Ceftriaxone induced acute multi-organ failure syndrome in a Saudi boy with sickle cell disease

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ABSTRACT

تعد متلازمة فشل الأعضاء المتعدد (MOFS) من مضاعفات مرض الأنيميا المنجلية النادرة والمهددة للحياة، وهي نتيجة نوبات انسداد الأوعية الدموية الشديد. هذا تقرير عن حالة لطفل سعودي مصاب بفقر الدم المنجلي، أصيب بحالة متلازمة فشل الأعضاء المتعدد (MOFS) الحاد نتيجة إصابته بتحسس شديد لعقار السيفترايكسون، وقد تحسنت حالته بعد إجراء تغيير الدم وغسيل الكلى البريتوني.

Multi-organ failure syndrome (MOFS) is a rare life threatening complication of sickle cell disease. It is precipitated by severe vaso-occlusive episodes. We report a Saudi boy with sickle cell anemia, who developed acute MOFS following anaphylaxis to ceftriaxone administration. He had a dramatic recovery after red blood cell exchange transfusion and peritoneal dialysis.

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Acute multi-organ failure in sickle cell disease (SCD) was defined as organ failure of 2 or more of the following organs: lung, liver, or renal according to the Acute Physiological and Chronic Health Evaluation-II (APACHE-II) Criteria.[1] It is one of the catastrophic complications of severe sickle cell pain episodes. The criteria used to define dysfunction of 3 major organs were demonstrated by Hassell et al.[2] This syndrome usually occurs in patients with otherwise mild SCD. The onset of organ failure is usually associated with fever, rapid fall in hemoglobin (Hb) level, platelet count, non focal encephalopathy, and rhabdomyolysis.[2] We present a case of severe acute multi-organ failure induced by ceftriaxone administration in a child with sickle cell anemia who had a dramatic recovery after exchange transfusion and peritoneal dialysis to highlight this rare occurrence.

Case report. A 5-year-old Saudi boy, a known case of SCD since the age of 3 years, who used to have frequent episodes of painful vaso-occlusive crisis (VOC), and 2 episodes of acute chest syndrome was admitted at a local private hospital with fever, cough, and back pain, with a diagnosis of painful VOC and sepsis. He received one dose of intravenous (IV) ceftriaxone; where he immediately developed anaphylactic reaction in the form of skin rash, fever, chills, hypotensive, and shock, with a fall of Hb and platelets count. Four hours later he was referred to Madina Maternity and Children's Hospital with complaints of fever, cough, back pain, and seizures. His medical history included approximately 4 episodes of painful crisis per year, 2 episodes of acute chest syndrome, and one episode of febrile seizure at one year of age. There was no history of drugs allergies. His baseline Hb was 8 g/dl (normal range [NR]: 10.5-14 g/dl) leukocyte count 12.000/mm^3 (NR: 6,000-15,000), platelet count of 300.000/mm^3 (NR: 150,000-450,000), and the Hb electrophoresis findings were: HbS - 77%, HbF - 20%, and HbA_2 - 3%. On physical examination he was lethargic, but could be easily aroused, cyanotic with oxygen saturation of 83% on room air, temperature - 38.5^{0}C, pulse - 90/min, respiratory rate - 40/min, blood pressure - 132/82. He showed puffiness of eyes and pallor. The heart sounds were normal, except soft systolic murmurs, and the lung examination revealed bilateral course crepitation. The abdomen was mildly distended with a tender liver 3 cm below the costal margin. On admission, the white blood cell count was 25.000 mm^3, Hb - 10 g/dl, platelet

count - 137.000/mm^3, and 22% - reticulocytes. The serum sodium was 141 mmol/L, potassium - 5 mmol/L, chloride - 106 mmol/L. The blood urea nitrogen was 20 mmol/L, serum creatinine was 283 mmol/L, serum calcium was 1.4 mmol/L, phosphorus was 2.6 mmol/L, and the serum bilirubin was 21 µmol/L. The aspartate transaminase was 654 u/L, the alanine transaminase - 932 u/L, and the albumin - 21 g/L. The prothrombin time was 13.7 seconds, and the partial thromboplastin time was 39.8 seconds. The blood sugar was 5 mmol/L. The arterial blood PH was 7.2, with a partial pressure of oxygen of 95 mm Hg, partial pressure of carbon dioxide of 31 mm Hg, and bicarbonate of 11 mmol/L. The chest x-ray showed bilateral pneumonic infiltrate (**Figure 1**). The CT scan and MRI of the brain were normal. The electroencephalogram showed abnormal background activities, however, there was no epileptiform discharge. He was immediately admitted to the Pediatric Intensive Care unit with the diagnosis of multi-organ failure syndrome (MOFS), and treated immediately with red blood cell (RBC) exchange transfusion, broad-spectrum antibiotics, intravenous fluids, and conservative management of acute renal failure. The percentage of Hb S decreased from 55-16 after exchange transfusion. On the third day, he remained edematous, hypertensive, lethargic and oliguric with raising blood urea nitrogen and serum creatinine, so peritoneal dialysis was performed, and he was started on hydralazine to control his blood pressure. His acute chest syndrome and liver impairment improved dramatically after exchange transfusion, however, his renal failure improved gradually with peritoneal dialysis over 10 days. On day 13, he developed a generalized seizure, which was controlled with anti-epileptic drugs. The MRI and MRA were repeated and proved to be normal, with no evidence of infarction stroke. He stayed in the hospital for 30 days, where he remained afebrile and normotensive. Blood and urine culture showed no growth and serologies for hepatitis A, B, and C were negative. He was discharged with normal liver and renal function, and the pulmonary infiltrate resolved. However, he was maintained on anti-epileptic drugs by a neurologist, and was tapered gradually at the outpatient clinic. He was started on hydroxyurea and remained stable at outpatient follow up for approximately one year. He responded well to hydroxyurea with the absence of painful VOC and acute chest syndrome after discharge. His average laboratory investigations at outpatient follow up were: alanine aminotransferase - 42 mmol/L, aspartate aminotransferase - 35 mmol/L, total bilirubin - 8 µmol/L, with a blood urea nitrogen of 4.9 mmol/L, serum creatinine of 43.8 µmol/L, serum calcium of 2.3 mmol/L, and serum phosphorus of 1.4 mmol/L. The Hb was 9.9 g/dl, the leukocytes count - 9.000 mm^3, mean corpuscular volume - 111.5 FL, and platelet count of 162.000/mm^3, and the percentage of Hb F rose from 20-32%.

