Haemolytic crisis induced by rasburicase administration revealing G-6-PD deficiency

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We present a patient with Burkitt's lymphoma who suffered a severe haemolytic crisis after treatment with rasburicase. This case report underlines the high incidence of glucose-6-phosphate dehydrogenase deficiency in some ethnic groups and the importance of a detailed patient and family history before starting treatment, even in case of emergency. Glucose-6-phosphate dehydrogenase is an essential enzyme since it makes the synthesis of NADPH + H from NADP possible, which determines the reducing power (NADPH) of the cell. Every defect in this physiological process, notably glucose-6-phosphate dehydrogenase deficiency, may thus result simultaneously with the use of rasburicase in acute or chronic haemolysis according to the importance of the deficiency. Management is based on stopping the incriminated drug and on supportive therapy consisting of administering packed red blood cells if the anaemia is poorly tolerated.

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Introduction

Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency is a relatively frequent pathology in some ethnic groups and a correctly carried out medical history generally makes it possible to avoid prescribing medication which can cause haemolysis among these patients and therefore have detrimental clinical repercussions.

Case report

We report the case of a 27-year-old man of Moroccan origin hospitalised for epigastric pain and nausea.

The patient had no medical antecedent, didn't smoke or drink alcohol and had no other risk factors. He was under no medical therapy and had no known allergy.

At the time of his admission, the patient had been suffering from epigastralgia and nausea accompanied by intermittent pain in his right shoulder for two weeks. He reported pale stools and dark urine. His close relatives pointed out that he also had presented a transient jaundice. He was asthenic and anorexic, but had not lost weight. He had no fever, but did have night sweats. Treatment with omeprazole and domperidone had been ineffective.

Clinical examination only identified painful hepatomegaly near the right costal margin. There was no jaundice, splenomegaly or lymphadenopathy. Cardio-pulmonary and neurological examinations were unremarkable.

The routine admission laboratory tests showed a complete blood count within the normal range (Haemoglobin: 14g/dL; neutrophils: 4090/μL; lymphocytes: 2290/μL; platelets: 169000/μL), a mild inflammatory syndrome (CRP: 33mg/L; fibrinogen: 4,04g/L), liver cholestasis (total bilirubinemia: 13,3mg/L; alkaline phosphatases: 318UI/L; γGT: 344UI/L) and cytolysis (SGOT: 83UI/L; SGPT: 176UI/L; LDH: 990UI/L). There was no cardiac (creatine phosphokinase: 66UI/L; CK-MB: 2,2μg/L; CK-MB/creatine kinase: 3,4μg/100UI;

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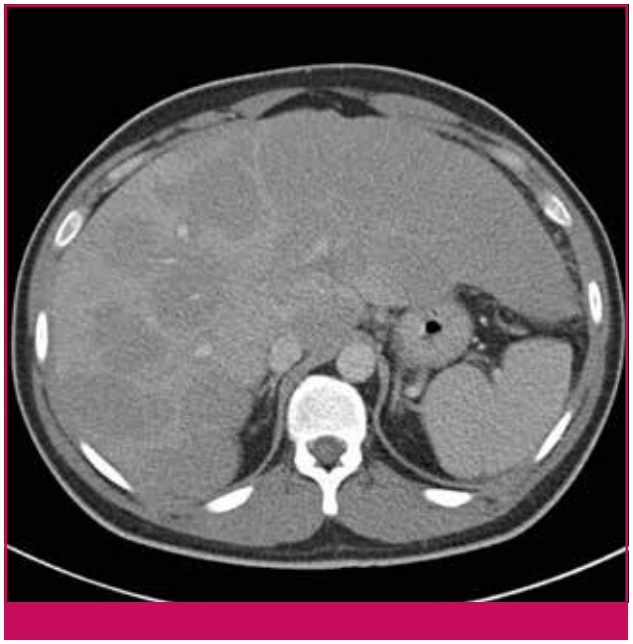

Figure 1. Abdominal CT scan of the patient at presentation showing multiple hepatic lesions.

troponin T < 0,01μg/L), kidney (urea: 0,32g/L; creatinine: 7mg/L; GFR: >60mL/min) or pancreatic (lipase: 26UI/L) impairment. There was no sign of denutrition (total proteins: 71g/L; albumin: 39g/L). Uric acid was slightly elevated (73mg/L).

Abdominal ultrasonography demonstrated multiple hepatic lesions suggestive of abscesses and associated with splenomegaly (12,5cm).

An abdominal CT scan (*Figure 1*) invalidated the presence of hepatic abscess and suggested a differential diagnosis between nodular steatosis, lymphoma, cholangiocarcinoma and hepatic lesions due to a systemic disease.

