CASE REPORT

Foot-strike haemolysis in an ultramarathon runner

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SUMMARY

This case report describes mild anaemia and intravascular haemolysis in an otherwise healthy 41-year-old ultramarathon runner. In long-distance endurance athletes, trace gastrointestinal bleeding and plasma volume expansion are recognised sources of mild anaemia, often found incidentally. However, repetitive forceful foot striking can lead to blood cell lysis in the feet, resulting in a mild macrocytic anaemia and intravascular haemolysis, as was demonstrated in the patient described herein. Mild anaemia in runners, often called 'runner's pseudoanaemia', is typically clinically insignificant and does not require intervention. However, an unexplained anaemia can cause undue worry for otherwise healthy patients and lead to costly further testing, providing an argument against routine testing with complete blood counts in healthy, asymptomatic patients.

BACKGROUND

The incidental finding of anaemia in a healthy ultramarathon runner was a cause for concern and prompted further testing. This case report aims to examine and explain possible aetiologies of asymptomatic anaemia in long-distance athletes and discuss the implications of both testing and diagnosis.

CASE PRESENTATION

A healthy 41-year-old male ultramarathon runner with a medical history significant only for Gilbert's syndrome presented for evaluation after a mild macrocytic anaemia was found incidentally on health screening. He was asymptomatic, yet these results were concerning to him. The laboratory results from this screening were notable for a haemoglobin of 13.5 g/dL (reference range 14.0–18.0 g/dL), haematocrit 40.3% (40.0%–52.0%) and mean corpuscular volume (MCV) of 98.5 fL (83.0–95.0 fL). History revealed that this gentleman trained on most days for ultramarathons during which he would run 50–100 miles at a time. He most often ran outdoors on pavement and wore running shoes which he replaced at the recommended intervals. Physical exam was normal and notably lacked any findings of hepatosplenomegaly.

INVESTIGATIONS

Further workup revealed a pattern of intravascular haemolysis, with laboratory evaluation demonstrating a haptoglobin of 15 mg/dL (30–200 mg/dL) and lactose dehydrogenase of 356 U/L (125–250 U/L). He also had an unconjugated

hyperbilirubinaemia with a bilirubin of 1.8 mg/dL (0.3–1.2 mg/dL) and a conjugated bilirubin of 0.6 mg/dL (0.0–0.5 mg/dL). The remaining elements of the complete blood count with differential, blood smear and reticulocyte count were all normal. Urinalysis was also within normal limits.

DIFFERENTIAL DIAGNOSIS

Serious causes of haemolytic anaemia to consider in any patient include disseminated intravascular coagulation, intrinsic haemoglobinopathies or membranopathies, immune-mediated haemolysis and drug-induced immune haemolysis. This patient had no risk factors for genetic or infectious causes of intravascular haemolysis, no signs of disseminated intravascular coagulation, took no medications and had no history of mechanical heart valve placement. Additionally, the mild nature of this patient's anaemia made these diagnoses less likely. Established explanations for mild anaemia specific to long-distance runners include bleeding from the gastrointestinal tract and plasma volume expansion.^{1–3} While the pathophysiology of gastrointestinal losses in long-distance runners is largely uncertain,^{1,2} a possible explanation is that deviation of blood away from the gastrointestinal tract during extended periods of exercise leads to bowel ischaemia.⁴ However, this chronic blood loss would likely result in a microcytic anaemia rather than the macrocytic anaemia demonstrated in the patient described here. Pseudoanaemia as a result of plasma volume expansion following extensive regular exercise has also been documented, believed to occur due to increased fluid intake and decreased renal excretion likely due to more sensitive action of aldosterone.³ However, a normal MCV is most often seen with dilutional pseudoanaemia.³ We did question whether this patient's history of Gilbert's syndrome could offer an explanation for his mild macrocytic, haemolytic anaemia. We reasoned that this was not likely the case as Gilbert's is a familial disorder that causes non-haemolytic jaundice⁵ and although haemolysis has been seen in patients with Gilbert's,⁶ this occurs in the absence of anaemia (unlike in our patient) and is not a result of a coinheritance but rather some physical insult or other stressor that leads to the clinical presentation of Gilbert's. Gilbert's itself is not known to cause a haemolytic pattern, and there have been no reported cases of unexplained haemolysis in Gilbert's syndrome; the haemolysis is always a result of something else that leads to Gilbert's becoming clinically evident in patients.⁵ It was also important to differentiate between extravascular and intravascular haemolysis. We were able to use iron studies, specifically