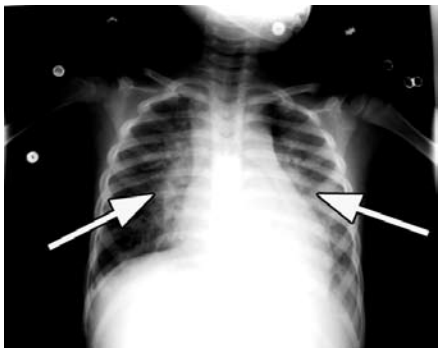

Figure 1 - Chest x-ray shows bilateral pulmonary infiltrates.

Discussion. Acute MOFS is one of the rare catastrophic life threatening complications of SCD. The obvious precipitating factor is the hypoxia produced by hypovolemic shock secondary to an anaphylactic reaction to ceftriaxone. Our patient had a severe type of SCD with frequent episodes of painful crisis and acute chest syndrome, with low baseline Hb in contrast to other reports,[2] where a benign clinical course with relatively high baseline Hb level was observed. In our patient, the ceftriaxone induced immune anaphylactic reaction resulted in this catastrophic complication. Ceftriaxone had been reported to cause fatal hemolysis in patients with SCD.[3] A similar case was reported in a patient with Hb SC disease following severe hemolysis induced by ceftriaxone.[4]

The onset of organ failure occurred simultaneously in our patient, supporting a possible mechanism of diffuse sickling during a severe vaso-occlusive pain episode with diffuse microvascular occlusion and tissue ischemia resulting in simultaneous dysfunction of multiple organs and development of rhabdomyolysis in most cases. Creatinine phosphokinase was not carried out in our patient to support the presence of rhabdomyolysis. The hypoxemia from shock contributed further to the sickling and vaso-occlusion with tissue ischemia. Infection was a possible contributing factor, although bacterial infection was not documented, however, the patient was not evaluated for viral or other atypical infection including *Chlamydia pneumoniae*, *legionella*, or *mycoplasma*.

Our patient developed anaphylaxis after first exposure to ceftriaxone despite skin testing before administration. This is consistent with other reports indicating that,

Table 1 - Previously reported cases with multi-organ failure syndrome in sickle cell disease.

Study	Hemoglobin type	No. of cases	Organs involved	No. of deaths
Hassell et al[2]	Hb SS 10 Hb SC 4	14	Lungs, kidneys, liver	1
Tedla et al[6]	Hb S – Thalassemia	1	Liver, kidneys	0
Boga et al[11]	Hb SS	7	Liver, kidneys	1
Geigel, Francis[12]	Hb SS	1	Kidneys, liver, central nervous system	0
Bolanos-Meade et al[13]	Hb SS	1	Kidney, central nervous system	1
Al-Hawsawi et al (Present study)	Hb SS	1	Lungs, liver, kidney	0

Hb SS - hemoglobin SS, Hb SC - hemoglobin SC, Hb S - hemoglobin S

hypersensitivity could not be demonstrated by skin testing.[5] The onset of acute organ failure was associated with a rapid fall in Hb level and platelet count, similar to a previous report by Hassel et al.[2]

The immediate manual RBC exchange transfusion was associated with rapid recovery of organ function and favorable outcome in our patient. A similar effect of exchange transfusion was previously reported.[2,6] RBC exchange is the recommended therapy for patients with SCD with MOFS. Patients with Hb levels more than 7g/dl should primarily be treated with manual or automated RBC exchange. If the Hb is less than 7g/dl and rapidly falling, a simple transfusion of packed RBCs to maintain a Hb of 10 g/dl may be adequate. The indications for RBC exchange transfusion include acute stroke, acute chest syndrome with severe hypoxia, acute MOFS, and priapism.[7] The goal of exchange transfusion is to decrease the concentration of Hb S to a value below 30%, and to lower the levels of erythrocytes expressed integrin α4/ß1 and surface glucoprotein IV (thrombospondin receptor, CD 36) to prevent interaction between RBCs, endothelial cells, and platelets.[8-10]

Plasma exchange transfusion after red cell exchange transfusion exerts a cumulative effect on red cell exchange and restores microcirculation to ischemic tissues, and is recommended in critically ill patients who have not benefited from red cells exchange transfusion in SCD patients with MOFS.[11,12] **Table 1** summarizes the number of subjects, types of SCD, pattern of organ involvement, and outcome of patients reported.[2,6,11-13]

In conclusion, although rare, the possibility of anaphylaxis occurring after the first dose of ceftriaxone resulting in MOFS in patients with SCD should be kept in mind. We recommend prompt recognition of this syndrome and immediate initiation of exchange transfusion to save the life of the patient.

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