Rasburicase Causing Severe Oxidative Hemolysis and Methemoglobinemia in a Patient with Previously Unrecognized Glucose-6-Phosphate Dehydrogenase Deficiency

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Introduction

Tumor lysis syndrome (TLS) is a serious metabolic complication of rapid cellular turnover in highly proliferative tumors and can be precipitated following the administration of chemotherapy resulting in cell death, as well as in intracellular content release, multiple electrolyte disturbances, acute kidney injury, potentially cardiac arrhythmia and death [1]. Rasburicase is a recombinant uric acid oxidase which rapidly converts insoluble uric acid to the far more soluble allantoin with concomitant release of hydrogen peroxide as a by-product [2]. Studies have demonstrated that rasburicase can reduce serum urate levels, faster and with less acute kidney injury compared to allopurinol [2, 3]. Therefore, rasburicase is recommended in patients with frank clinical TLS and can be considered in patients at high risk of TLS, or in those in whom allopurinol is contraindicated [1]. Although ras-

Key Words
Methemoglobinemia · Oxidative hemolysis · Rasburicase

Abstract
Rasburicase is frequently used in tumor lysis syndrome (TLS). Although it is very well tolerated, it can cause severe oxidative hemolytic anemia and methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. We report another case of rasburicase-induced methemoglobinemia in a patient with previously unrecognized G6PD deficiency and review the cases of methemoglobinemia and oxidative hemolysis reported in the literature to date. Patients from ethnicities in which G6PD deficiency is prevalent at high risk of TLS should be screened for G6PD deficiency prior to administration of rasburicase where practical. Asymptomatic decrease in oxygen saturation by oximetry and cyanosis are signs of methemoglobinemia; patients recover with conservative measures including supplemental oxygen and packed red cell transfusion.
buricase is usually very well tolerated, patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are prone to developing methemoglobinemia and hemolytic anemia. Erythrocytes in patients with G6PD deficiency are prone to developing methemoglobinemia and hemolytic anemia. Hemoglobin (Hb) leads to methemoglobin formation, Heinz body formation, red cell rigidity and destruction by macrophages in the reticuloendothelial system [4, 5]. G6PD deficiency is the most common disease causing enzymopathy in humans, affecting 400 million people worldwide, with Africa, South East Asia and the Mediterranean being the areas of highest prevalence [6]. Despite this prevalence, and the recent increased utilization of rasburicase, only 10 cases of methemoglobinemia have been reported to date, the majority of these in pediatric settings and few described in detail [4, 7–14]. We report on a case of rasburicase-induced methemoglobinemia (RIM) and hemolytic anemia in an adult patient with (previously undiagnosed) G6PD deficiency.

**Case Report**

A 46-year-old man of mixed Mauritian-Chinese background was referred to our institution for management of relapsed chronic lymphocytic leukemia (CLL). His CLL, diagnosed 6 years previously, presented as progressive cervical lymphadenopathy and peripheral blood lymphocytosis (262 × 10⁹/l), with marked anemia (Hb 60 g/l, reference range 130–150). Histology and flow cytometry were consistent with CLL, with no evidence of high-grade transformation. Initial therapy comprised FCR (fludarabine, cyclophosphamide, rituximab) which resulted in a partial remission (PR) lasting 2 years. He was then treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) achieving PR, lasting less than 6 months. At this point, he was referred to our institution for a phase II clinical trial of the pro-apoptotic BH3-mimetic agent Navitoclax [15]. This was administered for 18 months, with maximal response being PR. He withdrew from this study due to progressive disease and entered a phase 1 clinical trial of a second-generation molecule of the same class, ABT199 [16].

