CASE REPORT

Methaemoglobinaemia in a G6PD-deficient child treated with rasburicase

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SUMMARY

A 5-year-old boy from the Congo, was admitted for hyperleucocytic acute lymphoblastic leukaemia, with a high risk of tumour lysis syndrome (TLS). He had splenomegaly and mediastinal lymphadenopathy on chest X-ray. We started steroids and hyperhydration with rasburicase to prevent TLS. Respiratory failure with mediastinal enlargement developed rapidly. A few hours after intensive care unit (ICU) admission, he was started on mechanical ventilation. Chemotherapy was started immediately given the strong suspicion of mediastinal compression. Low oxygen saturation with high partial arterial oxygen pressure persisted. Blood tests confirmed 20% methaemoglobinaemia and glucose-6-phosphate dehydrogenase (G6PD) deficiency. Allopurinol was substituted for rasburicase. The methaemoglobinaemia disappeared rapidly and he was discharged from the ICU after 72 h. In case of rasburicase use, a close clinical monitoring is mandatory, especially in populations where G6PD deficiency is highly prevalent. Methaemoglobinaemia must be suspected in case of low oxygen saturation when all other potential causes have been ruled out.

BACKGROUND

- ▶ Rasburicase is widely used in children at high risk for tumour lysis syndrome (TLS).
- ▶ Rasburicase can induce methaemoglobinaemia, particularly in case of glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- ▶ Patients from populations with high prevalence of G6PD are usually screened before rasburicase administration.
- ▶ When an emergent intravenous administration is needed, patients at high risk for TLS could be treated with rasburicase before the results of G6PD testing if their medical history is not consistent with G6PD deficiency.

CASE PRESENTATION

A 5-year-old boy from the Congo with an unremarkable medical history was admitted to the paediatric haematology department for acute lymphoblastic leukaemia (ALL). On admission, he was in good general condition with normal heart rate (95/min), blood pressure (110/72 mm Hg) and respiratory frequency (25/min). His height was 118 cm and his body weight was 26 kg, yielding a calculated body surface area of 0.94 m². Physical examination was normal except for splenomegaly and cervical lymphadenopathy. Blood counts showed 374 000/mm³ leucocytes with 340 000/mm³ lymphoblasts, haemoglobin 7 g/dL and platelets 58 000/mm³. He had no kidney failure or metabolic

abnormalities; thus, calcaemia, phosphataemia and kalaemia were normal for age. Serum uric acid (SUA) was 318 µmol/L. Chest X-ray showed mediastinal lymphadenopathy with slight mediastinal enlargement. There were no clinical signs of mediastinal compression.

We started emergent specific ALL treatment, given the high leucocyte count and potential mediastinal involvement seen on chest X-ray. Steroids were started according to FRALLE 2000T. TLS was prevented as recommended¹ using intravenous rasburicase injection (0.2 mg/kg) before the first intravenous steroid dose (60 mg/m²/day), combined with hyperhydration (3 L/m²/day).

A few hours after admission, respiratory failure developed with mediastinal enlargement on chest X-ray and high-oxygen requirement according to pulse oximetry, prompting admission to the paediatric intensive care unit (PICU). Despite the high risk of cardiorespiratory arrest during intubation related to the mediastinal enlargement, he was intubated and mechanically ventilated (MV) after failure of non-invasive ventilation started at admission. Mediastinal ALL progression was suspected and confirmed by further mediastinal enlargement on a new chest X-ray. Steroids were maintained at the same doses and chemotherapy (cyclophosphamide, vincristine and daunorubicin) started immediately given the strong suspicion of mediastinal compression. Since mediastinal progression was marked on serial chest X-rays and to avoid transporting this fragile, ventilated patient, we did not perform chest CT.

On day 2, low bedside pulse oximetry saturation persisted despite a high-inhaled oxygen fraction under MV. Arterial blood gas analysis performed twice showed high-partial arterial oxygen pressure (PaO₂=263 mm Hg). Haemodynamic status was normal, with steroid-induced sinus bradycardia (60 bpm) and normal cardiac function by echocardiography. Diuresis was normal under regular furosemide infusions (25 mg/day). The tumour syndrome decreased and blood counts showed 179 000/mm³ leucocytes with 139 000/mm³ lymphoblasts, 4.9 g/dL haemoglobin and 50 000 platelets/mm³. Other biological markers confirmed TLS with moderate kidney failure (creatinine 90 µmol/L), hyperkalaemia (5.7 mmol/L), hyperphosphataemia (2.86 mmol/L), hypocalcaemia (1.63 mmol/L), hyperuricaemia (198 µmol/L) and lactic dehydrogenase elevation (14 000 IU/L) with moderate biological disseminated intravenous coagulation (prothrombin, 28%; fibrin degradation products, 8 IU/mL; and factor V, 18%). He had no fever

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under broad-spectrum antibiotics started before PICU admission. A new chest X-ray showed a clear decrease in mediastinum size.

