Jejunal ischaemia – rare aetiologies and a surgical dilemma

F. Geranmayeh[1], S. Usman[2], R. Bhutiani[1]

(1) Department of surgery, Central Middlesex Hospital, North West London Hospitals NHS trust, London NW10 7NS, UK ; (2) Imperial College London, South Kensington Campus, London SW7 2AZ.

Abstract

Superior Mesenteric Artery thrombosis can lead to acute mesenteric ischaemia with devastating consequences. The main dilemma for the surgeon is the delay in diagnosis and a definitive treatment, as these patients may present with signs of peritonism but not frank peritonitis until the ischaemia results in infarction and or perforation. We report a detailed literature search and a unique case of jejunal ischaemia in the setting of undiagnosed Antiphospholipid Syndrome and Factor V Leiden heterozygosity where a delayed diagnosis resulted in an unnecessary prolongation of patient's morbidity. (Acta gastroenterol. belg., **2008**, 71, **263-266**).

Key words : antiphospholipid syndrome ; factor V Leiden heterozygosity ; jejunal ischaemia.

We report a unique case of jejunal ischaemia in the setting of undiagnosed Antiphospholipid Syndrome (APS) and Factor V Leiden (FVL) heterozygosity. This triad is rather unusual and to the best our knowledge has not been reported in the literature.

Case report

A 51-year-old gentleman presented to our accident and emergency department with one day history of sudden onset, severe colicky central abdominal pain radiating to both flanks. The pain had started after consumption of a homemade egg sandwich. It was associated with nausea, six episodes of vomiting mainly gastric contents, and one loose motion without any blood in the stools. He had no other symptoms.

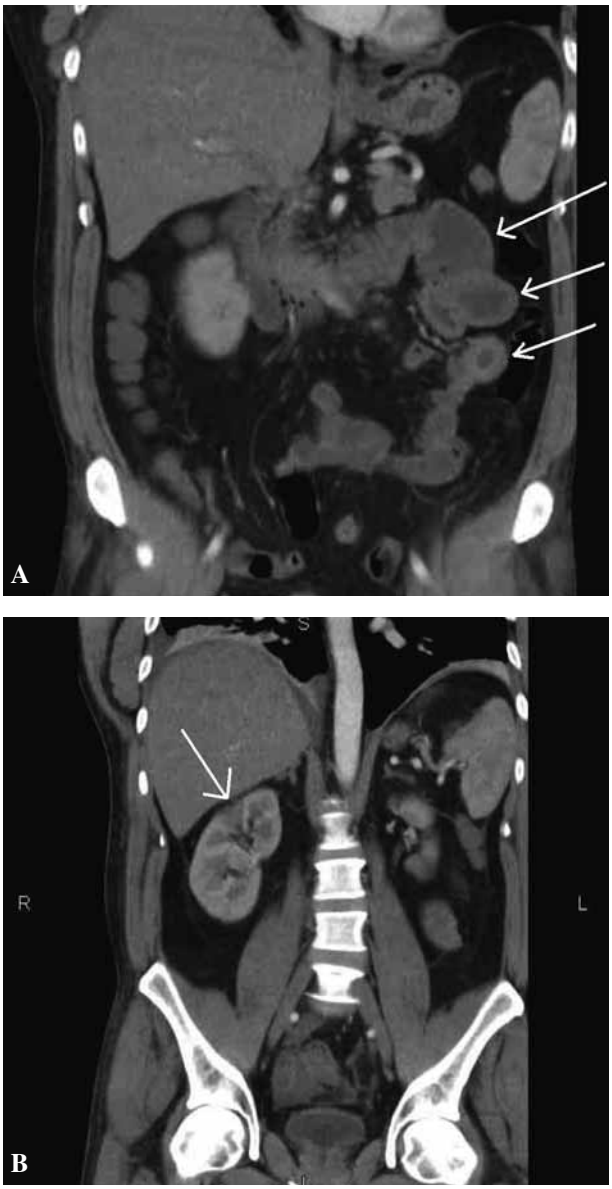
Ten years earlier, this gentleman had been diagnosed with low-grade microscopic colitis (moderate inflammatory cell infiltration of lamina propria with focal distortion of crypts but no active cryptitis). He had been taking Mesalazine and Imodium until five years previously when his symptoms resolved. He was intermittently taking non steroidal anti inflammatory drugs for osteoarthritis. His modifiable cardiovascular risk factors include smoking ten cigarettes a day for forty years and a weekly consumption of ten units of alcohol. He was not known to be diabetic, hypertensive or hyperlipidaemic on admission but was later shown to have a total cholesterol of 6.5 (the upper limit of normal), HDL 0.89 (0.9-1.5), LDL 4.63, HDLR 7.3 (0-5) and triglycerides 2.15 (0.3-1.8). He had a positive family history of cardiovascular disease as his brother died in his fifties due to a cerebral infarct.