Infectious serologies ruled out HAV, HBV, HCV, HIV, brucella, bartonella, coxiella or taenia infections.

A liver biopsy provided the final diagnosis of Burkitt's lymphoma. The patient received hyperhydratation and allopurinol prophylaxis.

The patient was then transferred to our haematology department for further testing. Bone marrow biopsy revealed massive infiltration by the lymphoma and the PET-scan showed disseminated hepatic lesions associated with peritoneal involvement, a right renal lesion and an intensely hypermetabolic bone marrow. Neuromeningeal assessment disclosed no CNS involvement.

The patient was placed on corticotherapy. Allopurinol was replaced by rasburicase. Two days later, routine evaluation of oxygen disclosed venous oxygen saturation at 60%. Oxygen saturation in arterial blood was 80% and there was 15% methemoglobin. The haemoglobin dropped from 11.6g/dL the night before to 9,1g/dL in the morning and 6,5g/dL in the afternoon (*Figure 2*). The patient then developed intense hemoglobinuria associated with drowsiness and deep asthenia. More exhaustive family history revealed that two of his brothers suffered from G-6-PD deficiency and that the patient himself presented an episode of hematuria at the age of eighteen after ingesting beans. The diagnosis of G-6-PD deficiency was confirmed and the patient was transferred to the intensive care unit for two days where he evolved favourably after transfusion of packed cells without any use of vasoactive drugs. He started his chemotherapy after returning to our department and went into complete remission.

Table 1. List of drugs to avoid in G-6-PD deficiency.

Dapsone
Methylthionium chloride (methylene blue)
Nitrofurantoine
Phenazopyridine
Primaquine
Rasburicase
Tolonium chloride (toluidine blue)

Discussion

Pathophysiology

G-6-PD is an enzyme that catalyses the transformation of glucose-6-phosphate (G-6-P) into 6-phosphoglucono-δ-lactone within the pentose phosphate pathway (*Figure 3*).[1] This step is essential as it also makes the synthesis of NADPH + H^+ from $NADP^+$ possible, determining the reducing power (NADPH) of the cell.

NADPH enables erythrocytes to reduce the oxidised glutathione, glutathione-disulfide (GSSG) produced from reduced glutathione and H_2O_2, the latter coming from the release of O_2 superoxide. As the function of glutathione is to prevent damage to important cellular components caused by reactive oxygen species, G-6-PD plays an essential role in the regeneration of the reducing power of erythrocytes, preventing the attack on membrane lipids by oxidising agents and *in fine* impeding cell lysis. Every defect in this physiological process, especially G-6-PD deficiency, will result in acute or

