

Successful Management of Acute Mesenteric Ischaemia in a Pregnant Woman with Protein S Deficiency

Dear Editor,

Protein S is an endogenous anticoagulant that functions as a cofactor to activated protein C in the cleavage of clotting factors Va and VIIIa. Protein S deficiency, both hereditary and acquired forms, is a rare clinical condition, which usually manifests clinically as venous thromboembolism. Adverse pregnancy outcomes associated with protein S deficiency include recurrent fetal loss, intra-uterine growth retardation (IUGR) and intra-uterine death.¹ Acute mesenteric venous thrombosis is one of the rare manifestations of isolated protein S deficiency. We report a pregnant patient with hereditary protein S deficiency who presented with an acute abdomen, later diagnosed as acute mesenteric ischaemia secondary to acute mesenteric venous thrombosis.

Case Report

A 38-year-old primigravid Chinese woman presented at 7 weeks gestation of a pregnancy conceived via in vitro fertilisation (IVF), with a 2-day history of persistent, non-radiating epigastric pain associated with multiple episodes of vomiting. On examination, she was hypotensive with a blood pressure of 70/40 mmHg that responded to fluid challenge. Physical examination revealed a grossly-distended abdomen with prominent guarding and rebound tenderness in the epigastric and umbilical regions.

Investigations

Ultrasound of the abdomen and pelvis revealed free fluid around the liver and right kidney, a single in-utero viable fetus and moderate amount of free fluid in the pouch of Douglas. Laboratory studies demonstrated a haemoglobin level of 10.6 g/dL and white blood cell count of $35.7 \times 10^9/L$. The Prothrombin time was slightly prolonged—at 16.8 s, and the activated partial thromboplastin time was within normal range.

Treatment

Decision was made for emergency laparotomy.

Intraoperatively, moderate amount of hemoserous intra-peritoneal fluid was noted. A total length of 294 cm of ischaemic small bowel, extending from proximal jejunum to distal was resected, followed by primary anastomosis of the remaining ends, with a resultant viable bowel of approximately 60 cm. A thrombosis induced ischaemic event was suspected and confirmed with a duplex ultrasound performed immediately after the surgery, which revealed complete thrombosis of the superior mesenteric vein. The histological report showed haemorrhagic necrosis of the resected small bowel with moderate ischemic changes.

Postoperatively, the patient underwent a haematological work-up, results of which revealed that she had a significantly low functional protein S activity of 17% (first trimester: 55% to 130%) with mildly decreased levels of antithrombin activity—67% (range, 80% to 130%) and normal protein C activity—73% (range, 70% to 150%). Additionally, there was an absence of lupus anticoagulant, cardiolipin and B2 glycoprotein antibodies. It was thus surmised that protein S deficiency was the most likely cause of the venous thromboembolism in this patient, who was then started on 60 mg twice-daily dose of subcutaneous Clexane, titrated to a targeted anti-factor Xa assay of 0.5 to 1.0 IU/ML (therapeutic range). Total parental nutrition (TPN) via a peripherally inserted central catheter (PICC) was also instituted due to short gut syndrome following extensive small bowel resection.

Outcome and Follow-up

The patient successfully weaned off TPN at 20 weeks gestation to full enteral nutrition. Her pregnancy required luteal support with vaginal progesterone (Crinone) pessary and close antenatal surveillance by haematologists, surgeons and obstetricians. She remained antenatally well with satisfactory weight gain and normal fetal scans, subsequently delivering a baby girl weighing 2615 g. Subcutaneous Clexane was stopped on the morning of the delivery and was restarted on the second postoperative day. Recovery was uncomplicated without any thromboembolic events and subsequent 2-monthly follow-ups were uneventful.

Discussion

During pregnancy, levels of most procoagulant factors rise while that of some natural anticoagulants such as protein S fall to 40% to 60% of normal level² as part of the adaptive mechanism to ensure effective bleeding control during delivery and puerperium. With regard to this, the testing for protein S deficiency during early pregnancy using reference ranges derived from non-pregnant population is inappropriate and requires confirmation at least 3 months post-delivery. Subsequent blood tests done at 1 month and 3 months post-delivery showed persistently subnormal free protein S level of 55% and 60% (ref range, 65% to 140%) respectively, hence confirming an inherent protein S deficiency in the patient.

Obstetric complications in protein S deficiency such as recurrent early fetal loss, non-recurrent fetal loss and IUGR are postulated to be due to excessive thrombosis of the placental vessels, leading to placental infarction and secondary uteroplacental insufficiency. The most common manifestation of protein S deficiency is venous thrombosis of the lower extremities, accounting for up to 90% of all events. Our patient, in this case, presented with an atypical site of thrombosis—the superior mesenteric vein—which has an incidence of less than 5%. Such unusual sites, when observed, characteristically suggest an underlying inherited thrombophilia rather than acquired thrombophilia.³ This correlates to the significantly low free protein S levels in our patient (17%), which is likely hereditary.

The haematological workup for this patient included a screening panel for hereditary thrombophilia, consisting protein C, protein S and antithrombin III as recommended.⁴ Genetic testing for Factor V Leiden and prothrombin gene mutation were not done in view of the extremely low prevalence in local population as well as the lack of any significant family history or previous thrombotic events.

Even though the true cause of low protein S level in this patient had yet to be confirmed, the risk of another episode of catastrophic venous thrombosis and associated risks to the fetus was a strong indication to start her on low molecular weight heparin (Enoxaparin) administration. Furthermore, studies have concluded that starting Enoxaparin at either 40mg/day or 80 mg/day at 5 to 10 weeks of gestation, throughout pregnancy, and for 6 weeks postpartum to pregnant women with serious complications of thrombophilia was safe and effective for improving pregnancy outcome and reducing late pregnancy complications.⁵

Conclusion

In conclusion, maternal thrombophilic conditions such as protein S deficiency pose major risks for adverse maternal

and fetal outcomes. To our knowledge, this is the first locally reported case of successful management of a pregnancy complicated by mesenteric venous thrombosis secondary to protein S deficiency. Hence, the assessment of pregnant woman presenting with atypical venous thrombosis should include screening for underlying thrombophilias followed by appropriate treatment. Maternal treatment and careful fetal surveillance are mandatory in the management of these high-risk pregnancies.

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