*Investigation vignette*

# Unexplained Anaemia after Massive Transfusion for Haematemesis

**CASE REPORT**

A 48 year old man with a history of significant ethanol abuse (approximately 16 litres of wine per week) presented following a 'collapse'. He had no previous history of alcohol related liver disease and no other significant co-morbidities. He was found at home by his family confused with limited history available other than a report of haematemesis prior to his collapse.

On presentation, he was hypovolaemic, hypothermic, confused and uncooperative. There was dried blood around the mouth. He had clear lung fields and a soft abdomen. There were no stigmata of chronic liver disease other than jaundice and scratch marks. Initial laboratory investigations revealed severe anaemia with leucocytosis, thrombocytopoenia, marked hypoglycaemia, hyperkalaemia, jaundice, coagulopathy, acidaemia and renal impairment (Table 1). Shortly after presentation he had a cardiac arrest from which he was successfully resuscitated and transferred to the intensive care unit (ICU) for further treatment. External rewarming and dextrose, 4 units of packed cells (PC), 2 units of fresh frozen plasma (FFP), omeprazole, octreotide and vitamin K (10 mg) were administered intravenously. An urgent upper gastrointestinal endoscopy was performed, which demonstrated a superficial duodenal ulcer with mild blood ooze. Adrenaline was injected with good effect. A computed tomogram of the abdomen did not reveal any significant intraabdominal or retroperitoneal fluid collection to explain the presumed blood loss. A provisional diagnosis of acute upper gastrointestinal haemorrrahage in the setting of alcoholic liver disease was made.

During the first 36 hours in ICU, the patient's haemoglobin (Hb) continued to fall despite further transfusions. After a total of 21 units of PC, 24 units of FFP, 4 pooled units of platelets and 6 units of cryoprecipitate the haematological parameters were as follows: Hb 78 g/L, Plt 47 x $10^9$/L, INR 2.0 and APTT 27.3. There was minimal blood detected following repeated aspiration of the nasogastric tube and rectal examination was negative for blood. He was clinically coagulopathic with visible bleeding from all vascular access points. A second endoscopic examination revealed additional bleeding points in the gastric fundus but the duodenal ulcer was not actively bleeding. A review of the peripheral blood film of the first blood sample taken revealed the answer.

| | | |
|---|---|---|
| Haemoglobin | 47 | (135 - 180 g/L) |
| White Cell Count | 21.6 | (4.0 - 11.0 x $10^9$/L) |
| Platelets | 127 | (150 - 400 x $10^9$/L) |
| Sodium | 132 | (134 - 146 mmol/L) |
| Potassium | 6.7 | (3.4 - 5.0 mmol/L) |
| Urea | 12.1 | (3.0 - 8.0 mmol/L) |
| Creatinine | 296 | (60 - 120 umol/L) |
| Glucose | <0.5 | (3.5 - 5.3 mmol/L) |
| Bilirubin | 287 | (<20 umol/L) |
| Albumin | 34 | (35 – 50 g/L) |
| AST | 423 | (< 43 U/L) |
| GGT | 67 | (< 60 U/L) |
| INR | 4.0 | (0.9 - 1.3) |
| APTT | 55.0 | (21.0 - 33.0 secs) |
| pH | 7.06 | (7.35 - 7.43) |
| Bicarbonate | 9 | (22 - 28 mmol/L) |
| Lactate | 20 | (<1.5 mmol/L) |
| Base Excess | -19 | (-3-3 mmol/L) |

**Figure 1**. Venous blood analysis

**Diagnosis: Acute spur cell haemolytic anaemia.**

The peripheral blood film was reviewed by the on call Haematologist who commented: "The red cells show mild anisocytosis and polychromasia, marked macrocytosis and many acanthocytes… The striking feature is the presence of numerous sphero-acanthocytes in keeping with the 'spur cell' haemolytic anaemia seen with severe liver failure." Further investigation confirmed a low haptoglobin level 0.26 g/L [0.40 - 2.5]; high lactic dehydrogenase 455 U/L [125 - 250] and a slightly elevated reticulocyte count 2.1% [0.2 - 2.0] consistent with haemolysis.

Spur cell haemolytic anaemia is an uncommon disease seen in about 5% of all patients with severe hepatocellular disease, and is usually associated with advanced alcoholic liver cirrhosis. It is characterised by bizarre shaped erythrocytes with highly variable spike-like projections around the cell membrane, giving rise to "spur cells" or acanthocytes (from the Greek "acantha", meaning a thorn) classically seen in peripheral blood films.[1] The irregular spikes are caused by an increase of cholesterol to phospholipid in the cell membrane, rendering the erythrocytes more rigid and less able to undergo deformation in the spleen. This reduction in cell fluidity and deformability results in their entrapment and destruction in the spleen.[2]

There are several haemolytic syndromes associated with chronic liver disease which include: transient haemolysis associated with fatty metamorphosis of the liver, chronic mild haemolysis associated with spherocytes and splenomegaly, stomacytosis and haemolysis associated with severe hypophosphataemia (echinocytes). Clinically, spur cell anaemia is more severe than those mentioned and the Hb usually falls to less than 10 g/L and can be as low as 5 g/L, as seen in this patient.

