid cells. This paves the path for the broad classification of acute leukaemias into myeloid or B/T lymphoid. Morphologically, cytochemically and immunophenotypically,¹ BAL is diagnosed when the blast cells express both myeloid and lymphoid characteristics. Such instances of mixed lineage may occur either due to malignant transformation of precursor cells capable of differentiating into, or expressing characteristics of, more than one lineage (lineage promiscuity),² or from aberrant gene regulation, not normally observed in normal haematopoietic differentiation (lineage infidelity).³ The WHO recommends the European Group for Immunologic Classification of Leukemia (EGIL)⁴ criteria for the diagnosis of BAL (table 2). BAL is typically diagnosed when the score is greater than two for myeloid and one for lymphoid lineages. The blasts in such patients co-express B-lymphoid and myeloid markers more commonly than do T-lymphoid and myeloid ones.⁵

This group of leukaemia as compared to 'pure' lymphoid and myeloid ones is rare. A recent paper by Gujral *et al*⁶ reported

on 2689 instances of acute leukaemia from India, of which 32 were diagnosed with BAL, thus yielding an incidence of 1.2%. Other studies report incidences varying from 1% to 8%.^{7 8}

The prevalence of G6-PD deficiency, the most common self-limiting X-linked enzymopathy, varies from 0% to 27% among different castes, tribes, ethnic, religious and linguistic groups in India.⁹ Although sickle-cell disease is the most common haemoglobinopathy prevalent around the world, HbE disease is, by far, the commonest variant in Southeast Asia, where its prevalence is estimated to be around 30%.¹⁰

There are very few studies from India that look into the clinical manifestations arising out of the co-occurrence of haemoglobinopathies and the G6-PD deficiency state. Balgir¹⁰ reported the haematological profile of 29 instances of co-occurrence of different haemoglobinopathies and G6-PD deficiency among tribals of Eastern India. The study showed that female heterozygotes and homozygotes of G6-PD deficiency in association with haemoglobinopathies showed reduced values of haematological indices (Hb level, MCV, MCH, MCHC and red blood cell count) compared to normal individuals. Red cell indices were found to be further reduced in male G6-PD deficiency co-occurring with haemoglobinopathies in a homozygous condition, including HbE disease. In the same study, he reported two males, one aged 60 years and the other five, with co-occurrence of HbE trait and G6-PD deficiency. Both the patients showed less than two SD reduction in red cell indices. The results were similar in another patient with conjoint HbE disease and G6-PD deficiency. In the present child, the severe anaemia that was observed at admission might be the result of coexisting acute leukaemia.

Anaemia in leukaemia occurs due to insufficient bone marrow as a result of malignant infiltration of the bone marrow by the leukaemic cells. G6-PD deficiency causes haemolysis, and HbE trait is a haemoglobinopathy. Thus, the present patient represents the convergence of these independent events, which is most likely an extremely unusual coincidence. Nonetheless, as this report exemplifies, although acute leukaemia per se might lead to low Hb, combined with low platelet count, even without HbE trait and G6-PD deficiency, it is clinically important and helpful to rule out the possibility of a second aetiology as well if a child presents with acute leukaemia with a very low Hb level.

Learning points

- ▶ Although biphenotypic acute leukaemia is relatively uncommon, it should be considered in all children presenting with acute leukaemia.
- ▶ Although acute leukaemia per se might lead to low haemoglobin, combined with low platelet count, even without haemoglobin E trait and glucose 6-phosphate dehydrogenase (G6-PD) deficiency, it is clinically important and helpful to rule out the possibility of a second aetiology as well if a child presents with acute leukaemia with a very low haemoglobin level.

Contributors MD was involved in the diagnosis and initial workup; RT was involved in the critical literature review and manuscript preparation; BB was involved in the manuscript drafting and review.

Competing interests None declared.

Patient consent Obtained.

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Table 2 EGIL Scoring system for the definition of BAL

Scoring points	B-lymphoid	T-lymphoid	Myeloid
2	CD79a	CD3	Anti-MPO
	CD22	Anti-TCR α/β	
	Cyto IgM	Anti-TCR γ/δ	
1	CD19	CD2	CD117
	CD10	CD5	CD13
	CD20	CD8	CD33
		CD10	CD65
0.5	TdT	TdT	CD14
	CD24	CD7	CD15
			CD64

BAL, biphenotypic acute leukaemia; EGIL, European Group for Immunologic Classification of Leukemia; MPO, myeloperoxidase; TCR, T cell receptor; TdT, terminal deoxynucleotidyl transferase.

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