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Case Report

Protein S deficiency causing postpartum stroke following twin delivery in a multiparous woman: a case report and review of literature

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ABSTRACT

Protein S deficiency is a thrombophilia known to cause venous thromboembolism. During pregnancy, it can present as deep vein thrombosis or adverse feto-maternal events such as stillbirth or intrauterine growth restriction. Its link to arterial thrombosis remains controversial. We report a case of a 31-year-old multiparous woman with no known comorbidities who developed acute left upper limb pain on postpartum day 20 following an uneventful twin delivery. Her condition progressed to giddiness, vomiting, seizures, and poor sensorium. Imaging studies revealed extensive ischemic infarctions involving the posterior circulation and thrombotic occlusions in the upper limb vasculature. She was managed with anticoagulation therapy, antibiotics for ventilator-associated pneumonia, and a left parieto-occipital decompressive craniotomy due to worsening sensorium. Thrombophilia workup identified isolated Protein S deficiency, while other markers of thrombophilia, including Protein C, antithrombin III, and factor V Leiden mutation, were normal. Despite complications, her sensorium improved with comprehensive management, and she was discharged on long-term anticoagulation. This case highlights the need for heightened awareness of postpartum thrombotic events in women with no antenatal complications. Protein S deficiency, though rare, should be considered in the differential diagnosis to ensure prompt and effective intervention, reducing morbidity and mortality in postpartum women.

Keywords: Anticoagulation, Arterial thrombosis, Craniotomy, Hemiplegia, Hypercoagulable state, Postpartum stroke, Pregnancy, Protein S deficiency, Thrombophilia, Venous thromboembolism

INTRODUCTION

Protein S deficiency is a rare inherited thrombophilia, affecting 1 in 500 to 3,000 individuals, and is primarily associated with venous thromboembolism.[1,2] In pregnancy, although rare, congenital Protein S deficiency increases the risk of thrombosis and may lead to poor pregnancy outcomes. Diagnosis during pregnancy is challenging due to physiological changes in coagulation, and it often presents with deep vein thrombosis or adverse maternal-fetal outcomes.[3] The coagulation and the fibrinolytic systems undergo significant changes during pregnancy, which makes diagnosing protein S and C deficiency challenging.[3] The rate of developing thrombotic events is higher in pregnant females with a deficiency of any natural anticoagulant like protein S.[4] It has not been determined yet if protein S deficiency has a predilection for either gender; however, it seems that clinical manifestations of VTEs are more likely to present in women due to risk factors such as oral contraceptive pill (OCP) usage, pregnancy, and hormone replacement therapy.[5]

CASE REPORT

A 31-year-old multiparous woman with no known developed acute left upper limb pain of throbbing nature on postpartum day 20 following an uneventful twin

delivery. The next day, she had giddiness and a fall, after which she had 3 episodes of vomiting, which were nonprojectile and non-bilious with food content in vomitus. Later, on the same day, she had involuntary movements of the left upper and lower limbs that lasted for 10 minutes, associated with frothing of saliva. There was no tongue bite or involuntary micturition. She was found to have poor sensorium and was intubated in the nearby hospital.

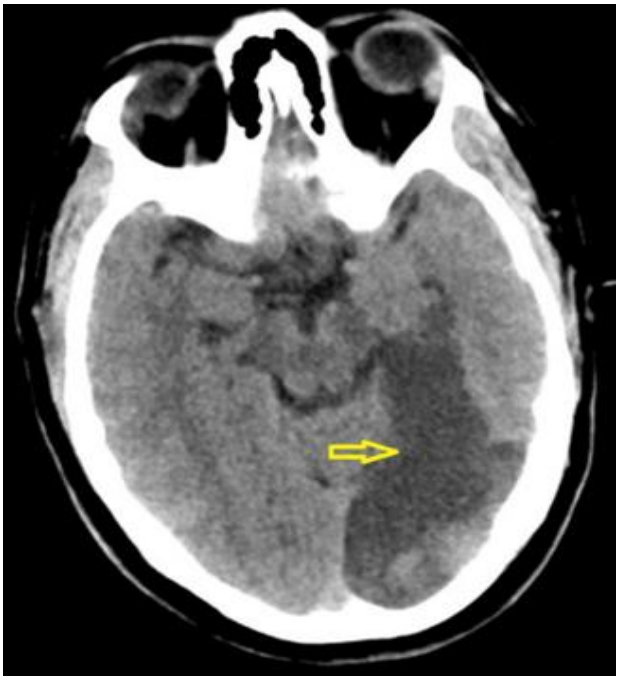

Figure 1: Non-contrast CT imaging of brain revealing a hypodense lesion in the left occipital region (yellow arrow) suggestive of an acute infarct.

