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Case Report

Mesenteric venous thrombosis in Protein S deficiency: case report and literature review

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CASE REPORT

A 31-year-old woman presented with a two day history of sudden onset severe constant epigastric pain associated with nausea and coffee-grounds vomiting. She had a long history of heartburn treated by her general practitioner with intermittent omeprazole. There was no history of melaena, peptic ulcer or gallstone disease. However she had had pulmonary embolism post-partum six years before and had been on warfarin for six months. Apart from intermittent omeprazole, she was not on any regular medication or oral contraceptive prior to admission. On physical examination she was tender in the epigastric and peri-umbilical regions with some guarding. The remainder of the examination was unremarkable. Haematological and biochemical investigations were normal except for an increased WCC of 28 x 10^9/L and ESR of 50 mm/hr. Ultrasound scan of abdomen was unremarkable. Barium meal and gastroscopy confirmed the presence of a large hiatus hernia with linear reflux oesophagitis but no peptic ulcer. She was re-commenced on omeprazole regularly which settled her symptoms quickly and she was discharged. She was readmitted two days later as an emergency with relapse of her symptoms. Repeat examination showed a mildly distended abdomen with guarding and rebound tenderness. Plain abdominal radiographs showed mildly dilated loops of small bowel. A laparotomy was performed and a long segment of small bowel infarction involving the jejunum was found. There was thrombus in the superior mesenteric vein but the mesenteric arteries were patent. The infarcted small bowel was resected to healthy margins and intestinal continuity restored with end-to-end anastomosis. Her post-operative recovery was complicated by adult respiratory distress syndrome requiring prolonged endotracheal intubation and tracheostomy in the intensive care unit. Thrombophilic screens carried out in the first and second postoperative week before commencement of warfarin therapy

TABLE

Classification of the causes of mesenteric venous thrombosis

Primary (30 per cent)
Antithrombin III deficiency
Protein C deficiency
Protein S deficiency
Platelet disorders
Myeloproliferative disorders
Splenectomy
Polycythaemia rubra vera
Pregnancy
Puerperium
Contraceptive pills
Secondary (60 per cent)
Intra-abdominal sepsis
Pancreatitis
Inflammatory intestinal disease
Trauma
Portal hypertension
Sclerotherapy of varices
Malignancy
Idiopathic (10 per cent)

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confirmed protein S deficiency (free protein S level measured by ELISA was less than 30%) with normal levels of antithrombin III and protein C. She was started on long-term therapy with warfarin and she made a gradual recovery. She remains well at six-month review. Screening of her first-degree relatives shows no evidence of familial thrombophilia. However her father had died in his forties of vascular disease and had most probably deep venous thrombosis, as he had suffered from venous ulceration of the lower limbs.

DISCUSSION

Mesenteric venous thrombosis (MVT) is an uncommon but distinct clinical entity. More cases have been cited in the literature over the last two decades. It is estimated to account for up to 20% of all cases of intestinal infarction. Its incidence, or at least its recognition, appears to be increasing.[1] Acute, subacute and chronic forms of MVT are currently recognised.[2] These forms may differ in the symptoms they produce, the methods by which they are diagnosed, and the treatment they may require. Acute MVT has a more insidious and unpredictable course than other forms of visceral ischaemic syndromes. It tends to affect younger patients, and the mortality rate is as high as that of the arterial counterpart. The most frequent presenting symptoms are non-specific abdominal pain, anorexia and diarrhoea. These symptoms are present for longer than 48 hours in 75% of the cases in some series.[3] Often the diagnosis was delayed and over 60% of these cases underwent a surgical procedure. Despite the increased awareness of the condition, the mortality remains high (more than 30%) and has not improved in the last 20 years. The long term survival rate is significantly worse in the acute form of MVT than that of the chronic disease and there is also a higher recurrence rate. The prognosis is directly related to the degree of intestinal infarction and the underlying cause.

