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Case Report

A Rare Case of Hypercoagulable State Due to Combined Inherited Thrombophilia Protein C & S Deficiency and Possible Anti Phospholipid Syndrome Complicated by a Pulmonary Embolism Causing Cardiac Strain

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ABSTRACT

This is case report of a 31 year old male patient who came to emergency department with complaints of sudden onset shortness of breath associated with cardinal signs of cardiac strain followed on to be diagnosed with combined inherited thrombophilia due to protein S and protein C deficiency along with a possible antiphospholipid syndrome (APS). The case was complicated by pulmonary embolism with cardiac strain as indicated by grossly elevated NT-ProBNP and 2D Echo changes like global LV Hypokinesia and PASP of 60mmHg.

KEYWORDS

• Hypercoagulable state • Protein C deficiency • Protein S deficiency • Inherited thrombophilia • Antiphospholipid syndrome (APS) • Pulmonary embolism • Cardiac strain

INTRODUCTION

Thrombophilia occurs due to deficiency of Protein S and Protein C which is an extremely rare condition and even rarer in combination. The possibility of Anti phospholipid syndrome occurring simultaneously along protein deficiencies makes the clinical prognosis grave and complicated.[1]

Pulmonary embolism occurrence in young male patients should raise an alert for

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underlying thrombophilic states especially when it occurs alongside echocardiographic changes or biomarker evidences of cardiac strain on heart[2].

Hypercoagulability or thrombophilia is the increased tendency of blood to thrombose. A normal and healthy response to bleeding for maintaining hemostasis involves the formation of a stable clot, and the process is called coagulation. Hypercoagulability describes the pathologic state of exaggerated coagulation or coagulation in the absence of bleeding. Different constituents of the blood interact to create a thrombus. Arterial thrombosis, such as in myocardial infarction and stroke, is different from venous thromboses, such as deep venous thrombosis (DVT) and pulmonary embolism (PE). Pathophysiology and treatment differ for arterial and venous thrombosis, but risk factors overlap.[3,4]

Thromboembolism describes the migration of a local thrombus to distant areas leading to luminal obstruction. Different hypercoagulable states and thrombophilic diseases cause hypercoagulability. As early as 1906 Wasserman *et al.*, described the antiphospholipid syndrome. In 1965 Egeberg *et al.*, discovered antithrombin III deficiency.[5] During the 1980s protein C (Griffin, 1981) and protein S (Comp, 1984) deficiencies were introduced. Dahlbäck discovered activated protein C resistance in 1993, which is commonly caused by the factor V Leiden mutation.[5-7]

CASE REPORT

31 year old male patient came to ER with chief complaints of shortness of breath – NYHA 4 associated with profuse 'Ghabrahat' and dizziness since 4-5 days exacerbated since morning of the day of arrival.

No H/O Fever/Chest Pain/Leg pain/ Vomiting/Pedal oedema

The patient was given IV crystalloids, IV proton pump inhibitors, and admitted to the hospital. Esophagogastroduodenoscopy (EGD) revealed large esophageal varices (*Figure* 1) that were subsequently ligated via Esophageal Variceal Band Ligation (EVBL).

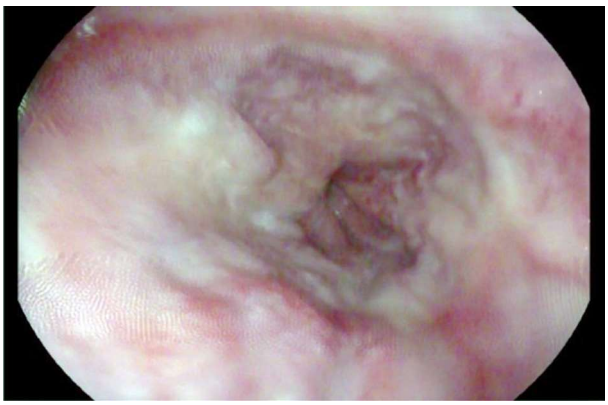


Figure 1: Esophagogastroduodenoscopy image showing esophageal mucosa with large varices

USG abdomen (*Figure* 2) of the patient revealed chronic portal vein thrombosis involving the splenic vein with cavernous transformation at the Porta-hepatis without any signs of cirrhosis or irregularities in the liver parenchyma.