Clinically, he had low-grade pyrexia (37.5 °C). His abdomen was generally tender all over with evidence of peritonism, but not peritonitis. No abnormal masses were felt and the bowel sounds were normal. Digital rectal examination did not reveal any blood or other abnormality. A full blood count showed elevated white cell count (18.4 * 10^9/L), neutrophil count (16.9 * 10^9/L), and normal haemoglobin (15.9 g/dl). C reactive protein was 13 mg/L and erythrocyte sedimentation rate was 13 mm/hr. Prothrombin time (PT) was 13.7 (11.5-16.0) and Activated Partial Thromboplastin Time (APTT) was 25.1 (26.0-38.0). A plain abdominal X-ray revealed no abnormities. A working diagnosis of gastroenteritis or exacerbation of Ulcerative Colitis was made. On the second day, the patient had an episode of fresh rectal bleeding followed by altered rectal bleed. An upper GI endoscopy and colonoscopy failed to localise the source of the bleeding. A Computerized Tomography (CT) scan of the abdomen with intravenous contrast demonstrated a circumferential thickening (up to 9 mm) over 30 cm length of jejunum (Fig. 1C). There was an ill-defined area of low intensity in the upper pole of the right kidney (Fig. 1B) and some cortical scarring in the left kidney. The scan also revealed a small filling defect in a segmental branch of the Superior Mesenteric Artery (SMA) suggestive of branch SMA thrombosis (Fig. 1C). ECG and echocardiogram were within normal limits and a thrombophillia screen was requested prior to treating the patient with daily 18,000 UI of Low Molecular Weight Heparin, Dalteparin Sodium (Fragmin) as advised by the haematologists. Warfarin loading dose was commenced six days later.

At no stage during his stay did the patient show clear signs of acute intestinal obstruction, acute peritonitis, or metabolic acidosis expected in patients with significant intestinal ischaemia, necessitating surgical intervention. The patient's symptoms resolved on conservative treatment and he was discharged home seven days later with an International Normalized Ratio (INR) of 2.9, and the

Correspondence to : Mr. Rajinder Bhutiani. Department of surgery, Central Middlesex Hospital, North West London Hospitals NHS trust, London NW10 7NS, UK.

Submission date : 11.02.2007
Revised version : 07.10.2007
Acceptance date : 03.02.2008



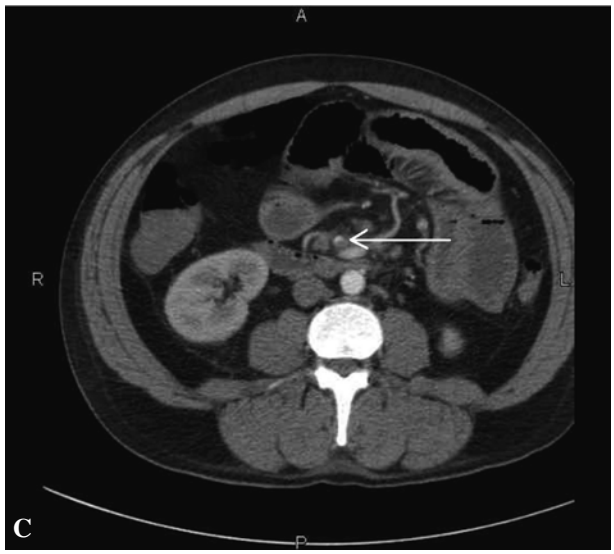


Fig. 1. — Abdominal CT with arterial contrast from the first admission with abdominal pain. White arrows show : A) Circumferential jejunal wall thickening. B) Decreased uptake of contrast in the upper pole of right kidney in keeping with infarction. C) Small filling defect in a segmental branch of SMA.

presumptive diagnosis of jejunal ischaemia secondary to segmental branch SMA thrombosis. He was advised to continue Warfarin with regular dose monitoring.

