

## CASE REPORT

# Bowel ischaemia: the clue in routine initial haematology testing

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## Abstract

This case report describes a patient with an abdominal sepsis and a CT scan showing portal vein thrombosis, splenic vein thrombosis and splenomegaly. Laparotomy findings include 1 metre of ischaemic small bowel, which is resected. Laboratory measurements show erythrocytosis, leukocytosis and thrombocytosis. This combination of findings is suspect for the diagnosis of one of the myeloproliferative disorders: essential thrombocythemia, primary myelofibrosis, chronic leukaemia, or polycythemia vera (PV). PV is a chronic myeloproliferative disorder characterised by erythrocytosis which results in hyperviscosity of the blood. The hyperviscosity may play a significant role in thrombosis. If left untreated, median survival is two years. Of the patients with PV, 95-99% have a point mutation of the JAK2 gene. The major treatment goal is the prevention of thrombosis by haematocrit control. In order to achieve this, phlebotomy in combination with a myelosuppressive agent, such as hydroxyurea, is recommended in patients with a high risk of thrombosis. It is crucial to make the diagnosis of PV, since treatment can prevent further thrombotic complications and increase survival.

## Introduction

Patients with bowel ischaemia are a challenging group since it is often difficult to make a timely diagnosis in this potentially life-threatening disease. The diagnosis is based on the combination of history and physical examination, complemented by laboratory results and radiological findings. Bowel ischaemia results from intestinal hypoperfusion. The four major causes of acute mesenteric ischaemia are superior mesenteric artery embolism, superior mesenteric artery thrombosis, mesenteric venous thrombosis and non-occlusive ischaemia. Non-occlusive ischaemia may result from a prolonged period of hypoperfusion, for example in a patient with a low cardiac output for a significant amount of time. The most common cause of acute bowel ischaemia is acute

insufficiency of mesenteric arterial blood flow. This results in high mortality rates above 60%.<sup>1</sup>

Often, a cause for bowel ischaemia can be determined, for example after aorto-iliac surgery or obstruction by atherosclerotic plaques. However, sometimes the cause of bowel ischaemia may be less evident. We describe a patient in which careful evaluation of the whole of Virchow's triad led to a conclusion.

## Case report

A 54-year-old woman was seen in the Emergency Department with a one-day history of increasing abdominal discomfort, vomiting and neurological deterioration. The abdominal pain had started after a barbecue. Before this episode, the patient had been healthy and in good condition. There had been no recent weight loss. Her medical history consisted of hypertension, cystectomy of an ovarian cyst in 1980, and in 2007 the patient received adjuvant chemotherapy followed by surgical removal of a mammary tumour (ductal carcinoma in situ). The patient did not use drugs, was a non-smoker and did not drink alcohol.

Upon admission the patient was somnolent with a Glasgow Coma Score of 11. The airway was free. Oxygen saturation was 90% with 5 litres of oxygen per minute. There were normal breath sounds bilaterally upon auscultation of the lungs. The patient was hypotensive (70/20 mmHg) with tachycardia (130 beats per minute). Furthermore, she was pale and sweaty. Her temperature was 37.6 °C.

Upon examination, the abdomen was diffusely painful to palpation. There were no signs of peritonitis.

Volume resuscitation was started with 500 ml of NaCl 0.9% resulting in an increase in blood pressure to 120/80 mmHg and the oxygen supply was increased to a Venturi mask with 60% oxygen.

Laboratory measurements showed leukocytosis (29.6 x 10<sup>9</sup>/l, N 4.0-10.0 10<sup>9</sup>/l), C-reactive protein of 308 mg/l (N

0.5 mg/l), thrombocytosis ( $686 \times 10^9/l$ , N 150-350 $10^9/l$ ) and a haemoglobin of 9.8 mmol/l (8.7-10.6 mmol/l). With 60% oxygen the arterial blood gas analysis showed pH 7.62 (N 7.35-7.45), partial pressure of carbon dioxide ( $P_{aCO_2}$ ) 3.6 kPa (N 4.6-6.0 kPa), partial pressure of oxygen ( $P_{aO_2}$ ) 17.0 kPa (N 9.5-13.5 kPa), arterial saturation ( $S_{aO_2}$ ) of 0.99 (N 0.96-1.00), bicarbonate ( $HCO_3^-$ ) of 28 mmol/l (N 21-25 mmol/l), base excess (BE) 7.10 mmol/l (N -3.00-3.00 mmol/l) and lactate 3.4 mmol/l (N 0.5-1.6 mmol/l). The venous blood gas showed a saturation ( $S_{aO_2}$ ) of 0.80 (N 0.40-0.70).