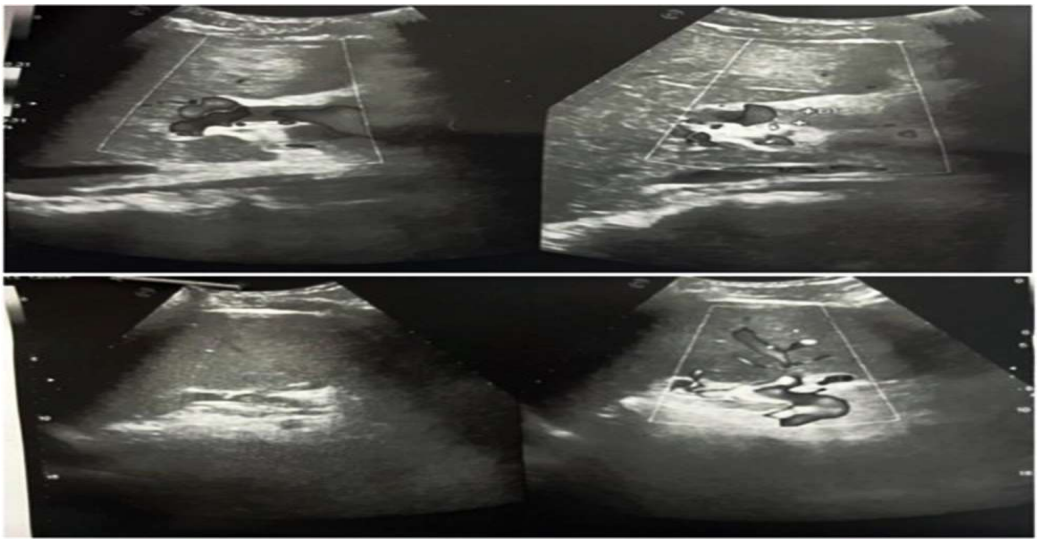
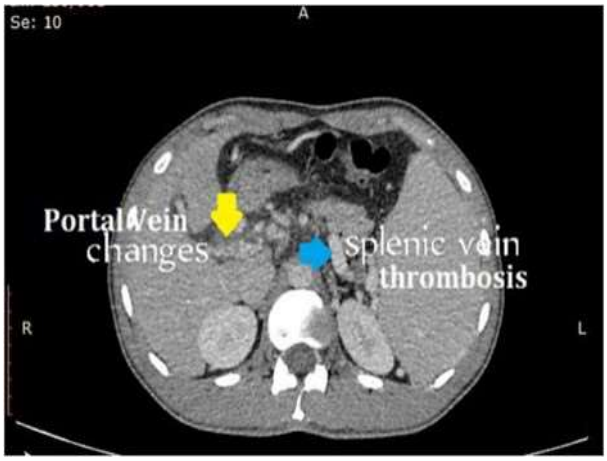


Figure 2: USG Doppler abdomen/hepatobiliary suggestive of Portal and Splenic Vein thrombosis

CT abdomen with IV contrast was requested that confirmed noncirrhotic chronic Portal vein thrombosis with cavernous transformation and splenomegaly (*Figures* 3 & 5).



