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# Hypoxic Respiratory Failure Due to Three Hits: Pulmonary Embolism, Rasburicase-Induced Methaemoglobinaemia And Haemolytic Anaemia In A Patient with Previously Undiagnosed Glucose-6-Phosphate Dehydrogenase Deficiency

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**ABSTRACT**

We present a 35-year-old male patient who developed hypoxic respiratory failure from three concurrent pathologies–acute pulmonary embolism, methemoglobinemia and oxidative haemolytic anaemia from previously undiagnosed glucose-6-phosphate dehydrogenase deficiency, precipitated by rasburicase therapy for tumour lysis syndrome following chemotherapy for non-Hodgkin's lymphoma. Hypoxia resolved upon treating all pathologies, highlighting the need to consider these rare differential diagnoses.

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## Introduction

Tumour lysis syndrome (TLS) is a potentially fatal complication of chemotherapy for malignancy, where byproducts of cellular damage can lead to severe electrolyte disturbances and organ failure. Uric acid is one of these by products that can cause severe acute kidney injury. Second-line treatment involves rasburicase – a recombinant enzyme that catalyses uric acid oxidation into allantoin for renal excretion, thus mitigating uric-acid mediated renal damage [1,2].

Glucose-6-phosphate (G6PD) deficiency is a relatively common condition affecting 400 million people worldwide – particularly in Asian, Middle Eastern and African populations – where affected individuals are at increased risk of oxidative hemolysis from medications [2]. G6PD deficient patients are also at increased risk of methaemoglobinaemia when treated with rasburicase, as the catalytic process produces hydrogen peroxide which can induce oxidative damage and conversion of ferrous to ferric iron in the setting of G6PD, leading to methemoglobinaemia on top of oxidative haemolytic anaemia [1,2]. Methaemoglobinaemia can result in hypoxic respiratory failure due to increased oxygen binding affinity and therefore reduced oxygen delivery, effectively causing a leftward shift in the oxygen dissociation curve [1,2].

We present a case of a patient who developed hypoxic respiratory failure from three concurrent pathologies – acute pulmonary embolism, methaemoglobinaemia and oxidative haemolytic anaemia from undiagnosed glucose-6-phosphate dehydrogenase deficiency, precipitated by rasburicase therapy for tumour lysis syndrome following chemotherapy for non-Hodgkin's lymphoma. A 35-year-old Iraqi gentleman was electively admitted to hospital for treatment of newly diagnosed non-Hodgkin lymphoma with R-CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisolone). His medical history was also notable for mild pulmonary arterial hypertension, and previous cholecystectomy for calculous cholecystitis.

After receiving his first cycle of chemotherapy, he subsequently developed an acute kidney injury with elevated serum creatinine. Concurrently his serum phosphate, potassium and uric acid were elevated but serum calcium was marginally low. He was diagnosed with tumor lysis syndrome and treated with intravenous normal saline, Sodium carbonate, calcium gluconate and rasburicase infusion. Repeated blood tests showed normalisation of uric acid, potassium and phosphate, and improvement in renal function.

However, he began to develop hypoxia with oxygen saturation decreasing to 90% on room air, and requiring supplementary oxygen via high flow nasal cannulae (HFNC). Computerised Tomography Pulmonary Angiogram revealed a right subsegmental pulmonary embolism, but bedside echocardiography showed normal left ventricular systolic function and only mildly elevated

right heart pressures similar to his previous echocardiogram findings 6 months ago.

The patient was started on a heparin infusion to treat the pulmonary embolism, but the hypoxia did not improve despite improvements in his electrolytes and kidney function. Over the course of his admission, his haemoglobin was noted to decrease from 140 g/L to 100 g/L over the course of 4 days. He was transfused with two units of packed red blood cells which improved his oxygen saturation to 94% and improved his haemoglobin to 110 g/L. Haemolysis investigations were remarkable for an elevated lactic acid dehydrogenase, and increased total and indirect bilirubin. He otherwise had a negative direct coombs test, normal platelet and reticulocyte count, and normal Troponin. Per-rectal examination did not reveal melaena. Upper and lower gastrointestinal endoscopy could not be done due to persistent hypoxia. Abdominal Computerised Tomography with angiography did show any active bleeding source. Pulmonary function tests showed normal volumes and diffusing capacity of the lungs for carbon monoxide (DLCO).

Repeated physical examination was unremarkable apart from moderate splenomegaly and right supraclavicular lymphadenopathy which were present for at least two months in the setting of non-Hodgkin lymphoma. There was no evidence of telangiectasia. The peripheries were warm and well perfused.

In view of persistent anaemia and hypoxia, the patient was transfused with two additional units of packed red blood cells. Haemoglobin improved to 120 g/L the following day, but the patient remained hypoxic, saturating at 92% with HFNC at 40 L/min and 40% FiO2. Paired arterial blood gas showed PaO2 of 60mm/hg and oxygen saturation of 86% with normal PaCO2 and pH.

The patient had an oxygen saturation gap of 6% which prompted specific testing for dyshaemoglobinaemia. Carboxyhaemoglobin less than 1%, Sulfhaemoglobin was undetectable and Methaemoglobin was markedly elevated at 8%. Methaemoglobinaemia was diagnosed as a cause of hypoxia.

Further peripheral blood film analysis showed bite cells and Heinz bodies. NADPH enzyme activity was markedly decreased at 0.4 units/gram of hemoglobin – confirming the diagnosis of G6PD deficiency. Hence, methylene blue therapy was not given.

The patient was ultimately diagnosed with three pathologies causing hypoxic respiratory failure – acute pulmonary embolism, methaemoglobinaemia and oxidative hemolytic anaemia from G6PD deficiency, with the latter two pathologies precipitated by rasburicase therapy.

Rasburicase was stopped after three days upon diagnosis. He received a further two units of packed red blood cells, an iron infusion and vitamin C. His oxygen saturations improved to 97% on room air with no further oxygen saturation gap. Methemoglobin decreased to 3% on repeated testing. The patient made a full recovery and continued anticoagulation for pulmonary embolism. He continued to receive chemotherapy and follow-up with his Haematologist.

## Discussion

We present a case of a young Iraqi male patient with hypoxic respiratory failure secondary to three aetiologies – acute pulmonary embolism, methaemoglobinaemia and oxidative hemolytic anaemia – in the setting of rasburicase therapy and underlying undiagnosed G6PD deficiency. Hypoxia fully resolved upon treating all three of these conditions and with cessation of rasburicase.

Rasburicase-induced methaemoglobinaemia is a rare entity that can occur in susceptible individuals, particularly those with G6PD deficiency [1,2]. There have been several case reports describing this phenomenon, predominantly in Asian and Middle Eastern populations, in keeping with the geographical distribution of G6PD deficiency [2,3]. To the best of our knowledge, this case represents only the second formal report of rasburicase-induced methaemoglobinaemia from Australasia [4].

While there are several case reports of rasburicase-induced methaemoglobinaemia and oxidative haemolytic anaemia from G6PD deficiency, to the best of our knowledge, this is the first of such a case with concurrent pulmonary embolism contributing hypoxic respiratory failure [1,4-16].

Given the multicultural communities particularly in Australasia, we hope this case will bring greater awareness of this phenomena and clinicians will consider this rare entity as a differential diagnosis in a patient who develops hypoxic respiratory failure following rasburicase therapy. Patients may also need to be screened for G6PD deficiency prior to starting oxidative hemolysis-inducing medications, such as rasburicase.

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