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Acute pulmonary embolism and deep vein thrombosis due to protein S deficiency in a young female presenting with chest pain

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Abstract
Protein S deficiency is a major risk factor for venous thromboembolism, posing a diagnostic challenge due to atypical presenting complaints. Acute pulmonary embolism is a common, treatable but potentially fatal condition, currently third most common cause of cardiovascular death. It is important for physicians to consider pulmonary embolism as a differential diagnosis in young adults presenting atypical symptoms with dilated right atrium, right ventricle and elevated pulmonary artery pressure on echocardiography. Computed tomography pulmonary angiography (CTPA) confirms pulmonary artery thrombosis. Prompt management with anticoagulant should be done to improve the outcome of patients.

Keywords: Protein S deficiency, pulmonary embolism, young female, deep vein thrombosis

Introduction
Protein S is a vitamin K-dependent glycoprotein which functions as cofactor for activated protein C in degradation of coagulation factors Va and VIIIa. Deficiency of protein S is inherited or acquired disorder causing increased risk of thrombosis with prevalence of 0.03% to 0.13% in general population and 1% to 13% in patients with venous thromboembolism. We present the case of a young female with no risk factors presenting with atypical symptom diagnosed with pulmonary thromboembolism and was found to have protein S deficiency on further investigation.

Case Report
A 25 year old young, lady come to the OPD with complaints of persistent chest pain from last 7 days. She had no fever, shortness of breath or any recent trauma. She had no comorbidity, non-smoker. Examination revealed a blood pressure (BP) of 110/70 mmHg, heart rate (HR) of 110/min, respiratory rate (RR) of 18/min and oxygen saturation (SpO_2) of 97% at room air. Initial laboratory investigations revealed mild anemia (Hb 11.7 g/dl) with normal leucocyte and platelet count (TLC 9.71 X 10^9/L, Platelet count 159 X 10^9/L). Liver function and renal profile were within normal limits. Cardiac enzymes were within normal range (CPK 55 U/L, CK-MB 0.8 ng/ml, Trop I 0.02 ng/ml). Initial electrocardiogram (ECG) showed sinus tachycardia at a rate of 110 beats per minute. 2D ECHO revealed no regional wall motion abnormality, good left ventricle function however RA, RV were dilated and she had mild pulmonary arterial hypertension. The D Dimer was raised (6919 ng/ml). Chest x ray showed well defined rounded opacity in right lower zone likely representing consolidation (figure 1). In view of these findings, Computed tomography pulmonary angiography (CTPA) was done which revealed presence of thrombus in distal main pulmonary trunk, right and left pulmonary and its ascending and descending branches suggestive of pulmonary thromboembolism (figure 2,3). Venous doppler of lower limb revealed deep vein thrombosis involving left common, external iliac, common, superficial and deep femoral and popliteal veins with extension into short saphenous vein (figure 4, 5, 6, 7, 8, 9). She was managed with subcutaneous enoxaparin and was started on oral vitamin K antagonist, warfarin with international normalized ratio (INR) monitoring.

Further investigation showed homocysteine 12.4 micromol/L, factor V Leiden mutation, prothrombin gene mutation, MTHFR gene mutation, antinuclear antibody, and vasculitis panel were all negative, anti phospho lipid antibody IgG 2.18 AU/ml, anti phospho lipid antibody IgM 0.67 AU/ml, antithrombin III 122%, protein C 91%, but her protein S (free) level was low at 15.1%.

Her chest pain improved and was discharged on day 6 on oral anticoagulant. She was continued on oral anticoagulant and was doing well on regular follow up from last 6 months.