A computed tomography (CT) scan revealed left occipital hypodensity (Figure 1), suggestive of an acute infarct in the brain, and left lung consolidation suggestive of aspiration pneumonia. She was started on Piperazillin-Tazobactum and metronidazole empirically and referred to a tertiary care centre for further treatment.

She had recently delivered her twin babies (one male and one female) at full term by normal vaginal delivery. Delivery was institutional, and there were no complications during the antenatal period, intrapartum, or immediate postpartum. Before this conception, there was a history of intake of Oral contraceptive pills for 2 months for polycystic ovarian syndrome. She had her first child 5 years back, which was a full-term vaginal delivery. One year back, she had a missed abortion at 2 months of gestation, which was medically managed. There was no history of diabetes, hypertension, obesity, or any other chronic medical or surgical illness in the past. She never smoked tobacco, drank alcohol, or consumed illicit drugs. The patient had no prior history of arterial or venous thrombosis. Her mother had uncontrolled sugar, underwent below-knee amputation, and had a stroke at the age of 60 years.

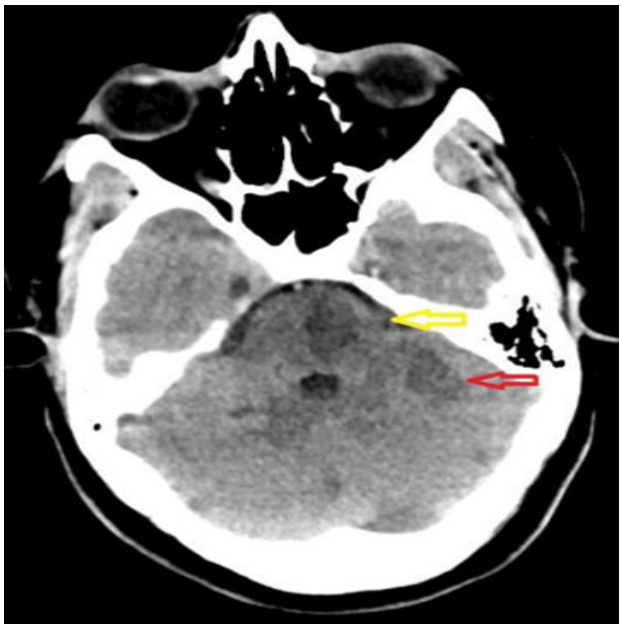

Figure 2: Non-contrast CT scan of the brain demonstrates a hypodense area in the left cerebellar hemisphere (yellow arrow), and in the left pons (red arrow) consistent with acute infarct.

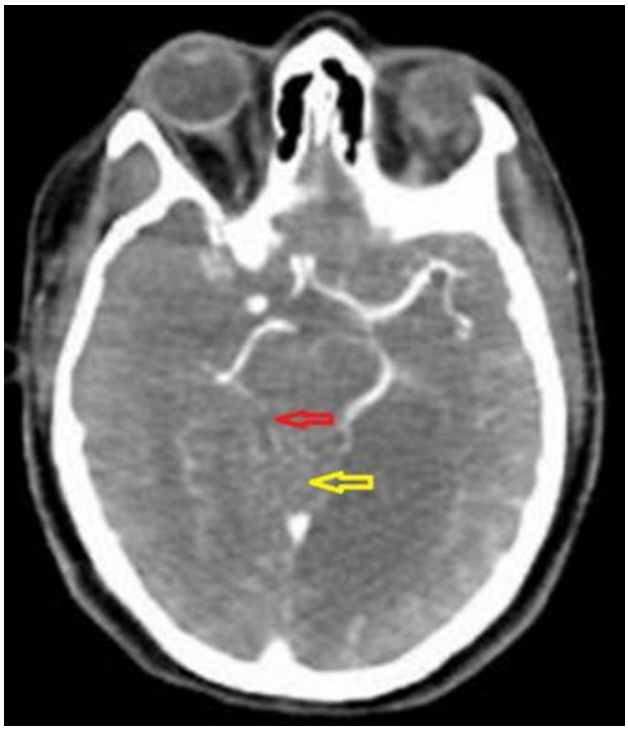

Figure 3: Axial view of CT Angiogram of the carotid and the vertebrobasilar arteries showing non-visualised distal basilar artery (yellow arrow) and P1 segment (pre-communicating segment) of the left PCA (red arrow) representing occlusion.