Here's how it should be:

- **Yellow arrow** → Splenic vein
- **Blue arrow** → Portal vein

Figure 3: CT Abdomen & Pelvis axial view shows thrombosis of the Portal (yellow arrows) and Splenic (blue arrows) veins along with splenomegaly, and without any signs of cirrhosis

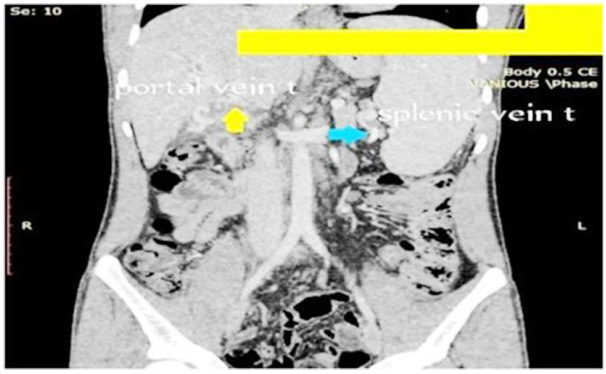


Figure 4: CT Abdomen & Pelvis coronal view shows thrombosis of the Portal (yellow arrows) and Splenic (blue arrows) veins, splenomegaly, and no signs of cirrhosis

After confirmation of thrombosis on imaging and before initiation of any anticoagulant therapy, a coagulation profile (*Figure* 5) was sent to check for levels of Antithrombin III, Protein C & S, Lupus anticoagulant, Anti-Cardiolipin antibodies, Anti-Beta 2 glycoprotein antibodies, and Homocysteine levels to figure out the primary etiology. The results revealed a combined deficiency of both Protein S and C which was confirmed by repeat testing on follow-up appointments.

Figure 5: The patient's coagulation profile shows low Free Protein S and Protein C levels

The Patient was prescribed Direct Oral anticoagulants for an indefinite period due to his inherited thrombophilic state.

On Arrival Vitals

BP – 130/90 mmhg

HR – 108 BPM/min

RR – 20 /min

SPO2- 99% on room air

TEMP – AFEB – 98F

RBS – 128 mg/dl

General Examination

- General Physical Exam: Pallor (-), Icterus (-), Cyanosis (-), Pedal Edema (-), Lymphadenopathy (-)
- CVS: S1, S2 normal, no murmurs
- Respiratory: Bilateral air entry present, No added sounds
- Abdomen: Soft, non-tender, No organomegaly
- CNS: Conscious, Oriented

Routine baseline investigations on arrival included complete blood count (CBC), renal and liver function tests (RFT, LFT), serum electrolytes, random blood sugar, coagulation profile (PT/INR, aPTT), and D-dimer.[8] All parameters were within normal limits except for an elevated D-dimer (value: XXXX ng/mL, normal <500 ng/mL) and marginally raised serum creatinine (if applicable else state normal).[9]

Additionally, a thrombophilia workup was initiated, which included levels of Antithrombin III, Protein C and Protein S, Lupus anticoagulant, Anti-Cardiolipin antibodies, Anti-Beta 2 glycoprotein antibodies, and plasma Homocysteine to determine the underlying etiology of the hypercoagulable state.[10]

Hospital Course and Investigations

Initial evaluation with 2D Echocardiography revealed:

- RA, RV dilation
- Thrombus in transit (RA → RV → PA)
- Moderate TR, PASP ~60 mmHg
- LVEF: 40%, generalized hypokinesia
- TAPSE: 14 mm, IVC: 2.2 cm with blunted response

The patient was thrombolysed with Alteplase (100 mg over 2 hours) for pulmonary embolism with thrombus in transit.[11] Alteplase was chosen over Streptokinase for systemic thrombolysis as it is associated with faster clot lysis, a shorter plasma half-life allowing easier titration, and a lower risk of immunogenic reactions. Additionally, current European Society of Cardiology (ESC) and American College of Chest Physicians (ACCP) guidelines recommend Alteplase as the first-line thrombolytic agent in acute high-risk and select intermediate-risk pulmonary embolism cases.[12]

Supportive care included IV antibiotics (Magnex forte) initiated as per protocol for prophylaxis following esophageal variceal band ligation to prevent procedure-related bacteremia, given the presence of portal hypertension and varices.[13] No clinical or laboratory evidence of active infection was identified, and antibiotics were discontinued after 48 hours following an uneventful post-procedural period.[13]