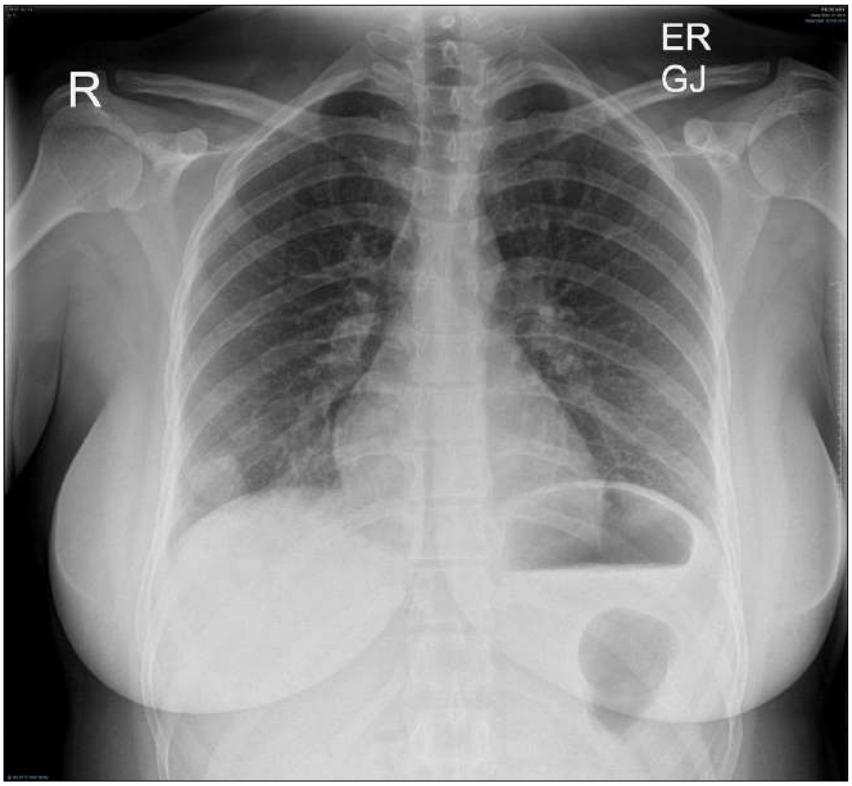

Fig 1: Chest x ray showed well defined rounded opacity in right lower zone likely representing consolidation

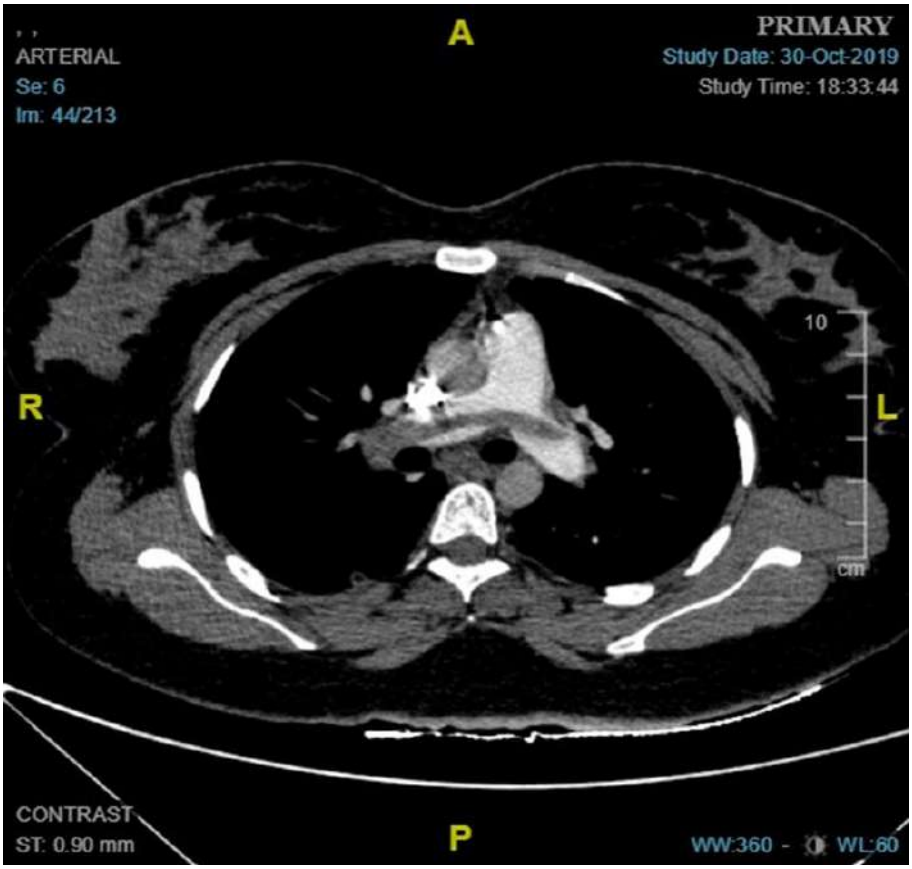

Fig 2: Computed tomography pulmonary angiography (CTPA) was done which revealed presence of thrombus in distal main pulmonary trunk, right and left pulmonary and its ascending and descending branches suggestive of pulmonary thromboembolism