Blood tests showed 20% methaemoglobinaemia (measured by spectrophotometric assay on ABL radiometer 825 Blood Gas analyser) and G6PD deficiency <1 UI/gHb (measured by quantitative spectrophotometric assay).²

INVESTIGATIONS

- ▶ Chest X-ray showed no new abnormalities but indicated on day 2 a decrease in mediastinal enlargement.
- ▶ We did not perform chest CT, as his critical ventilatory status did not allow transport in the radiology department.
- ▶ Echocardiography was normal, particularly without any indirect signs of pulmonary hypertension.
- ▶ Arterial blood gas with 100% inhaled fraction of oxygen under MV showed pH=7.42; PaO₂=263 mm Hg; PCO₂=37 mm Hg; and HCO₃⁻=24.2 mmol/L.
- ▶ Blood analysis confirmed G6PD deficiency.
- ▶ Specific assay showed 20% methaemoglobinaemia.
- ▶ No genetic test was performed for G6PD mutation as the patient needed an emergent hematopoietic stem cell transplantation.

DIFFERENTIAL DIAGNOSIS

Before blood gas analysis:

- ▶ Pulmonary leucostasis: not present at diagnosis, no specific lung infiltrates on chest X-rays performed during respiratory failure.
- ▶ Pleural effusion: not found on medical examination, chest X-ray or chest ultrasound.
- ▶ Increased mediastinal compression: decrease in mediastinal enlargement on chest X-ray (day 2).
- ▶ Pulmonary infection: no evidence on clinical examination or on chest X-ray. The patient was under broad-spectrum antibiotics started before PICU admission.

After blood gas results:

- ▶ No other diagnosis than methaemoglobinaemia can explain the discrepancy between low oxygen pulse oximetry and high partial arterial oxygen pressure.

TREATMENT

After we suspected rasburicase-induced methaemoglobinaemia related to G6PD deficiency, we substituted allopurinol to rasburicase without changing any other specific treatments. A red blood cell transfusion was performed because of anaemia (4.9 g/dL) and high-oxygen requirements. All other components of the standard protocol were maintained. Chemotherapy and steroids were administered following FRALLE 2000T recommendations and the first therapeutic lumbar puncture, on day 5, was normal.

OUTCOME AND FOLLOW-UP

The patient achieved a complete remission but the high level of residual molecular disease prompted hematopoietic stem cell transplantation with a cord blood unit after nelarabine intensification. Aplasia was still present on day 30 post-transplantation.

DISCUSSION

TLS is a frequent and potentially life-threatening complication of initial therapy for haematological malignancies. Specific treatment is recommended before steroids or chemotherapy initiation in intermediate-risk and high-risk situations.¹ The urate oxidase rasburicase is widely used in children and adults at high risk for TLS³ and generally induces a large SUA decrease within

a few hours after the first dose. SUA is then monitored regularly to decide when to give an additional dose. Despite strong SUA-lowering efficacy, rasburicase has not been shown to improve long-term clinical outcomes compared to other widely used drugs such as allopurinol, which is less expensive.^{4, 5} In 2013, Cairo and an expert TLS consensus panel recommended rasburicase as a first-line treatment in patients at high risk for TLS and no 'history consistent with' G6PD deficiency.¹

Rasburicase converts SUA to allantoin, which is far more soluble in urine, by producing hydrogen peroxide.⁶ Since its first use in 2001,⁷ rasburicase has exhibited side effects ranging from a simple rash to severe anaphylaxis, haemolysis and methaemoglobinaemia. Antibody development may occur in fewer than 1% of exposed patients.⁶ Methaemoglobinaemia is a form of haemoglobin in which the iron of haem is oxidised to the ferric (Fe³⁺) form. Normally, oxidation is reversed by two pathways, the NADH-dependent pathway and the NADPH-independent pathway.⁸ NADPH generation by G6PD is essential to protect against oxidative stress.⁹ Finally, production of hydrogen peroxide as a by-product of uric acid oxidation to allantoin by rasburicase constitutes an oxidative stress that may trigger methaemoglobinaemia in susceptible patients with G6PD deficiency.