A computed tomography scan revealed infarcts in the left cerebellum, left medulla, pons, and occipital lobe (Figure 2). A CT Angiogram was performed that showed the top of the basilar and left Posterior Cerebral Artery (PCA) occlusion (Figure 3) with entire PCA territory involvement and thalamus showing haemorrhagic transformation. Upper limb venous doppler showed complete thrombus in brachial venae commitants, and arterial doppler showed no colour flow on left subclavian and axillary artery, with non-opacification of brachial, radial, and ulnar artery.

The patient was started initially on Aspirin 150 mg per day. On the second day of admission, there was deterioration of sensorium with a GCS of E1VTM5. In view of progressing infarct and anisocoria, left parietooccipital decompressive craniotomy was done. Post surgery, sensorium improved to E3VTM5, and the pulse in the brachial, radial, and ulnar arteries improved to biphasic flow. Antibiotics were continued since the patient developed multiple fever spikes, and heparin was added for anticoagulation.

During her period of hospitalization, she had an unremarkable complete blood count (CBC), serum electrolytes, renal and liver function parameters. Total Leucocyte count was 15000 cells/microlitre (normal range: 4000-11000 cells/microlitre). A thrombophilia workup and metabolic panel were done in view of both arterial and venous thrombosis. Fasting lipid profile was found to be abnormal with triglyceridemia of 277 mg/dl (normal range: <150 mg/dl), for which Atorvastatin 20 mg per day was added.

There was no indication of a factor V Leiden mutation in the hematologic workup. The levels of fibrinogen and homocysteine were normal. Beta-2 glycoprotein, anticardiolipin antibodies, antinuclear antibodies, and lupus anticoagulants did not appear to be contributing factors to hypercoagulability. Protein S activity level was down to 20%, but antithrombin III and protein C levels were normal.

In subsequent CT imaging, hemorrhagic transformation of infarcts in the pontine and occipital regions was noted, necessitating withholding of heparin. With persistent fever spikes, endotracheal aspirate, blood, and urine cultures were sent, all of which were reported as sterile, and procalcitonin levels were found to be normal. Antibiotics were stepped up to Meropenem. Since fever spikes were persisting after 48 hours of antibiotics, Central fever was suspected and settled with one dose of naproxen. Heparin injections were restarted for limb ischemia 8 days after the craniotomy. After 3 days of heparin therapy, the patient was started on 5 mg of warfarin to prevent future clot formation.

Patient's sensorium further improved to E4VTM6, and she was weaned off from ventilator. She was tracheostomised with a 28 Jackson tracheostomy tube. She had persistently increased tracheal secretions and one episode of fever. Repeat procalcitonin levels were 35 ng/ml (normal range: <0.05 ng/ml), with an Endotracheal aspirate growing *Klebsiella pneumoniae* sensitive to minocycline. With Minocycline, the fever settled, tracheal secretions reduced, and repeat procalcitonin levels were in an increasing trend. She was simultaneously combating a urinary tract infection for which she was treated with amikacin.

Repeat NCCT brain showed a resolving infarct size. The left brachial, radial, and ulnar arteries had a biphasic pulse. Currently, she is adhering to her medication regimen. There is a paucity of right-side movements, and is on physiotherapy. Power in the right upper and lower limbs is 0/,5 with 3/5 power in the left side.

DISCUSSION

Protein S is a coagulation-regulatory protein that acts as a cofactor to activated protein C in the breakdown of clotting factors Va and VIIIa. In order to ensure sufficient haemostasis throughout birth and puerperium, the levels of most procoagulant factors increase during pregnancy, whereas those of some natural anticoagulants, including protein S, decrease to 40% to 60% of their normal levels.[6]

The incidence of thrombosis due to protein S deficiency is 0-6% antenatally and 7-22% in the immediate postpartum.[7] Protein S deficiency, although rare, usually presents as venous thromboembolism. Recurrent pregnancy loss, intrauterine growth restriction (IUGR), and intrauterine demise are among the worst pregnancy outcomes related to protein S deficiency.[6]

We conducted a literature review to understand the presentation of protein S deficiency complicating pregnancy. There are case reports of stillbirth, pulmonary embolism, and DVT developing antenatally or immediate postpartum.