The patient returned to the hospital, ten days after discharge, with the same symptoms of colicky central abdominal pain and generalised abdominal tenderness without signs of overt peritonitis. Full blood count revealed a white cell and neutrophil count of 21.7 and 17.37 * 10^9/L respectively with a 3.1 g/dl haemoglobin drop (from 15.9 to 12.8) compared to the initial presentation. C reactive protein was 26 mg/L and INR was 2.1. A repeat CT scan of the abdomen showed a partial resolution of previous jejunal dilatation as well as a new 3cm splenic infarct. On day two of the second admission, the patient developed colicky pain in the left iliac fossa. An abdominal ultrasound scan showed no significant difference from the previous CT scan. He continued on full dose anticoagulation therapy. The thrombophillia screen requested at the time of first admission, revealed the presence of Lupus Inhibitor (LI), previously known as Lupus Anticoagulant, and anticardiolipin IgG antibodies (13.0), in keeping with the diagnosis of APS. Interestingly, the patient additionally exhibited FVL heterozygosity and a low level resistance 1.77 (normal range : ratio of 2-4) to Activated Protein C (APC), a natural anticoagulant. The value of non-normalised APC ratio in this patient was 0.80 (0.7-1.4) prior to warfarin therapy. Anti Nuclear, Anti Smooth Muscle, Anti Mitochondrial, and Anti Gastric Parietal Cell Antibodies together with Rheumatoid Factor were negative. The patient's symptoms resolved with conservative management and he was discharged with life long Warfarin therapy and a follow up appointment with the haematologist.

At eight months follow up repeat anticardiolipin IgG antibody was positive (19.7) with a negative anticardiolipin IgM (0.9) confirming the diagnosis of APS. APTT was 39.0 (26.0-38.0), and International Normalised Ratio was 3. He had cut down smoking to 2-3 cigarettes per day and consumed minimal alcohol. He had no recurrence of abdominal symptoms since his discharge, but he was being investigated by the vascular surgeons for left calf claudication on walking. He had palpable femoral artery, popliteal artery, or dorsalis pedis. There was no evidence of abdominal aortic aneurysm and he was managed conservatively.

Discussion

There are three categories of intestinal ischaemia namely acute mesenteric ischaemia (AMI), chronic mesenteric ischaemia (intestinal angina), and colonic

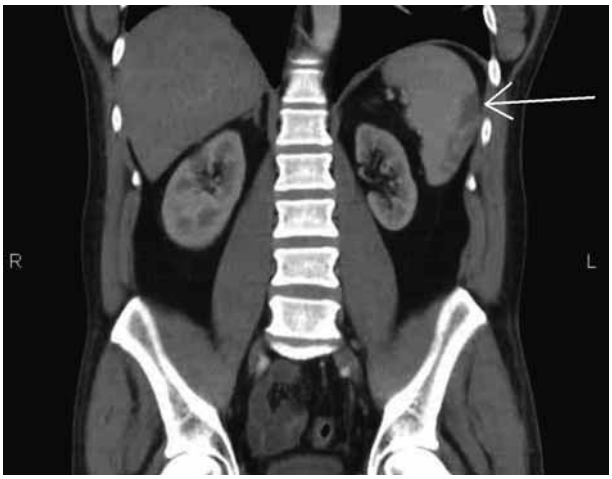


Fig. 2. — CT of abdomen and pelvis from the second admission with abdominal pain. A new wedge shaped low density area in the spleen, in keeping with infarction, can be seen (white arrow).

ischaemia (ischemic colitis). Jejunal infarctions due to SMA thrombosis per se are rare but potentially fatal despite surgical intervention. SMA thrombosis can lead to AMI with a mortality rate of 59% to 100% due to non-specific and delayed diagnosis (1,2). The variable mortality is due to the wide range of possible causes giving rise to this condition. The most common aetiologies of AMI in order of prevalence are embolic, thrombotic, venous thrombosis and non-occlusive disease (1).