Electrocardiogram (ECG): On arrival, a 12-lead ECG demonstrated sinus tachycardia with a heart rate of 108 bpm.[14] There was evidence of right ventricular strain with T-wave inversions in leads V1–V3 and a classic S1Q3T3 pattern, suggestive of acute pulmonary embolism. No significant arrhythmias or ST-T segment changes were noted.[14]

2D Echocardiography revealed: RA, RV dilation Thrombus in transit (RA → RV → PA)15

CT Pulmonary Angiography (16-Dec-2024):

Baseline renal function was assessed prior to contrast administration, and the patient's serum creatinine was 0.9 mg/dL (normal range: 0.7–1.3 mg/dL). Given the need for multiple contrast-enhanced studies, contrast-induced nephropathy (CIN) prophylaxis was initiated with intravenous isotonic saline at 1 mL/kg/hour, starting 6 hours before the procedure and continued for 12 hours post-procedure. No nephrotoxic medications were administered concurrently. Follow-up renal function tests performed 48 hours later remained within normal limits.[16]

Portal Vein Thrombosis (PVT) occurs when a thrombus partially or completely occludes the lumen of the Hepatic Portal Vein. Due to the widespread utilization of Doppler Ultrasonography in recent times, the diagnosis of PVT has become more prevalent. Still, in individuals without cirrhosis, PVT is a rare occurrence.[17]

PVT can present either acutely or chronically. Acute PVT presents with abdominal pain, nausea, emesis, fever, new-onset ascites, and metabolic acidosis. Chronic PVT, as in our patient, leads to the development of collaterals and portosystemic shunting occurs leading to esophageal and rectal varices, rectal bleeding, hematemesis, and splenomegaly.[18]

Detecting abnormalities related to portal vein thrombosis (PVT) is essential for accurate diagnosis and timely intervention. In approximately one-third of patients with PVT, cavernous transformation of the portal vein occurs which indicates an old thrombus. The ultrasonographic diagnostic triad includes failure to visualize the extra-hepatic portal vein, demonstration of high-level echoes in the porta hepatis, and visualization of multiple serpiginous vascular channels around the portal vein.[19]

Contrast-enhanced computed tomography (CT) is the optimal method for diagnosing portal vein thrombosis (PVT) and assessing potential underlying diseases. Key findings of PVT on dynamic CT include filling defects that partially or completely occlude the vessel lumen and rim enhancement of the vessel wall.

Etiologically, PVT can occur due to underlying malignancy, infection, use of oral contraceptives, acute pancreatitis, pregnancy, Liver disease, or coagulopathies.[20] Pro-coagulative states leading to PVT can either be acquired due to myeloproliferative disorders, antiphospholipid syndrome, and Paroxysmal Nocturnal Hemoglobinuria (PNH)[119,17] or inherited due to mutations in Prothrombin, anti-thrombin, protein C, protein S, or Factor V[17].

Fisher *et al*.[21] investigated twenty-nine adult patients with portal hypertension due to PVT. Their findings revealed that 62% of the patients exhibited deficiencies in one or more natural anticoagulant proteins. Among these cases, only 28% had combined deficiency of C and S proteins, 31% had deficiency in C protein and antithrombin, while 24% showed deficiencies in protein S and antithrombin. Additionally, 21% of cases had deficiencies in all 3 proteins simultaneously. Therefore, in cases of PVT, especially without any evidence of underlying cirrhosis or other risk factors, it is imperative to test for deficiencies of anticoagulant proteins.

CONCLUSION

This case highlights the importance of evaluating for multiple thrombophilic factors in young patients presenting with VTE. The coexistence of Protein C and S deficiency with possible APS represents a clinically significant and rare prothrombotic state, warranting long-term follow-up and anticoagulation therapy.

1. Combined Protein C and S deficiency is exceedingly rare but highly thrombogenic.
2. Pulmonary embolism with thrombus in transit requires urgent thrombolysis.
3. APS should be suspected even if initial antibodies are negative repeat testing is crucial.
4. Elevated NT-proBNP in PE suggests cardiac strain and may guide the need for aggressive therapy.
5. Young patients with thromboembolism should always be evaluated for inherited and acquired thrombophilia.

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