Table 1 summarises the eleven documented cases of thromboembolic events caused by protein S deficiency identified during pregnancy that are covered in our review. Eight of the cases that have been reported were primigravidae with no identifiable risk factors or comorbidities. Regarding the timing in relation to the thrombotic events, two cases occurred in the third trimester, three in the second trimester, and three in the first trimester. Only one case occurred in the postpartum period.

Our review found seven cases of venous thrombosis. Deep vein thrombosis was the presentation in two of these patients. They presented antenatally at 10 and 23 weeks and hence were managed with anticoagulants, followed by elective LSCS at term for obstetric indication. Three reported cases of cerebral venous thrombosis were found. Two reported cases of mesenteric venous thrombosis in early gestation required bowel resection and anastomosis. However, one of them expired antenatally due to surgical complications, and the other patient had a favourable fetomaternal outcome.

Table 1: Summary of published case reports of thromboembolic events in pregnancy and postpartum due to isolated Protein S deficiency.

Authors	Age (years)	Gravidity /parity	Gestational age	Clinical presentation	Diagnosis
Sugandha et al[1]	35	G3L2	10 weeks	Leg pain and swelling	DVT
Yoshida et al[8]	35	G4P3A1	5 weeks	Acute onset of right hemiplegia and motor aphasia	Stroke due to left MCA thrombosis
Diakite et al[7]	34	G1	35 weeks	Atypical chest pain	MI due to LAD artery thrombus
Alhousseini et al[9]	21	G1	33 weeks	Spontaneous prolonged deceleration, IUGR	Placental artery thrombosis
Makanjuola A[10]	28	G1	NA	Acute headache, vomiting, quadriparesis, papilledema	CVT stroke
Liu et al[6]	38	1	7 weeks	Acute abdominal pain	Mesenteric ischemia
Etoh[11]	37	NA	23 weeks	Leg pain and swelling	DVT
Atakan et al[12]	25	G1	20 weeks	Acute abdominal pain	Mesenteric ischemia
Burneo et al[13]	21	G1	14 weeks	Headache	CVT
Galan et al[14]	NA	NA	Postpartum	Headache, hypertension, status epilepticus	CVT
Tharakan et al[15]	NA	NA	NA	Stillbirth	Stillbirth, postpartum pulmonary embolism

Abbreviations: CVT, cerebral venous thrombosis; DVT, Deep vein thrombosis; MI, myocardial infarction; LAD, left anterior descending artery; MCA, middle cerebral artery; NA, not announced.

Arterial thrombosis due to protein S deficiency was reported in only two cases. One patient had an acute MI due to left anterior descending artery thrombosis, and another woman had a large vessel occlusion stroke due to a left middle cerebral artery thrombus. In another woman, preterm LSCS was done for severe IUGR with oligohydramnios and spontaneous prolonged deceleration. Histopathological examination of the placenta revealed placental artery thrombosis with medial myocyte necrosis. There was one reported case of stillbirth with postpartum pulmonary embolism in the mother. Venous thrombosis of the lower limbs is the most frequent presentation of protein S insufficiency, making up 90% of all cases.[6] Our patient, in this case, presented with an atypical site of thrombosis indicative of hereditary rather than acquired thrombophilia. Significantly low protein S activity also suggests that thrombophilia is probably inherited. To the best of our knowledge, this is the first case of postpartum stroke due to arterial thrombus occurring in a woman with protein S deficiency.

CONCLUSION

Protein S deficiency, primarily associated with venous thromboembolism, poses significant risks during pregnancy, often presenting as deep vein thrombosis or adverse maternal-fetal outcomes. Pregnancy further reduces protein S levels, increasing peripartum thrombotic risk. Early diagnosis, adequate anticoagulant therapy, and fetal monitoring are crucial. Multidisciplinary care involving obstetricians, cardiologists, pediatricians, and anesthesiologists is essential for optimal outcomes, emphasizing the need to assess thrombosis risk factors in postpartum women. This case highlights the need to extensively identify all risk factors of thrombosis in newly delivered women for the early and effective management of postpartum thrombosis.

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