Bradbury *et al* classified MVT into primary, secondary and idiopathic according to the cause of the disease (Table[4]). Primary MVTs are due to inherited or acquired thrombophilia such as protein S deficiency, as in this case report. Previous history of thromboembolism or family history is usually present and it is important to obtain a detailed past medical and family history. With increasing sophistication of haematological tests, more idiopathic cases will be identified as primary MVT. Secondary MVTs are usually due to intra-abdominal pathology such as sepsis or inflammatory process. Despite the various possible causes, MVT remains as a rare occurrence.

The diagnosis of MVT remains a challenge to the clinicians. Symptoms and signs are usually non-specific and the hallmark is pain that is out of proportion to the physical findings. Despite the advance of imaging techniques, pre-operative diagnosis is made only in 10-15% of cases.[4] A high index of suspicion is paramount in respect of diagnosis and improved clinical outcome. Ultrasonography and duplex scan may provide information about the blood vessels concerned. Contrast enhanced computed tomography (CT) has proved to be useful in demonstrating venous thrombus, ascites, intestinal wall thickening, intestinal dilatation and pneumatosis intestinalis.[5] It has established the diagnosis of MVT in up to 90% of cases in some series.[6] Mesenteric angiography is probably still the investigation of choice but false negative studies are frequent when thrombosis involves only segmental veins. With improvement of imaging techniques, contrast enhanced CT may soon replace angiography as the first-line investigation. The role of MRI in MVT has not been fully explored but its availability and expense will probably limit its use.

There is no defined standard for treatment of MVT, and various modalities have been described.[7,8] Treatment usually involves a combination of surgical procedures, thrombolysis and anticoagulation. In the presence of an acute abdomen, laparotomy is usually necessary to exclude or to excise necrotic bowel. Second-look operation may be required if viability of bowel is questionable. Successful conservative management with efficacious anticoagulant therapy and careful follow-up imaging has also been reported.[6] Whatever type of treatment is used, prompt diagnosis and institution of treatment are crucial to the improved outcome. The possibility of an underlying hypercoagulable state should always be searched for as MVT could be the first manifestation of the disease. If this is the case, long term anticoagulation should be used and the first- degree relatives should be screened as they are at a high risk of developing thromboembolism.

Protein S (PS), a vitamin-K dependent glycoprotein, is a protein C cofactor which is

necessary for the full anticoagulant effect of activated protein C. In plasma, PS is partly free and partly bound to C4b- binding protein. Only free PS functions as a cofactor for activated PC in the inactivation of Factor Va and Factor VIIIa. Many laboratories prefer to express free PS antigen levels as a percentage of 'normal' free PS levels. This practice is acceptable but each laboratory must establish its own normal ranges for total and free PS antigen. In our laboratory, the normal range for free PS antigen is 7-140% (the free PS antigen level was 27% in this reported case).

Protein S deficiency is an autosomal-dominant inherited disorder of coagulation, either homozygous (purpura fulminans at neonatal age) or heterozygous. However acquired deficiencies of PS have been described recently in several conditions such as malignancy, pregnancy, nephrotic syndrome and acute phase reactions. The true prevalence of inherited PS deficiency is unknown as not all the individuals with the inherited PS deficiency will necessarily develop thrombosis. Some studies have indicated a frequency of 2-5% in patients with deep venous thrombosis or pulmonary embolism. This is as prevalent as protein C deficiency (5-8%) but less common than antithrombin III deficiency (12-15%).[9] Patients with phenotypic PS deficiency have a 50% chance of developing recurrent thrombosis before age 45.[10] However MVT is a rare manifestation of this inherited disorder. Frequently these thrombotic events are accompanied by some precipitating factors such as intake of oestrogen-containing oral contraceptives and pregnancy. In the present case however, no such triggering factors were identified.

The importance of warfarin therapy in hereditary thrombophilia cannot be over-emphasised. However the duration of therapy remains controversial. In patients with recurrent thromboembolism, particularly affecting the cerebral or splanchnic circulation (as in this case), long-term anticoagulant therapy is essential. In asymptomatic patients or those with only a single episode of thromboembolism, prophylactic treatment to cover high risk events such as pregnancy or surgery may be adequate.

With the history of recurrent thromboembolism in a young patient, hereditary and acquired thrombophilia must be considered and the importance of early implementation of anticoagulant therapy should not be underestimated.

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