The differential diagnosis included sepsis with an intra-abdominal focus such as diverticulitis or pancreatitis. Gastroenteritis was considered since the symptoms had started following a barbecue. Bowel ischaemia and bowel perforation due to malignancy were also considered. Pancreatitis was unlikely since serum amylase and urine amylase were low.

The patient received tazobactam/piperacillin intravenously since it is a broad-spectrum penicillin with bactericidal activity against Gram positive, Gram negative and anaerobic bacteria. An abdominal CT scan was performed since this would most likely differentiate between a diagnosis which warrants a conservative approach, such as pancreatitis, or a diagnosis where an intervention such as surgery is necessary.

The neurologist was consulted to evaluate the patient's neurological status. The neurologist found a Glasgow Coma Score of 11, without signs of lateralisation. His conclusion was that the patient's somnolence was most likely due to encephalopathy in sepsis. His advice was to treat the sepsis first and that neurological re-evaluation could take place at a later stage.

The abdominal CT scan showed thickening of the small bowel and ascites in combination with portal vein thrombosis, splenic vein thrombosis and splenomegaly. There were no signs of perforation (figures 1 and 2). This combination of findings was

**Figure 1.** Contrast-enhanced CT slice showing the presence of splenomegaly



**Figure 2.** CT slice of the abdomen demonstrating thickening of the small bowel



suspect for bowel ischaemia. However, it was taken into account that the combination of portal vein thrombosis, splenic vein thrombosis and splenomegaly may be caused by a malignant tumour. Therefore, a laparotomy was performed. One metre of ischaemic small intestine was resected, 40 cm distal of the ligament of Treitz with stapling of both ends; 1.75 meters of small intestines were left in the abdomen. The pulsations of the ileocolic artery were present. Neither an anastomosis nor a stoma was performed at this phase due to the unstable condition of the patient during this operation and because a further extension of bowel ischaemia was anticipated. A second-look laparotomy was planned for the following day. The patient was transported to the intensive care unit (ICU) in a stable postoperative condition.

Upon admission to the ICU, the patient was sedated with propofol and intubated. Ventilator settings were  $FiO_2$  40%,  $peep$  6, 15 times a tidal volume of 500 ml. Oxygen saturation was 100%. She was haemodynamically dependent on high-dose norepinephrine. After several fluid challenges the norepinephrine dose could be lowered. The diuresis was approximately 30 ml per hour. Serum lactate decreased from 3.4 mmol/l to 1.3 mmol/l over the course of several hours. Antibiotic therapy was continued. The patient did not receive steroids.

The second-look laparotomy the following day showed vital intestines. Hence, an end-to-end anastomosis was performed. Postoperatively, anticoagulation was started using a full dose of low-molecular-weight heparin. One day after the second-look laparotomy, the patient could be weaned off the norepinephrine. Extubation took place the following day. After extubation the Glasgow Coma Score was maximal. After three days in the ICU the patient was discharged to the ward, where she made a slow, but uneventful recovery.

In search of an explanation for the ischaemia, the recent medical history was re-evaluated. Upon admission to our hospital the patient had mild pyrexia in association with leukocytosis ( $29.6 \times 10^9/l$ ), thrombocytosis ( $686 \times 10^9/l$ ), haemoglobin  $9.8 \text{ mmol/l}$  and an MCV of  $85.3 \text{ fl}$ . In retrospect, a year before the current admission, the patient had been diagnosed with a thrombocytosis ( $524 \times 10^9/l$ ) in combination with a haemoglobin of  $10.0 \text{ mmol/l}$  without leukocytosis (white cell count  $9.9 \times 10^9/l$ ). These abnormalities were found during a routine check-up after breast carcinoma. No definitive diagnosis was made at this time and no follow-up took place.

The combination of these abnormalities with portal vein thrombosis, splenic vein thrombosis associated with splenomegaly and an ischaemic bowel, led to the suspected diagnosis of polycythemia vera (PV). In the differential diagnosis, essential thrombocythemia, primary myelofibrosis and a chronic leukaemia were considered.

Microscopic evaluation of the resected bowel revealed ischaemic necrotic mucosa with transmural ischaemic changes with loss of mucosa and extensive vascular thrombosis. A bone marrow aspirate was analysed. This did not typically fit the diagnosis of PV, since the number of megakaryocytes was not increased. For a definitive diagnosis of PV, an analysis for JAK2 mutation was performed. A mutation of JAK2 V617F typical of PV was found.

Following the diagnosis of PV the patient was commenced on hydroxyurea and a coumarin (Acenocoumarol).

## Discussion

In this patient, the diagnosis of ischaemic bowel disease seemed likely when considering the clinical findings in combination with the CT scan showing extensive venous thrombosis. This diagnosis was confirmed by laparotomy.

