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Acute favism-induced haemolysis with symptomatic methaemoglobinemia in a patient without glucose-6-phosphate dehydrogenase deficiency

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Abstract
Finding of low oxygen saturations is common in the emergency department and usually managed with oxygen therapy. However, persistently low oxygenation despite oxygen therapy can present as a diagnostic and management challenge. We present the case of a 4-year-old boy who presented with low oxygen saturations and signs of intravascular haemolysis. After extensive investigation, the cause was concluded to be methaemoglobinemia with glucose-6-phosphate dehydrogenase deficiency-induced haemolysis. We conclude that the diagnosis of methaemoglobinemia should be considered in a patient who presents with the triad of low oxygenation without respiratory distress and clear lung fields on auscultation and chest x-ray.

Keywords: G6PD deficiency, methaemoglobinemia, favism, haemolysis, paediatric

Introduction

Elevated methaemoglobin (metHb), is by definition more than 1% of haemoglobin with ferric iron instead of ferrous one, as observed in many patients with fava bean-ingestion-induced haemolysis (favism) [1].Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymopathy of red blood cells (RBCs) affecting 400 million individuals worldwide [2]. It renders RBCs vulnerable to oxidative-stress-induced intravascular haemolysis. Thus, G6PD deficient patients may present to the emergency department (ED) with a typical clinical scenario of intravascular haemolysis along with elevated methaemoglobin (metHb).This is, however, rare in patients without a prior diagnosis of G6PD deficiency. We report a paediatric case of acute favism-induced haemolysis with symptomatic methaemoglobinemia who was previously unknown G6PD-deficient.

Case presentation

A 4-year-old boy with a past history of asthma requiring no prophylactic medications was brought to the paediatric ED with a 2-day-history of tactile fever, episodes of food-content vomiting, and tea-coloured urine followed by skin yellowish discolouration on the day of the presentation. His mother reported a history of ingesting fava bean during the last 2 days prior to the presentation, but denied any history of recent sick-contact, recent travel, previous similar episode, neonatal jaundice, or similar prior presentations.

Moreover, no family history of haematological diseases and his parents are not consanguineous. He is up to date on his vaccines according to the Saudi vaccine schedule [3] and has no known allergies to food, drug or dye.

Upon presentation, he looked alert, oriented, mildly dehydrated with dry mucous membranes, jaundiced, and pale but neither cyanosed nor in respiratory distress. His oxygen saturation was recorded to be 88%, and 15 L/min O2 through a non-rebreather mask was commenced. Other vital signs were: heart rate: 140 bpm, respiratory rate: 32 bpm, BP: 110/68 mmHg, and temperature: 39oC.

On examination, scleral icterus along with conjunctival pallor were noted. Chest auscultation revealed equal bilateral vesicular breathing without added sounds in addition to audible first and second heart sounds with physiological murmur (systolic medium-pitched sound). Abdominal examination was insignificant for tenderness or hepato-splenomegaly. Neurological exam showed grossly intact motor function with no neck stiffness. Bedside urine dipstick was positive for urobilinogen.

Despite oxygen therapy, O2 saturation only reached 90% and a subsequent venous blood gases (VBG) examination was conducted that showed metabolic acidosis with normal O2 tension (Table-1).

Furthermore, a chest x-ray was performed that was reported to be normal with no significant findings (Image-1). Subsequently, methaemoglobinemia was suspected and further blood tests were conducted (Table-2).

Based on the investigation results, a diagnosis of acute favism-induced intravascular haemolysis with symptomatic methaemoglobinemia was made. As the possibility of G6PD deficiency-induced haemolysis was raised by the presence of blister cells in the peripheral blood film and the fact that no methaemoglobinemia-induced end-organ damage observed, the management was directed towards the acute haemolysis. The patient was managed with 2 units of packed RBC over 4 hours. After the first and second blood transfusions, O2 saturation improved to 94% and 95% on 15 L/min O2 while the metHb level went down to 4% and 2%, respectively.

The patient remaine d in hospital for 4 days. On discharge, his Hb was 11.9 g/dl with metHb: <1%.