At formal reassessment prior to commencing ABT199 on FISH testing, his CLL was shown to harbor del(11q) in 33% of cells and a subclone of cells with del(17p) in 7.5%, indicative of unfavorable prognosis. Imaging demonstrated bulky intra-abdominal and pelvic lymphadenopathy (maximum diameter 8 cm), with his marrow 70% infiltrated with CLL. Baseline investigations included Hb 10.9 g/dl (reference range 13.0–15.0), white blood cell count 7.6 × 10⁹/l (4.0–11.0; lymphocytes 3.6), creatinine 109 μmol/l (60–120), lactate dehydrogenase 499 U/l (230–460) and urate 0.4 mmol/l (0.21–0.42). Previous experience with ABT199 had demonstrated clinical and biochemical tumor lysis in those patients with bulky lymphadenopathy or high circulating lymphocyte count. Moreover, this patient had demonstrated biochemical evidence of TLS with Navitoclax. Hence, he was pre-emptively admitted for administration of intravenous rasburicase (dose 6 mg; patient weight 82 kg) in addition to intravenous hydration and biochemical monitoring. Approximately 12 h following administration of rasburicase, he became hypoxic and tachypneic, with no abnormal findings on respiratory examination and a normal chest X-ray. Direct antiglobulin test and coagulation studies were unremarkable but blood film was consistent with oxidative hemolysis (fig. 1). Relevant clinical and laboratory features are summarized in table 1. He developed progressive respiratory distress, increasing oxygen requirements and was transferred to the intensive care unit. The patient was transfused with packed red blood cells to maintain Hb 7.0 g/dl, continued intravenous fluids and received ascorbic acid 1 g daily postoperatively for antioxidant effect which was discontinued after 5 days [12, 17]. Methylene blue was not administered. On day 4, the patient stabilized clinically and biochemically and was discharged to the ward. A screening test for G6PD deficiency was abnormal, and quantitative testing (Cobas C501 analyzer, Roche Diagnostics, Basel, Switzerland; Trinity Biotech G6PDH reagent, Jamestown, N.Y., USA) at the time was 4.8 IU/g Hb (reference range 8.8–17.6). He remains on ABT199 8 months later and has achieved an excellent response without further complication [18].

**Discussion**

This case serves as an important reminder that RIM and hemolytic anemia are infrequent but important complications with potentially severe consequences, which all clinicians prescribing the agent should be aware of, able to promptly recognize and efficiently manage.

**Fig. 1.** Blood film demonstrating CLL (long arrow) and numerous blister cells (short arrows). Photograph: courtesy of Dr Piers Blombery (Olympus BX50, Olympus Corporation, Tokyo, Japan).
An asymptomatic drop in oxygen saturation by oximetry within 24 h of rasburicase administration, with or without cyanosis, should alert the clinician to the probability of methemoglobinemia, particularly in male patients of a high prevalence ethnicity. More severe methemoglobinemia can cause weakness, lethargy and headache; and hemolytic anemia can result in jaundice, hemosiderosis, tachycardia and breathlessness.

Prompt evaluation with full blood count and film, hemolysis screen and arterial blood gas (which may have brownish discoloration) will confirm the diagnosis. Once the diagnosis is established, treatment is largely supportive with administration of supplemental oxygen and red blood cell (not exchange) transfusions. Methylene blue, effective in methemoglobinemic patients with normal levels of G6PD, should be avoided in G6PD deficiency, as such patients lack nicotinamide adenine dinucleotide phosphate and are unable to reduce methylene blue, which can add to the oxidative stress and theoretically worsen hemolysis [4]. Ascorbic acid (1 g orally, postoperatively) has been used empirically in a prior case [12] for its antioxidant effect based on preclinical data [17]. In this case, the patient recovered after 5 days but required blood transfusions totaling 8 units.

Although the Food and Drug Administration has a boxed warning recommending testing of G6PD levels prior to administration of rasburicase, and avoiding administration in G6PD-deficient individuals, in practice, this is infrequently done [19]. Rather than screening for G6PD deficiency in all patients likely to receive rasburicase, a more rational approach would be to limit screening to individuals of ethnicity with a high prevalence, such as African, South East Asian and Mediterranean, racial groups with a gene frequency estimated at 5–25% [6]. G6PD deficiency is rare in individuals of Northern European ancestry [20].