Common risk factors for bowel ischaemia are advanced age, atherosclerosis, low cardiac output, cardiac arrhythmias such as atrial fibrillation, severe cardiac valvular disease, recent myocardial infarction and intra-abdominal malignancy.<sup>1</sup> However, none of these risk factors were present in this patient. Up to 75% of patients with mesenteric venous thrombosis have an inherited thrombotic disorder. A number of conditions are associated with acquired forms of hypercoagulability. The thrombocytosis, leukocytosis and erythrocytosis found in this patient had probably resulted in the thrombosis of the portal vein and the splenic vein. This combination of findings is suspect for the diagnosis of PV.

PV was first formally described by Vaquez in 1892.<sup>2</sup> PV is a chronic myeloproliferative disorder characterised by erythrocytosis which results in hyperviscosity of the blood. The risk of thrombotic events, such as cerebrovascular events, myocardial infarction, pulmonary emboli but also ischaemic bowel disease is increased in PV. The hyperviscosity may play a significant role in thrombosis.<sup>3,4</sup> Beside erythrocytosis,

leukocytosis and thrombocytosis may be present, but not all three lines have to be involved.<sup>5</sup> Population-based epidemiological studies have suggested an incidence trend for PV of approximately 1.9-2.6 per 100,000.<sup>6-8</sup> If left untreated, the median survival of patients with PV is less than two years.<sup>9</sup> Most patients die from thrombotic complications.

PV should be suspected in patients who have elevated haemoglobin or haematocrit levels, portal venous thrombosis and splenomegaly.<sup>10</sup> Besides these, there are other common signs and symptoms, as listed in *table 1*.<sup>10</sup> Secondary causes of overproduction of normal red blood cells are much more common than PV. There are diagnostic criteria for PV which were proposed by the Polycythemia Vera Study Group (PVSG) (*table 2*).<sup>11</sup>

An increased number of megakaryocytes in a hypercellular marrow found by bone marrow aspiration and biopsy has been considered to be one of the diagnostic hallmarks of PV.<sup>12</sup> Chromosome 9p24 houses the JAK2 gene, which has point mutation involving exon 12 or 14 in 95-99% in patients with PV.<sup>13</sup> In our case the patient had a mutation of JAK2 V617F. However, absence of JAK 2 V617F does not exclude a myeloproliferative neoplasm. Three cases of PV occurring after treatment of acute myeloid leukaemia have been described.<sup>14-16</sup> Whether the current case of PV should be considered to be secondary to chemotherapy for breast carcinoma is unclear.

**Table 1.** Signs and symptoms of polycythemia vera

More common	Less common
Elevated haematocrit level	Bruising/epistaxis
Elevated haemoglobin level	Erythromyalgia
Plethora	Haemorrhagic events
Pruritus after bathing (itching)	Hepatomegaly
Splenomegaly	Ischaemic digits
Weight loss	Transient neurological symptoms
Weakness	Atypical chest pain
Sweating	(hyperaemic and inflamed condition of the extremities)

**Table 2.** The Polycythemia Vera Study Group diagnostic criteria for polycythemia vera

The diagnosis of PV requires the presence of all three major criteria or the presence of the first two major criteria and any two minor criteria after excluding secondary erythrocytosis.	
Major criteria	Minor criteria
Increased red cell mass	Platelet count $> 400,000 \mu l^{-1}$
- Males $\geq 36 \text{ ml kg}^{-1}$	White blood cell count $> 12,000 \mu l^{-1}$ *
- Females $\geq 32 \text{ ml kg}^{-1}$	Leukocyte alkaline phosphate score $> 100^*$
Arterial oxygen saturation $\geq 92\%$	Serum vitamin B12 $> 900 \text{ pg ml}^{-1}$ or
Splenomegaly	Serum unbound B12 binding capacity $> 2200 \text{ pg ml}^{-1}$
	* In the absence of fever or infection

There are several therapeutic options for PV. The major goal is the prevention of thrombosis by haematocrit control. It is advised to maintain the haematocrit at less than 45% in men and less than 42% in women.<sup>17</sup> Phlebotomy in combination with a myelosuppressive agent, such as hydroxyurea, is recommended for patients with a high risk of thrombosis.<sup>18-19</sup> JAK2 inhibitors have been evaluated in clinical trials with significant positive outcomes such as reduction in splenomegaly.<sup>20</sup> The median survival of treated patients is more than ten years.<sup>21</sup>

In our patient, the diagnosis of PV could have been made a year earlier when routine haematology tests showed the presence of erythrocytosis and thrombocytosis. Most importantly, if treatment of PV had taken place, the current episode of bowel ischaemia would most likely have been prevented.

### Conclusion

PV, although rare, should be considered in all patients with bowel ischaemia when the cause is not evident. It is important to make the diagnosis, since treatment can prevent further thrombotic complications and increase survival. The diagnosis of PV should be suspected in any patient with erythrocytosis, leukocytosis or thrombocytosis.

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