We are aware of 11 reported cases of rasburicase-induced methaemoglobinaemia.^{10–18} Among them, seven were associated with G6PD deficiency and three occurred in childhood. The first two cases were reported in 2008, in G6PD-deficient boys, a 4-year-old Cambodian boy treated for Burkitt's lymphoma¹⁰ and a 12-year-old Laotian boy with ALL.¹² The third paediatric case was reported in 2011 in a 6-year-old Caucasian non-G6PD-deficient boy treated for ALL.¹³ Recently, two cases have been reported in African-American female patients.¹⁸ Patients from ethnic groups in which G6PD deficiency is highly prevalent are routinely screened for G6PD deficiency before rasburicase administration.¹⁸ However, G6PD testing may be unavailable in emergency. Furthermore, when a red blood cell transfusion is given just before starting the specific treatment for the haematological malignancy, the G6PD status cannot be determined for several weeks. Thus, in some cases, rasburicase therapy must be started before the G6PD status is confirmed, resulting in a risk of complications such as methaemoglobinaemia and haemolysis.

We should perhaps consider that belonging to an ethnic group in which G6PD deficiency is common constitutes a 'consistent medical history' warranting routine use of allopurinol instead of rasburicase as the first-line SUA-lowering drug. However, methaemoglobinaemia, after rasburicase administration, has also been reported in patients without G6PD deficiency.¹⁴ We therefore advocate routine clinical monitoring for methaemoglobinaemia throughout rasburicase use whatever the context. In our patient, a rigorous analysis of potential causes of hypoxaemia helped us to suspect a methaemoglobinaemia.

In the previously reported cases of methaemoglobinaemia due to rasburicase, methylene blue, ascorbic acid, transfusion or abstention have been used.^{10–18} Intravenous methylene blue is ineffective in G6PD-deficient patients as it works via the NADPH-dependent pathway.¹⁹ Ascorbic acid is used in congenital methaemoglobinaemia,²⁰ as ascorbate effectively decreases plasma methaemoglobin,^{21, 22} although the rate of the reaction is too slow for use as monotherapy.²³ Ascorbic acid has been successfully used in a G6PD-deficient patient with rasburicase-induced methaemoglobinaemia.¹⁶ In our patient, we gave a red blood cell transfusion after the switch from rasburicase to allopurinol because of the very high methaemoglobin

level (20%) responsible for major desaturation combined with profound anaemia (haemoglobin, 4.9 g/dL) due to multiple causes (bone marrow invasion, blood spoliation, dilution and haemolysis).

It is difficult to definitively attest that the small haemolysis reported in this patient was only caused by rasburicase-administration because biological markers of haemolysis are difficult to interpret in case of TLS and haptoglobin was not measured during the stay in PICU. Several other potential mechanisms could explain this anaemia. The short delay between rasburicase-administration and anaemia, the depth of anaemia (7.2–4.3 g/dL) and the increase of bilirubine from 7 to 46 µmol/L in 24 h may be in favour of a haemolysis due to rasburicase-administration.

In patients at high risk for TLS and belonging to ethnic groups where G6PD deficiency is highly prevalent, we suggest using allopurinol as the first option,¹⁸ followed by rasburicase if testing confirms normal G6PD function. If rasburicase is used first, a close clinical monitoring is mandatory and methaemoglobinaemia should be suspected after all other potential causes of hypoxaemia have been ruled out.

Learning points

- ▶ Candidates to rasburicase therapy should be routinely screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency, particularly if they belong to ethnic groups where G6PD deficiency is common.
- ▶ In emergency, allopurinol should be used as the first option in patients at high risk for tumour lysis syndrome and belonging to ethnic groups where G6PD deficiency is highly prevalent, followed by rasburicase if testing confirms normal G6PD function.
- ▶ If rasburicase is administered, patients should be monitored closely, and methaemoglobinaemia should be suspected when low oxygen saturation contrasts with high-partial arterial oxygen pressure.

Contributors SLG and DA took care of the patient. TB and SD drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version submitted for publication.

Competing interests None.