There have been previous reports of jejunal ischaemia associated with a variety of different conditions (3-12), however in an extensive literature search we have not been able to find any reports of small bowel ischaemia associated with both FVL heterozygosity and APS. We are reporting the first of such an interesting case, which proved to be a surgical dilemma as these are not commonly seen in surgery and the diagnosis was not made until the thrombophilia screen results became available. A prolonged APTT on admission could have raised the suspicion of APS, but our patient's admission APTT was not prolonged.

It is important to acknowledge that the combination of cardiovascular risk factors including smoking, hypertriglyceridaemia, low HDL, and family history of cerebral infarct in our patient's brother, are likely to have contributed to his problems. The two thrombophilic abnormalities, FVL and APS present here, may have played a precipitating role in the development of jejunal ischaemia. In fact the latter two may have also been partly responsible for the family history of the patient.

APS and small intestinal ischaemia

APS, first described in 1983 (13), is a systemic autoimmune disorder characterized by arterial and/or venous thrombosis and recurrent foetal loss. It may be accompanied by thrombocytopenia, elevated titres of anticardiolipin antibody, and LI. The latter is an Ig G or Ig M, causing a delay in the partial thromboplastin time in vitro whilst associated with thrombosis in vivo.

The gastrointestinal manifestations of APS include ; Budd-Chiari syndrome, atypical gastro-intestinal ulcers and bleeding, oesophageal varices secondary to portal vein thrombosis, visceral infarctions, and pancreatitis (14). APS presenting with jejunal ischaemia or infarction is uncommon and is associated with a poor outcome. Usually patients have been reported to suffer from mesenteric angina (15,16), which if undiagnosed, may result in acute intestinal ischaemia or infarction (16-18).

It has been suggested that APS can result in arterial and/or venous occlusion and hence intestinal ischaemia via three major mechanisms ; thrombosis, vasculitis or proliferative vasculopathy. The latter often involves proximal stenosis of superior and inferior mesenteric arteries and coeliac axis with intimal and medial hyperplasia (16,19). It runs a more protracted course and shows development of collaterals in contrast to patients with thrombosis.

In the reported cases, the patient's acute presentation of intestinal ischaemia or infarction has either been on a background of known APS or Anti Cardiolipin antibodies, mesenteric angina, or previous thrombotic disease. Our patient became a surgical predicament, as he did not exhibit any of the above features, resulting in delay in reaching a final diagnosis.

FVL and small intestinal ischaemia

FVL mutation is one of the most common genetic causes for venous thrombosis with a prevalence as high as 5% in white Europeans and Americans. A point mutation in Factor V gives rise to FVL (20), which can lead to the phenomenon of resistance to the natural anticoagulant activity of APC, a serine protease which inactivates Factors Va and VIIIa.

Our patient had a low APC resistance of 1.77 (2.0-4.0). A high APC resistance favours FVL, although a reduced APC resistance does not exclude FVL.

Our patient had a heterozygote gene defect for Factor V. There have been case reports of small bowel infarction in a patient homozygous for FVL mutation (21). Additionally colonic ischaemia (22) and mesenteric venous thrombosis (23-25) have been noted in those who show heterozygosity for FVL, but we found no reports of jejunal ischaemia secondary to SMA thrombosis that was associated with Factor V mutation heterozygosity.

It is interesting to note that Willeke et al also reported a patient with FVL heterozygosity resulting in ischaemic colitis (IC) which was initially thought to be Crohn's disease based on macroscopic appearances (22). As our patient had histological evidence of microscopic colitis ten years earlier, we wonder if the original diagnosis of colitis was in fact an ischaemic episode. The clinical symptoms and signs of ischaemic colitis often overlap with those of inflammatory bowel disease. Misdiagnosis

and thus treatment of IC with corticosteroids can worsen IC, and result in silent colonic perforations (26).