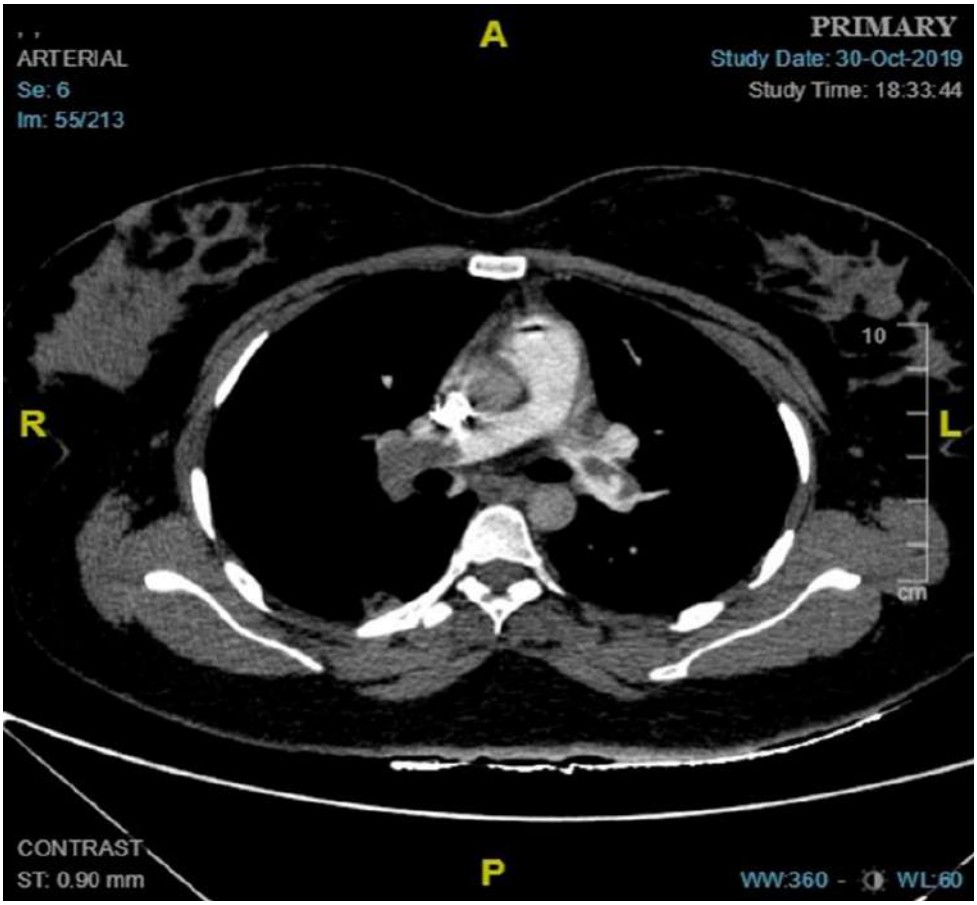

Fig 3: Computed tomography pulmonary angiography (CTPA) was done which revealed presence of thrombus in distal main pulmonary trunk, right and left pulmonary and its ascending and descending branches suggestive of pulmonary thromboembolism

Fig 4: Venous doppler of lower limb revealed deep vein thrombosis involving left common, external iliac, common, superficial and deep femoral and popliteal veins with extension into short saphenous vein