Table 1: VBG

Value	Result
pH	7.29
PaO2	96 mmHg
PaCO2	33 mmHg
HCO3	19 mEq/L

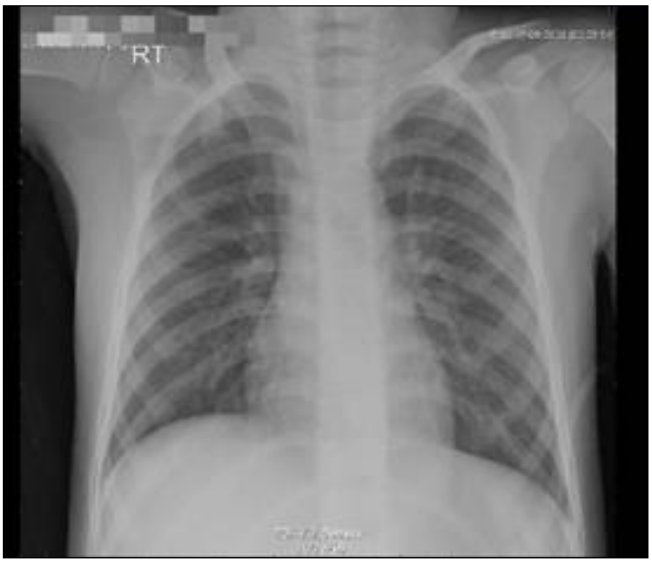

Fig 1

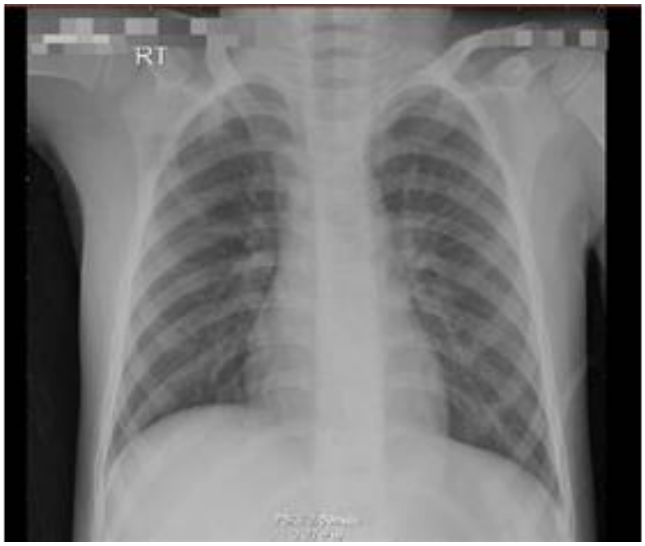

Fig 2: CXR.

Table 2: Laboratory tests.

Value	Result	Range
Hb	4.9 g/dl	11-14
RBC	1.75x1012/L	4-5.2
MCV	79.4 fL	75-87
Retic	4.81 %	0.5-2.5
WBC	25.35x109/L	5-15
PLt	254x109/L	200-450
LDH	2345 U/L	140-280
Total bilirubin	95 umol/L	1.71-20.5
Direct bilirubin	10.2 umol/L	0-3
MetHb	10%	<1%
Creatinine	29.7 umol/L	27-42
Urea	10.8 mmol/L	2.5-6.4
AST	133 U/L	15-37
ALT	24 U/L	16-63
PBF	Normocytic normochromic anaemia with blister cells.	
Direct Coombs test	Negative	

Discussion

Among paediatrics, symptomatic methaemoglobinemia in setting of acute intravascular haemolytic crisis has been reported in few cases worldwide [4-7]. To our knowledge, this is the first report of such a case in Saudi Arabia.

In addition to previously reported cases, this presentation highlights important diagnostic principles. First, in the setting of acute intravascular haemolysis accompanied by symptomatic methaemoglobinemia, fava bean ingestion should be sought in the history [1, 4-7]. However, the absence of such an important and common trigger for a haemolytic crisis that cannot otherwise be attributed to other pathologies must bring the ED physician's attention to the fact that a haemolytic crises may present as pure methaemoglobinemia in the setting of other inducers such as antibiotics, local anaesthetic agents, dapsone, sulfasalazine, or phenacetin, and potentially nitrates [8].

Second, the triad of desaturation in a non- respiratory distressed patient with clear chest auscultation and x-ray should always raise the suspicion of methaemoglobinemia. This is particularly important in the ED setting where cyanosis, often the most striking finding, may be masked by pallor.

Third, usually, 10-20% concentration of metHb is well-tolerated and does not progress to cyanosis [8]. However, functional anaemia of methaemoglobinemia with actual anaemia of haemolysis may contribute to symptoms, as was the case in our patient. The preferred management of this anaemia is exchange blood transfusion [8] after ruling out any end-organ damage.

Following acute management of methaemoglobinemia, G6PD deficiency must be considered as a differential. Importantly, the treatment of methaemoglobinemia with methylene blue has to be delayed as much as possible till G6PD deficiency is ruled out.

Lastly, in the setting of the SARS-CoV-2 (COVID-19) pandemic, self-medication with chloroquine must be inquired about as a possible unusual additional inducer [9].

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