Treatment of intestinal ischaemia depends on its causative pathology. However, anticoagulation or less frequently thrombolysis as well as surgical interventions (1) are the main line of treatment. The foremost dilemma for the surgeon is the delay in diagnosis and a definitive treatment, as these patients usually present with signs of peritonism but not frank peritonitis until infarction and or perforation set in. The optimum timing of surgery can sometimes be missed, resulting in high level of morbidity and mortality.

Conclusion

Jejunal ischaemia in association with APS and FVL results in high morbidity and mortality. Although an uncommon condition, it can be missed and may result in fatal outcome. We recommend an early thrombophillia screen in patients presenting with non-specific gastrointestinal symptoms and signs similar to our patient, in whom an initial definitive clinical diagnosis and management plan is difficult to formulate. A timely diagnosis and correct treatment is likely to save these patients from undergoing a major surgical operation and its consequences.

Acknowledgement

The authors would like to thank the patient and all the staff members who contributed to the management of this case. We would like to express our gratitude to Dr S.M.N. Abidi for his expert haematological advice.

References

1. LOOMER D.C., JOHNSON S.P., DIFFIN D.C., DE MAIORIBUS C.A. Superior mesenteric artery stent placement in a patient with acute mesenteric ischaemia. *JVIR*, 1999, **10** (1) : 29-32.
2. SAFIOLEAS M.C., MOULAKAKIS K.G., PAPAVASSILIOU V.G., KONTZOGLOU K., KOSTAKIS A. Acute mesenteric ischaemia, a highly lethal disease with a devastating outcome. *Vasa*, 2006, **35** (2) : 106-111.
3. KOBAYASHI T., ITO A., OKADA Y., KOJIMA N., FUJITA A., TERUYA M. Protein C deficiency as a cause of simultaneous acute thrombosis of the superior mesenteric vein and inferior vena cava with jejunal infarction. *Surgery*, 2005, **137** (4) : 482-483.
4. KASTIN D.A., ANDREWS J., SHAH R., GREEN D., FRYER J., BUCHMAN A. Multiple myeloma presenting as mesenteric venous thrombosis and intestinal infarction. *Dig Dis Sci*, 2005, **50** (3) : 561-564.
5. VEINOT J., LOGAN C., THOMAS M.J. Wegener's granulomatosis arteritis causing small bowel infarction. *Pathology*, 2003, **35** (3) : 268-269.
6. BROIDE E., SCAPA E., PEER A., WITZ E., ABRAMOWICH D., ESHCHAR J. Buerger's disease presenting as acute small bowel ischaemia. *Gastroenterology*, 1993, **104** (4) : 1192-1195.
7. KIRSHY D.M., GORDON D.H., NABIL A.A., ATWEH N.A. Abdominal computerized tomography in lupus mesenteric arteritis. *Comput. Med. Imaging Graph*, 1991, **15** (5) : 369-372.
8. VERBEKE J., PONETTE E., BAERT A.L. Ischaemic jejunitis caused by primary small bowel volvulus. *J. Belge Radiol.*, 1997, **80** (4) : 163-164.
9. SARDA A.K., MATHUR M., KAPUR M. Non-occlusive ischaemic enteritis. *Ann. R. Coll. Surg. Engl.*, 1990, **72** (1) : 18-21.
10. MELIS M., FICHERA A., FERGUSON M.K. Bowel necrosis associated with early jejunal tube feeding : a complication of postoperative enteral nutrition. *Arch. Surg.*, 2006, **141** (7) : 701-704.