The disorder may be associated with severe jaundice, splenomegaly, rapid deterioration of liver function, coagulopathy and hepatic encephalopathy.[1] The mainstay of diagnosis is via the blood film, with other laboratory studies showing evidence of haemolytic anaemia. Transfusion is of limited benefit, as the transfused cells will themselves become acanthocytic.

Specific treatment is limited but successful treatment with flunarizine, pentoxifylline and cholestyramine has been reported.[3] Splenectomy has been advocated for some patients, however virtually all patients who present acutely with this disease are unfit for surgery due to portal hypertension and severe coagulopathy. Furthermore, spur cell anaemia has been reported to occur following splenectomy.[4] Thus, the condition has a very poor prognosis. More than 90% of the patients die within one year of diagnosis, usually due to gastrointestinal bleeding, hepatic encephalopathy or sepsis.[5] Spur cell anaemia resolves after liver transplantation and in selected patients should be considered the treatment of choice.[6-8]

Acute anaemia can be due to haemorrhagic blood loss or haemolysis. However, due to some very similar clinical and laboratory features, it can be difficult to distinguish between the two, as occurred in this case. The assessment of an anaemic patient, as with any other patients, must include a careful history and examination, followed by appropriate laboratory investigations (Table 2).[9]

Table 2. Laboratory Test in Anaemia[9]

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|---|
| Full blood count – Hb, haematocrit, reticulocyte count |
| Red Blood Cell indices – MCV, MCH, MCHC, RDW |
| White Cell Count – Cell differentials |
| Platelet count |
| Peripheral blood smear/cell morphology – cell size, Hb content, anisocytosis (cell size variability), poikilocytosis (cell shape variability), polychromasia |
| Iron studies |
| Haemolysis markers – LDH, bilirubin, haptoglobin |
| Bone marrow – aspirate and biopsy |

A summary of the key clinical and laboratory features of acute haemorrhagic blood loss and haemolytic anaemia can be found in table 3.

The initial diagnosis of upper gastrointestinal haemorrhage was made from the positive history of ethanol abuse, along with reports of haematemesis and signs of dried blood around the mouth. Although the duodenal ulcer was not actively bleeding at the time of initial endoscopy, it was possible that it could have been the source of blood loss.

As there were several potential reasons for jaundice and coagulopathy in this patient including hypothermia, cirrhosis and vitamin K deficiency, acute haemolytic anaemia was not initially considered to be the most likely. A limited history from the patient and his family did not reveal any classical symptoms of acute haemolytic anaemia. Nevertheless, once all the appropriate laboratory results were reviewed, the correct diagnosis was made. Unfortunately our patient suffered the fate often described in the literature for the majority of patients with spur cell haemolytic anaemia. He continued to require blood products, which did not correct the underlying anaemia and coagulopathy. He was also deemed unfit for surgical intervention. The decision to palliate him was reached in conjunction with his family. He died five days after presentation.

**Table 3. Features of Acute Blood Loss and Haemolytic Anaemia**[9]

| | *Haemorrhagic Blood Loss* | *Haemolytic Anaemia* |
|---|---|---|
| Clinical Features | • Site of bleed usually obvious unless internal bleeding<br>• Signs and symptoms depends on volume of blood loss | • Aching pain in back, abdomen and limbs<br>• Headaches, malaise, vomiting, fevers and chills<br>• Pallor, jaundice, tachycardia and fatigue |
| Full blood count | • Low Hb<br>• Normal haematocrit initially<br>• Increase reticulocyte counts day 3 - 5 (usually less than 15%) | • Low Hb (rate of fall > 1.0 g/dL/week)<br>• Low haematocrit<br>• Increase reticulocyte count |
| White cell count | • Neutrophilic leucocytosis over 2 to 5 hours (10 - 20 x $10^9$/L) | • Neutrophilic leucocytosis more pronounced in acute settings |
| Platelet count | • Increases within 1 hour | • Thrombocytosis also more pronounced in acute settings |
| Blood film | • Initially normal<br>• Marrow reticulocytes may appear on film within 6-12 hours | • Usually demonstrates specific morphological abnormalities such as spherocytes, elliptocytes, stomatocytes, acanthocytes etc |
| Other blood markers | • Bilirubin usually normal, unless bleeding into body cavity or tissue space | • Increase red cell destruction – elevated bilirubin and LDH; decreased haptoglobin<br>• Intravascular haemolysis – haemoglobinaemia, haemoglobinuria, urine haemosiderin |
| Bone Marrow | • Erythroid hyperplasia, usually only 2 - 3 times normal | • Erythroid hyperplasia, may be up to 7- 8 times normal |
| Other tests | • Endoscopy<br>• Radiological and nuclear imaging | • Direct antiglobulin test (Coombs)<br>• Osmotic fragility test<br>• Hb electrophoresis |

Spur cell haemolytic anaemia is a rare condition, uncommonly seen in patients with advanced hepato-cellular disease. Acute haemorrhagic blood loss, on the other hand, is seen frequently in emergency departments and hospital wards. Nevertheless, it is always important to keep haemolytic anaemia in mind as an alternate diagnosis in patients with acute anaemia.

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