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REFERENCES

- 1 Cairo MS, Coiffier B, Reiter A, *et al.* Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *Br J Haematol* 2010;149:578–86.
- 2 Minucci A, Giardina B, Zuppi C, *et al.* Glucose-6-phosphate dehydrogenase laboratory assay: how, when, and why? *IUBMB Life* 2009;61:27–34.
- 3 Darmon M, Vincent F, Camous L, *et al.* Tumour lysis syndrome and acute kidney injury in high-risk haematology patients in the rasburicase era. A prospective multicentre study from the Groupe de Recherche en Reanimation Respiratoire et Onco-Hematologique. *Br J Haematol* 2013;162:489–97.
- 4 Lopez-Olivo MA, Pratt G, Palla SL, *et al.* Rasburicase in tumor lysis syndrome of the adult: a systematic review and meta-analysis. *Am J Kidney Dis* 2013;62:481–92.
- 5 Cheuk DK, Chiang AK, Chan GC, *et al.* Urate oxidase for the prevention and treatment of tumor lysis syndrome in children with cancer. *Cochrane Database Syst Rev* 2010;(6):CD006945.
- 6 Ueng S. Rasburicase (Elitek): a novel agent for tumor lysis syndrome. *Proc (Bayl Univ Med Cent)* 2005;18:275–9.
- 7 Pui CH, Mahmoud HH, Wiley JM, *et al.* Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma. *J Clin Oncol* 2001;19:697–704.
- 8 Yubisui T, Takeshita M, Yoneyama Y. Reduction of methemoglobin through flavin at the physiological concentration by NADPH-flavin reductase of human erythrocytes. *J Biochem* 1980;87:1715–20.
- 9 Pandolfi PP, Sonati F, Rivi R, *et al.* Targeted disruption of the housekeeping gene encoding glucose 6-phosphate dehydrogenase (G6PD): G6PD is dispensable for pentose synthesis but essential for defense against oxidative stress. *EMBO J* 1995;14:5209–15.
- 10 Borinstein SC, Xu M, Hawkins DS. Methemoglobinemia and hemolytic anemia caused by rasburicase administration in a newly diagnosed child with Burkitt lymphoma/leukemia. *Pediatr Blood Cancer* 2008;50:189.
- 11 Cheah CY, Lew TE, Seymour JF, *et al.* Rasburicase causing severe oxidative hemolysis and methemoglobinemia in a patient with previously unrecognized glucose-6-phosphate dehydrogenase deficiency. *Acta Haematol* 2013;130:254–9.
- 12 Bhat P, Sisler I, Collier AB III. Exchange transfusion as treatment for rasburicase induced methemoglobinemia in a glucose-6-phosphate dehydrogenase deficient patient. *Pediatr Blood Cancer* 2008;51:568.
- 13 Bauters T, Mondelaers V, Robays H, *et al.* Methemoglobinemia and hemolytic anemia after rasburicase administration in a child with leukemia. *Int J Clin Pharm* 2011;33:58–60.
- 14 Kizer N, Martinez E, Powell M. Report of two cases of rasburicase-induced methemoglobinemia. *Leuk Lymphoma* 2006;47:2648–50.
- 15 Ng JS, Edwards EM, Egelund TA. Methemoglobinemia induced by rasburicase in a pediatric patient: a case report and literature review. *J Oncol Pharm Pract* 2012;18:425–31.
- 16 Sonbol MB, Yadav H, Vaidya R, *et al.* Methemoglobinemia and hemolysis in a patient with G6PD deficiency treated with rasburicase. *Am J Hematol* 2013;88:152–4.
- 17 Bucklin MH, Groth CM. Mortality following rasburicase-induced methemoglobinemia. *Ann Pharmacother* 2013;47:1353–8.
- 18 Roberts DA, Freed JA. Rasburicase-induced methemoglobinemia in two African–American female patients: an under-recognized and continued problem. *Eur J Haematol* Published Online First: 21 Apr 2014. doi:10.1111/ejh.12350.
- 19 Rosen PJ, Johnson C, McGehee WG, *et al.* Failure of methylene blue treatment in toxic methemoglobinemia. Association with glucose-6-phosphate dehydrogenase deficiency. *Ann Intern Med* 1971;75:83–6.
- 20 do Nascimento TS, Pereira RO, de Mello HL, *et al.* Methemoglobinemia: from diagnosis to treatment. *Rev Bras Anestesiol* 2008;58:651–64.
- 21 Gibson QH. The reduction of methaemoglobin by ascorbic acid. *Biochem J* 1943;37:615–18.
- 22 Dunne J, Caron A, Menu P, *et al.* Ascorbate removes key precursors to oxidative damage by cell-free haemoglobin in vitro and in vivo. *Biochem J* 2006;399:513–24.
- 23 Da-Silva SS, Sajan IS, Underwood JP III. Congenital methemoglobinemia: a rare cause of cyanosis in the newborn—a case report. *Pediatrics* 2003;112:e158–61.

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