All previously reported cases (table 2) were males, and the majority of them were of either South East Asian (n = 4) or African American (n = 4) ethnicity consistent with the X-linked mode of inheritance and geographic distribution of G6PD deficiency. RIM has been reported, as in our case, with doses as low as 6 mg, and although it can develop as early as 90 min after administration [9], several cases showed clinical manifestations more than 6 h following dosage [8, 11]. This has implications for patients treated in the ambulatory care setting, in that 6 h of observation may not exclude the subsequent development of RIM after discharge. Less than half the cases reported cyanosis (n = 2) or dyspnea (n = 3), but most patients experienced biochemical hemolysis (n = 7) with a median nadir Hb of 6.0 g/dl (reference range for adult males 13.0–15.0). There is no apparent relationship between the dose of rasburicase administered and the peak methemoglobin level or nadir Hb level (data not shown). Most cases (n = 8) have required red cell transfusion support. Interestingly, 7/9 cases tested prior to transfusion were G6PD deficient. For the 2 patients with normal G6PD levels, one was Caucasian and the other ethnicity was not specified. Two patients were not tested, as G6PD deficiency was assumed: one due to the occurrence of the complication and African American ethnicity; the other case (ethnicity not specified) received concomitant primaquine and dapsone. Other enzymopathies were suggested (but not confirmed) as putative explanations for the manifestation of methemoglobinemia under oxidative stress [11]. All reported cases have recovered with resolution of methemoglobinemia, within 3–7 days, following cessation of rasburicase and supportive care.

### Table 1. Clinical and laboratory progress of our case

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ref. range</th>
<th>+9 h</th>
<th>+12 h</th>
<th>+24 h</th>
<th>+36 h</th>
<th>+42 h</th>
<th>+50 h</th>
<th>+60 h</th>
<th>+72 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, g/dl</td>
<td>13.0–15.0</td>
<td>10.8</td>
<td>10.0</td>
<td>8.0</td>
<td>6.7</td>
<td>6.0</td>
<td>6.6</td>
<td>7.6</td>
<td>7.5</td>
</tr>
<tr>
<td>RR, breaths/min</td>
<td>12–20</td>
<td>20</td>
<td>26</td>
<td>28</td>
<td>36</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>O₂ saturation, %</td>
<td>&gt;95 RA</td>
<td>95</td>
<td>88</td>
<td>87</td>
<td>90</td>
<td>87</td>
<td>92</td>
<td>93</td>
<td>87</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>80–100</td>
<td>NA</td>
<td>137</td>
<td>345</td>
<td>290</td>
<td>273</td>
<td>161</td>
<td>124</td>
<td>50</td>
</tr>
<tr>
<td>O₂ flow rate, l / method</td>
<td>–</td>
<td>RA</td>
<td>10 HM</td>
<td>40 HFNP</td>
<td>40 HFNP</td>
<td>40 HFNP</td>
<td>40 HFNP</td>
<td>3 NP</td>
<td>RA</td>
</tr>
<tr>
<td>F₁O₂</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.8</td>
<td>0.8</td>
<td>0.5</td>
<td>0.5</td>
<td>0.35</td>
<td>–</td>
</tr>
<tr>
<td>metHb, %</td>
<td>&lt;1.5</td>
<td>–</td>
<td>–</td>
<td>6.8</td>
<td>7.2</td>
<td>6.2</td>
<td>5.0</td>
<td>2.2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Time indicates hours following dose of rasburicase. Ref. range = Reference range; RR = respiratory rate; RA = room air; PaO₂ = arterial partial pressure oxygen; NA = not available; F₁O₂ = fraction inspired oxygen; HM = Hudson mask; HFNP = high-flow nasal prongs; metHb = methemoglobinemia.
The broad strategies that underpin the investigational therapy of methemoglobinemia include administering reductants, lowering concentrations of the offending oxidant and maximizing oxygen delivery. N-acetylcysteine and ascorbic acid have been proposed as alternative reductant therapies to methylene blue. Preclinical evidence for the role of ascorbic acid [21] has been validated by its successful use as primary therapy for methemoglobinemia [22, 23]. Unlike methylene blue, its antioxidant effect is independent of NADPH [17]. It is a safe and effective first-line treatment for methemoglobinemia in patients with G6PD deficiency [12]. Despite encouraging in vitro evidence [24], N-acetylcysteine had no significant effect on nitrate-induced methemoglobinemia in two small human controlled trials [25, 26]. The theoretical potential of cytochrome P450 (CYP450) inhibitors such as cimetidine is limited to methemoglobinemia induced by drugs such as dapsone and sulfasalazine, which are converted into their oxidant forms by CYP450 enzymes [27, 28]. There are no reports of CYP450 inhibitor therapy in acute methemoglobinemia [29]. They have no role in RIM because the oxidative action of rasburicase is CYP450 independent. Use of activated charcoal and exchange transfusion (ET) has been predominantly reported in the setting of acute oxidant poisoning. Their efficacy in methemoglobinemia management depends on the pharmacokinetics of the offending agent [28]. There are several accounts of ET used to rapidly and effectively treat severe methemoglobinemia that is refractory to antioxidant therapy [30–35]. One case of RIM has been successfully treated with ET after failure of methylene blue therapy in a patient later diagnosed with G6PD deficiency [8]. ET should be reserved for severe cases of methemoglobinemia refractory to reductant therapy. Hyperbaric oxygen therapy has been used to treat two cases of life-threatening isobutyl nitrite-induced methemoglobinemia (>70%) in conjunction with toluidine blue [36] and ET [32]. It may protect against hypoxic injury and independently lowers methemoglobinemia levels [37], possibly by competing with ingested oxidants for Hb [38]. It can be considered as an adjunctive therapy in life-threatening methemoglobinemia.