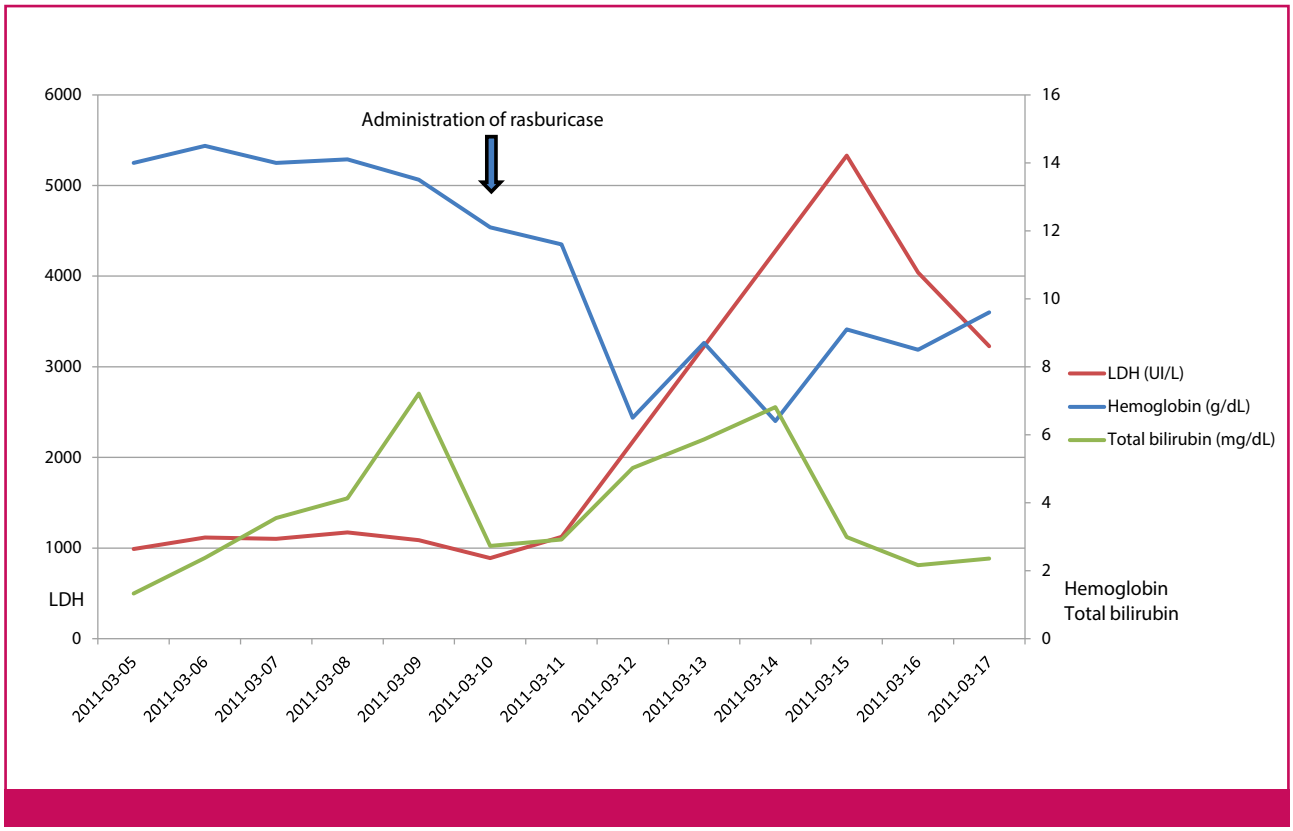

Figure 2. Evolution of biological parameters after administration of rasburicase.

chronic haemolysis according to the importance of the deficiency.

In our particular case, the administration of rasburicase, which is an oxidant agent, will cause a depletion of glutathione in the red blood cells and the oxidation of sulfhydryl-containing proteins of the membrane of the cell. The erythrocytes will become rigid and non deformable and then be destroyed by the reticuloendothelial macrophages.

The G-6-PD gene is localised on the long arm of chromosome X.[2] G-6-PD deficiency is consequently inherited as an X linked disease. All of the red cells in affected males are susceptible to haemolysis. The homozygous females are as severely affected as hemizygous males but concerning the heterozygous females, the severity will depend on the degree of X chromosome inactivation (lyonization) and the degree to which the abnormal G-6-PD variant is expressed. Each red blood cell expresses only one chromosome X. If it is the abnormal one, the cell will be susceptible to haemolysis.

The World Health Organisation classified the different forms of G-6-PD deficiency into five categories, according to enzyme activity.[3] The first category is the most serious form of G-6-PD deficiency and has chronic haemolytic anaemia. The second and third categories are characterised by intermittent episodes of acute haemolysis induced by infections, drugs and various other substances. The fourth category corresponds to normal enzyme activity, whereas the fifth category includes enzymes with supraphysiological activity.

Epidemiology

The number of people affected by G-6-PD deficiency is estimated at 400 million world wide, with the highest prevalence in Sub-Saharan Africa.[4] It is to be noted that some ethnic groups are more affected than others, particularly the Jewish Kurds among whom the prevalence can reach 60-70% in men.[5]

Clinical aspects

Most patients carrying G-6-PD deficiency are asymptomatic and the disease only manifests after eating beans, during an infection or after the administration of specific drugs, increasing oxidative stress in red blood cells. In these conditions, the oldest red blood cells undergo haemolysis because they contain less G-6-PD. This haemolysis classically appears between two to four days after administering the pro-oxidant agent with anaemia, jaundice, variable hemoglobinuria, asthenia and back pain.[6]