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serum haptoglobin, which binds free haemoglobin in the circulation. This complex is then rapidly metabolised and cleared by the liver, decreasing the serum haptoglobin level. In extravascular haemolysis, organs of the reticuloendothelial system such as the liver, spleen and bone marrow completely break down haemoglobin. For example, in the spleen, macrophages phagocytize red blood cells in their entirety, breaking haemoglobin down into its more basic constituents, which are released into circulation.⁷ Extravascular haemolysis does not result in haemoglobin being released directly into the circulation, and therefore does not affect serum haptoglobin levels. Intravascular haemolysis, on the other hand, leads to red blood cell lysis within the circulation (such as would occur within the blood vessels in the feet with repetitive forceful foot striking), introducing cellular contents such as haemoglobin directly into the circulation. Haemoglobin becomes bound by haptoglobin, and this haemoglobin–haptoglobin complex is metabolised by the liver, leading to a decrease in serum haptoglobin.⁸ A serum haptoglobin level below 25 mg/dL is associated with a positive predictive value of 87% for haemolysis when the level falls below this cut-off value. This patient had a serum haptoglobin level of 15 mg/dL, pointing towards an intravascular process.

OUTCOME AND FOLLOW-UP

We determined that this patient's presentation of asymptomatic anaemia was most likely attributable to intravascular haemolysis due to repetitive foot striking associated with his long-distance running. The biggest clinical consequence of this diagnosis for this patient was not reduced performance or long-term morbidity, rather it was undue worry that there was a more serious explanation. The medical expenses of the significant workup were likewise not insignificant. The explanation of foot-strike haemolysis was reassuring to the patient, and he continues to run long distances without the need for any interventions or treatment.

DISCUSSION

The primary mechanism underlying 'foot-strike' haemolysis is repetitive and forceful striking of the foot during long-distance running which leads to lysis of red blood cells in the small capillaries in the soles of the feet. The first case was described by Fleischer in 1881,⁹ who reported the passage of dark urine from a German soldier who demonstrated severe haemolytic anaemia after extended periods of marching on the field,¹⁰ hence the name 'march haemoglobinuria'. Since then, foot-strike haemolysis has been demonstrated to be the greatest contributor to anaemia in athletes, more so than other causes such as circulatory stress.¹⁰ (Haematuria is a sign of severe intravascular haemolysis, and as such was absent in the case of this patient with only mild anaemia and haemolysis¹⁰).

As a long-distance runner, this patient was concerned about how this anaemia might affect his performance. One small study of ultramarathon runners demonstrated that though there was a significant drop in serum haptoglobin following a 60km run, there were no statistically significant changes in haemoglobin, haematocrit or red blood cell count.¹¹ The drop in serum haptoglobin is a normal physiological response, allowing the body to salvage free haemoglobin released during haemolysis and reuse it to replenish intracellular haemoglobin.¹² Another study compared cyclists and runners and demonstrated no difference in plasma volume, total blood volume and red cell volume within a gender.¹³ This suggests that physiological mechanisms are adequate to prevent the development of clinically significant anaemia despite the destruction of red blood cells in runners.¹¹

Further, there is no evidence of clinical benefit to iron supplementation in long-distance runners with clinically insignificant anaemia.¹⁴

Learning points

- ▶ Foot-strike haemolysis occurs due to lysis of red blood cells in the small capillaries in the soles of the feet from repetitive foot striking, resulting in laboratory findings consistent with mild anaemia and intravascular haemolysis (macrocytic anaemia, low haptoglobin, elevated lactate dehydrogenase and in severe cases, haematuria).
- ▶ Other potential contributors to mild anaemia in long-distance runners include dilutional anaemia and minor gastrointestinal blood losses, which in the absence of concomitant foot-strike haemolysis would not be reflective of intravascular haemolysis on laboratory workup.
- ▶ These mild anaemias seen in long-distance runners are clinically insignificant and do not affect performance.^{9,11}
- ▶ There is no evidence of clinical benefit to iron supplementation in these individuals.¹²
- ▶ Routine blood counts in healthy, asymptomatic patients may do more harm than good, notably causing undue worry and unnecessary follow-up testing.

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Contributors AAF was the major contributor to writing the manuscript. All authors read and approved the final manuscript. KCD initially saw the patient in clinic, provided guidance for the content of the manuscript and provided substantial editing for the manuscript. MSW revised the manuscript critically for important intellectual content.

Competing interests None declared.

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