Fever and a painful knee

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A 21-year-old man presented with a five-day history of fever, painful right knee, abdominal pain, dysuria, diarrhoea, vomiting and bone pains. On examination, he was found to be

moderately dehydrated, mildly icteric, febrile (38°C), with a blood pressure of 90/70 mmHg. There was tenderness over the right knee, with no evidence of effusion. Laboratory findings are presented in box 1. Sick cell crisis with possible urinary tract infection was diagnosed. He was given intravenous rehydration, analgesics, co-trimoxazole, folic acid and anti-diarrhoeals.

The urine output remained 400 ml for two days after admission. Over the next two days diarrhoea was controlled, urine output increased and hydration returned to normal although he remained febrile (38°C). He complained of generalised muscle pains, darkening of urine, and painful swelling of right leg. On examination there was swelling and tenderness over the right calf muscles but the right knee was normal.

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Laboratory investigations
<ul style="list-style-type: none">• haemoglobin 12 g/dl• haematocrit 38%• white blood cells $12 \times 10^9/l$• neutrophils 88%• reticulocytes 5%• blood urea nitrogen 7.5 mmol/l• serum creatinine 160 $\mu\text{mol/l}$• serum bilirubin 21 $\mu\text{mol/l}$• urine:<ul style="list-style-type: none">appearance: cloudyprotein 1 +15 white blood cells + four red blood cells/high power field• X-ray (chest, abdomen, right knee): normal• serum electrolytes, phosphorus, glucose, hepatic enzymes: normal

Box 1

Questions

- 1 What is the most likely diagnosis and what diagnostic tests should be performed?
- 2 Suggest possible causes.

Answers

QUESTION 1

The most likely diagnosis is non-traumatic rhabdomyolysis. The usual clinical presentation of non-traumatic rhabdomyolysis is that of diffuse muscle aches and passage of dark urine. The diagnostic tests performed included urine examination: dark colour (red), high specific gravity (1.025), haem pigment (positive), paucity of red blood cells (3/high power field) and measurement of serum creatine phosphokinase (15 626 U/l), and lactic dehydrogenase (571 U/l).

QUESTION 2

Non-traumatic rhabdomyolysis occurs in comatose patients after overdoses of narcotics, sedatives or alcohol,^{1,2} and occasionally during systemic bacterial, viral or fungal infections (box 2).^{2,3} Rhabdomyolysis in sickle cell trait is rare and usually occurs due to abnormal muscular exercise,⁴ and rarely due to infectious causes.^{3,5}

The patient's blood and urine cultures grew *Escherichia coli* sensitive to gentamycin, norfloxacin, ciprofloxacin, and netilmycin and resistant to chloramphenicol, co-trimoxazole, and ampicillin. Oral norfloxacin was started. Abdominal ultrasound examination showed grade I parenchymal changes in both the kidneys without obstruction. On day 4, he became afebrile; pain and swelling of the calf muscles decreased; creatine kinase levels decreased to 1016 U/l, and urine was negative for myoglobin. Biopsy of the right gastrocnemius muscle showed necrosis of isolated muscle fibres with some regenerative changes. On day 7, serum creatine kinase was 170 U/l, and calf muscle swelling completely disappeared. At the time of discharge, he was afebrile; blood and urine cultures were sterile; blood biochemical values had normalised and

the calf muscles had returned to their normal state. He is well two months after discharge.

Questions

- 3 How do systemic infections predispose to muscle damage?
- 4 Describe the role of *E coli*-induced urinary tract infection in sickle cell disease?

Answers

QUESTION 3

Severely ill patients with systemic infections are often hypoxic, acidotic, and dehydrated; these together with concomitant electrolyte disorders and hypophosphataemia can predispose to muscle damage and subsequent renal failure.²⁻⁶ It is possible that the microbial organism has a direct effect on skeletal muscle enzymes as suggested from animal studies. Although the ultimate mechanism of non-traumatic rhabdomyolysis due to infections is unclear, available evidence suggests either decreased availability or impaired capacity of muscle to utilise energy substrates.²

QUESTION 4

E coli-induced urinary tract infections may affect patients with sickle cell disease at any age.^{7,8} Seventy per cent of patients with *E coli* bacteraemia had concomitant urinary tract infection in children affected by sickle haemoglobinopathies.⁸ Microinfarctions,⁷ injury to renal medulla and papilla as well as glomerular scarring probably contribute to the increased susceptibility for urinary tract infections in sickle haemoglobinopathies.⁷

Discussion

Sherry⁴ hypothesised that infection, dehydration, acidosis and hypoxaemia, and other unknown factors induce sickling in muscle tissue capillaries, leading to muscle infarction and rhabdomyolysis in sickle cell trait. The patient was noted to have sickle cell trait, urinary tract infection, vaso-occlusive crisis and subsequent *E coli* bacteraemia. Associated with these events were rhabdomyolysis and mild renal unsufficiency. Prompt treatment of the infection resulted in resolution of rhabdomyolysis and renal failure. The patient did not have hypokalaemia, hypophosphataemia, or other electrolyte abnormalities known to induce rhabdomyolysis. *E coli* infection is prevalent in the general population, and increased incidence of urinary tract infections due to *E coli* has been observed in sickle haemoglobinopathies.^{7,8} There has been only one case report of rhabdomyolysis in sickle cell trait in association with *E coli* bacteraemia,⁶ although other cases may have gone undetected. It is suggested that rhabdomyolysis should be considered as a possible complication of *E coli* sepsis, more so in sickle haemoglobinopathies, so that prompt therapy can be instituted.

Causes of non-traumatic rhabdomyolysis	
• overdoses of narcotics, sedatives, and alcohol	
• abnormal muscular exercise	
• infectious causes:	
bacterial	– <i>Clostridia</i> , <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Streptococcus pneumoniae</i> , <i>Salmonella typhimurium</i> , <i>Salmonella enteritidis</i> , <i>Salmonella typhi</i> , <i>Salmonella bonariensis</i> , <i>Legionella pneumophila</i> , <i>Francisella tularensis</i> , <i>Listeria monocytogenes</i> , <i>Escherichia coli</i>
mycoplasma	– <i>Mycoplasma pneumoniae</i>
viral	– Influenza A, Herpes simplex, Epstein-Barr, Echo virus, Coxsackie, HIV-1, Cytomegalovirus
fungal	– <i>Aspergillus fumigatus</i>
protozoal	– <i>Plasmodium falciparum</i>

Box 2

Final diagnosis

E coli septicaemia in sickle cell trait complicated by rhabdomyolysis and mild renal insufficiency.

Keywords: rhabdomyolysis, septicaemia, sickle cell trait

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