11. DE SURAY N., PRANGER D., BRENARD R. Portal vein thrombosis as the first sign of a primary myeloproliferative disorder : diagnostic interest of the V617F JAK-2 mutation. A report of 2 cases. *Acta Gastroenterol. Belg.*, 2008, **71** : 39-41.
12. GRUSELLE P., OOGHE P., CAUCHIE P., VAN DER CRUYSSEN G. Severe thrombophilic diathesis starting with hepatic vein thrombosis (BUDD-CHIARI syndrome) in a family with a new Protein S gene mutation. *Acta Gastroenterol. Belg.*, 2006 Jan-Mar, **69** (1) : 20-4.
13. HUGHES G.R.V. Thrombosis, abortion, cerebral disease and lupus anticoagulant. *Br. Med. J.*, 1983, **287** : 1088-1089.
14. CAPPELL S.C., MIKHAIL N., GUJRAL N. Gastrointestinal haemorrhage and intestinal ischaemia associated with anticardiolipin antibodies. *Dig. Dis. Sci.*, 1994, **39** (6) : 1359-1364.
15. TINCANI A., BOZZETTI F., TARDANICO R., CERRI G., BALESTRIERI G., LAZZARI F., MORASSI L., BERGONZINI R., CATTANEO R., RADAELI E. Antiphospholipid antibodies and intestinal pathology. *J. Rehumatol.*, 1993, **20** : 2169-2170.
16. SANCHEZ-GUERRERO J., REYES E., ALARCON-SEGOVIA D. Primary antiphospholipid syndrome as a cause of intestinal infarction. *J. Rheumatol.*, 1992, **19** : 623-625.
17. ASHESON R.A., MACKWORTH-YOUNG C.G., HARRIS E.N., GHARAVI A.E., HUGHES G.R.V. Multiple venous and arterial thrombosis associated with lupus anticoagulant and antibodies to cardiolipin in the absence of SLE. *Rheumatol. Int.*, 1985, **5** : 91-93.
18. HAMILTON M.E. Superior mesenteric artery thrombosis associated with antiphospholipid Syndrome. *West J. Med.*, 1991, **155** : 174-176.
19. PATEL Y.I., ST JOHN A., MCHUGH N.J. Antiphospholipid syndrome with proliferative vasculopathy and bowel infarction. *Rheumatology*, 2000, **39** (1) : 108-110.
20. BERTINA R.M., KOELEMAN B.P., KOSTER T., ROSENDAAL F.R., DIRVEN R.J., DE RONDE H., VAN DER VELDEN P.A., REITSMA P.H. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature*, 1994, **369** : 64-67.
21. CHRYSSOSTALIS A., HAGEGE H., ROSA-HEZODE I., CATTAN P., DE LACROIX-SZMANIA I., CABANIS P., BAYANI N., ABD ALSAMAD I., CHOUSTERMAN M. Chronic abdominal pain due to bowel ischaemia in a patient with Leiden factor V mutation. *Gastroenterol. Clin. Biol.*, 2004, **28** (3) : 301-303.
22. WILLEKE P., DOMAGK D., FLOER M., BRUWER M., KREUTER M., GAUBITZ M., DOMSCHKE W., KUCHARZIK T. Ischaemic colitis mimicking inflammatory bowel disease in a young adult receiving oral anticoagulation. *Scand. J. Gastroenterol.*, 2005, **40** (7) : 878-880.
23. SHAH S.R., GUPTA A.D., SHARMA A., JOSHI A., DESAI D., ABRAHAM P. Acute superior mesenteric vein thrombosis associated with factor V 'Leiden' gene mutation. *J. Assoc. Physicians India*, 2003, **51** : 611-613.
24. AL-JUBURI A., SCOTT M.A., SHAH H.R., RAUFMAN J.P. Heterozygosity for factor V Leiden and G20210A prothrombin genotypes in a patient with mesenteric vein thrombosis. *Dig. Dis. Sci.*, 2002, **47** (3) : 601-606.
25. BERGENFELDT M., SVENSSON P.J., BORGSTORM A. Mesenteric vein thrombosis due to factor V Leiden gene mutation. *British Journal of Surgery*, 1999, **86** : 1059-1062.
26. ALAPATI S.V., MIHAS A.A. When to suspect ischemic colitis. Why is this condition so often missed or misdiagnosed ? *Postgrad. Med.*, 1999, **105** : 177-187.