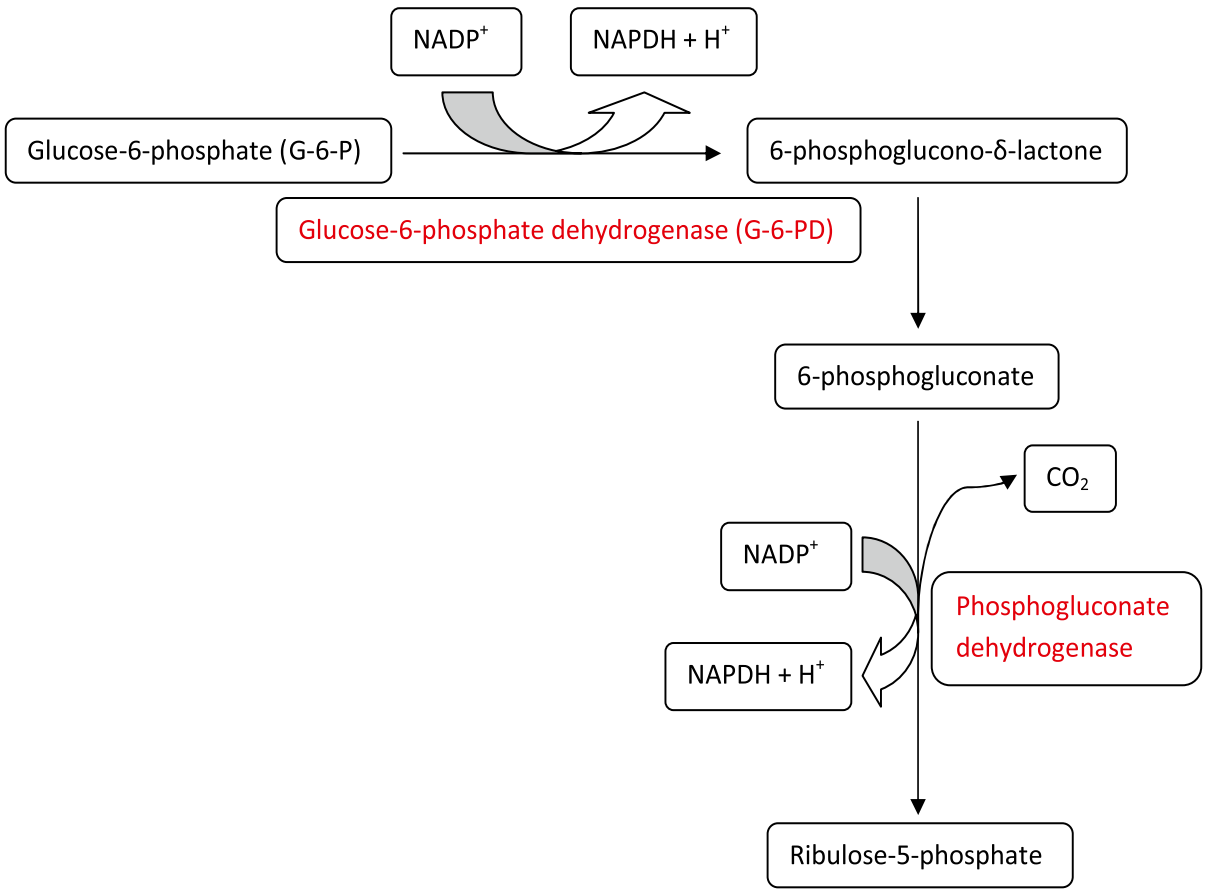

Figure 3. Regeneration of the reduced power of erythrocytes within the pentose phosphate pathway.

Treatment

Management is based on stopping the incriminated drug and on supportive therapy consisting of administering packed red blood cells if the anaemia is poorly tolerated. Prophylaxis is based on avoidance of drugs that may cause haemolysis in these patients. Some confusion exists as to the precise list of incriminated medicines and a recent literature review concluded that many medications had wrongly been accused following haemolysis developing in the context of an infection where patients received these drugs.[7] Authors concluded that only seven medicines in the pharmacopoeia have actually been proven noxious (*Table 1*).

The use of folic acid at 1mg/day can be beneficial to support erythropoiesis in patients affected by the more serious forms of the deficiency.

Modest results have been obtained in anecdotal cases after splenectomy or after administration of vitamin E.[8-10] Consequently, these treatments are generally not recommended.[11] Some improvement of the deficiency has been achieved by gene transfer using a viral vector in mouse stem cells.[12] However, this experimentation is still at the pre-clinical stage.

The acute haemolysis we report here was induced by rasburicase, a recombinant version of urate oxidase that catalyses the transformation of uric acid into allantoin. This medication has been used in the prophylaxis of hyperuricemia in haematological malignancies since 2001.[13] Though other cases have already been reported in the literature, this is a rare complication of this treatment.[14-21]

Conclusion

This case reminds us of the fact that G-6-PD deficiency is a relatively frequent pathology in some ethnic groups

Key messages for clinical practice

1. Glucose-6-phosphate dehydrogenase is an essential enzyme as it synthesises NADPH + H from NADP, which determines the reducing power (NADPH) of the cell. Every defect in this physiological process, notably glucose-6-phosphate dehydrogenase deficiency, will thus result in acute or chronic haemolysis according to the importance of the deficiency.
2. This defect is linked to chromosome X: a family history is an important aspect of the diagnosis.
3. Management is based on stopping the incriminated drug and on supportive therapy consisting of administering packed red blood cells if the anaemia is poorly tolerated.
4. List of drugs to avoid in glucose-6-phosphate dehydrogenase deficiency: dapsone, methylthioninium chloride (methylene blue), nitrofurantoine, phenazopyridine, primaquine, rasburicase, tolonium chloride (toluidine blue).

and that a correctly carried out medical history generally makes it possible to avoid prescribing medications that can cause serious haemolysis.

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