**Conclusion**

Rasburicase can cause severe oxidative hemolytic anemia and methemoglobinemia in patients with G6PD deficiency. Male patients from high prevalence ethnicities at high risk of TLS should be screened for G6PD deficiency.

**Table 2. Summary of reported cases**

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Sex</th>
<th>Ethnicity</th>
<th>Diagnosis</th>
<th>Rasburicase dose</th>
<th>Time to clinical onset</th>
<th>Methylene blue</th>
<th>Transfusion</th>
<th>Ascorbic acid</th>
<th>MetHb peak, %</th>
<th>Hb nadir, g/dl</th>
<th>G6PD deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pui [14]</td>
<td>12 M</td>
<td>African American</td>
<td>ALL</td>
<td>0.1 mg/kg</td>
<td>2 h</td>
<td>N</td>
<td>NA</td>
<td>Y</td>
<td>N</td>
<td>11</td>
<td>1.2</td>
<td>Y</td>
</tr>
<tr>
<td>Browning [10]</td>
<td>22.5 mg</td>
<td>3 h</td>
<td>N</td>
<td>NA</td>
<td>Y</td>
<td>5.3</td>
<td>10</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>Bosly [13]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kizer [11]</td>
<td>14 mg</td>
<td>&gt;8 h</td>
<td>NA</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>22</td>
<td>NA</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>Borinstein [9]</td>
<td>0.2 mg/kg</td>
<td>BD</td>
<td>NA</td>
<td>Y</td>
<td>N</td>
<td>3.3</td>
<td>17</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>Bhat [8]</td>
<td>10.5 mg</td>
<td>&gt;10 h</td>
<td>NA</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>10</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>Bauters [7]</td>
<td>6 M</td>
<td>Caucasian</td>
<td>ALL</td>
<td>0.1 mg/kg</td>
<td>NA</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>3.5</td>
</tr>
<tr>
<td>Sonbol [12]</td>
<td>52 M</td>
<td>African American</td>
<td>MM</td>
<td>6 mg</td>
<td>&gt;8 h</td>
<td>N</td>
<td>NA</td>
<td>Y</td>
<td>N</td>
<td>7.1</td>
<td>13</td>
<td>Y</td>
</tr>
<tr>
<td>Ng [4]</td>
<td>16 M</td>
<td>African American</td>
<td>BL</td>
<td>14 mg</td>
<td>2 h</td>
<td>NA</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>7.4</td>
<td>8</td>
<td>NA</td>
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<tr>
<td>Current case</td>
<td>46 M</td>
<td>Mauritian Chinese</td>
<td>CLL</td>
<td>6 mg</td>
<td>12 h</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>6.0</td>
<td>7</td>
<td>Y</td>
</tr>
</tbody>
</table>

metHb = Methemoglobinemia; M = male; ALL = acute lymphoblastic leukemia; NA = not available; N = no; Y = yes; CTCL = cutaneous T-cell lymphoma; DLBCL = diffuse large B-cell lymphoma; Bl = Burkitt lymphoma; BD = twice daily; MM = multiple myeloma.
ciency prior to administration of rasburicase. An asymptomatic decrease in oxygen saturation by oximetry and cyanosis are signs of methemoglobinemia; patients recover with conservative measures including supplemental oxygen and packed red cell transfusion. This paper highlights the need for clinicians to be familiar with this complication and its management, in particular the avoidance of methylene blue which may exacerbate oxidative hemolysis.

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Disclosure Statement

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