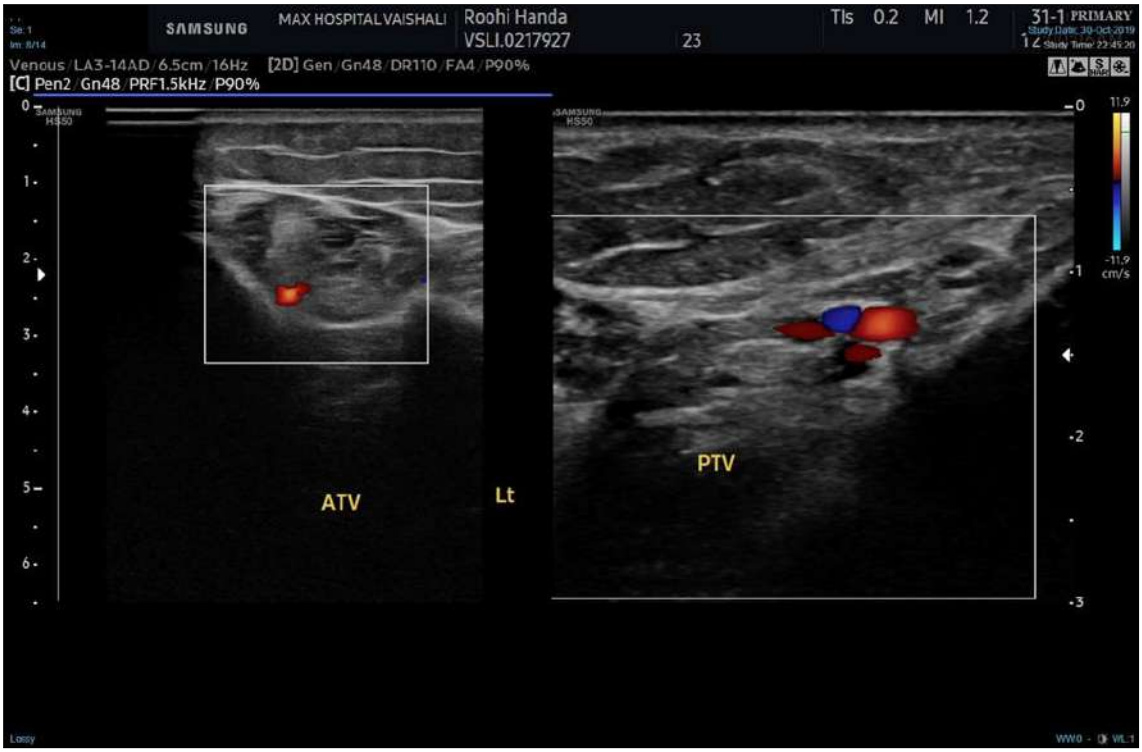

Fig 5: Venous doppler of lower limb revealed deep vein thrombosis involving left common, external iliac, common, superficial and deep femoral and popliteal veins with extension into short saphenous vein

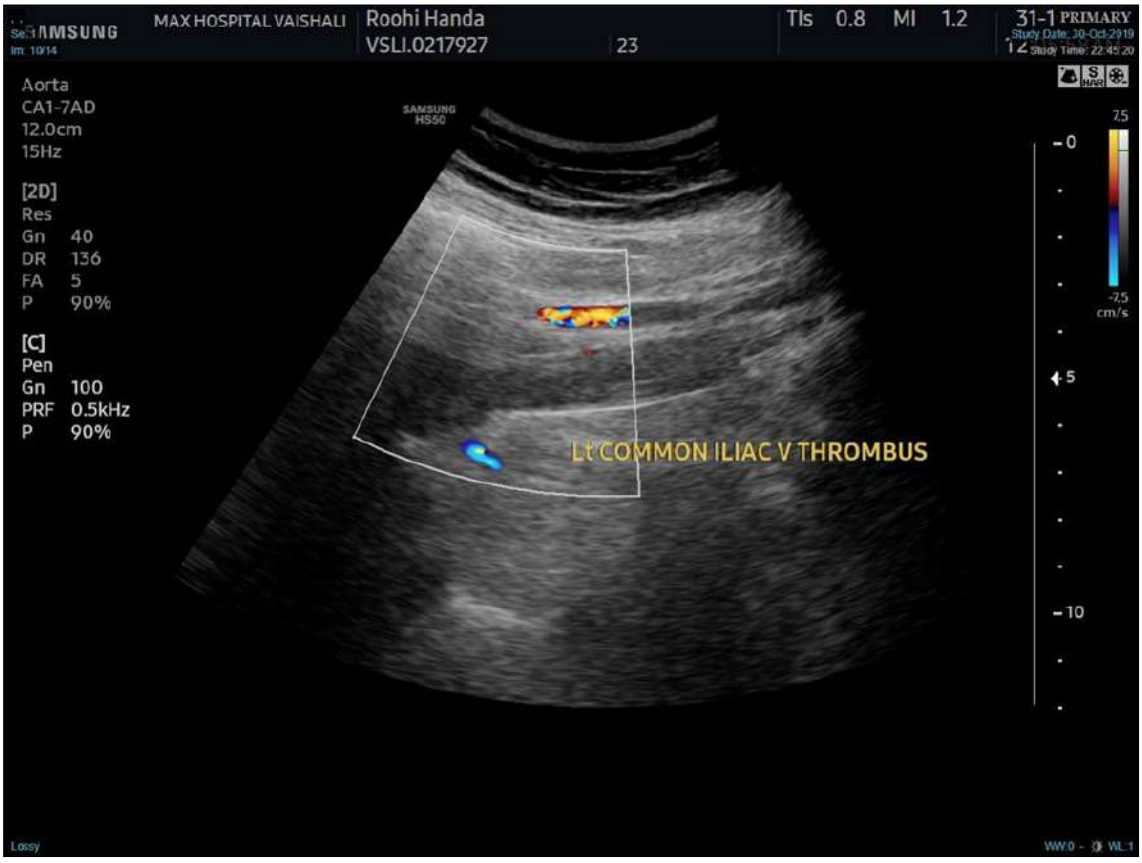

Fig 6: Venous doppler of lower limb revealed deep vein thrombosis involving left common, external iliac

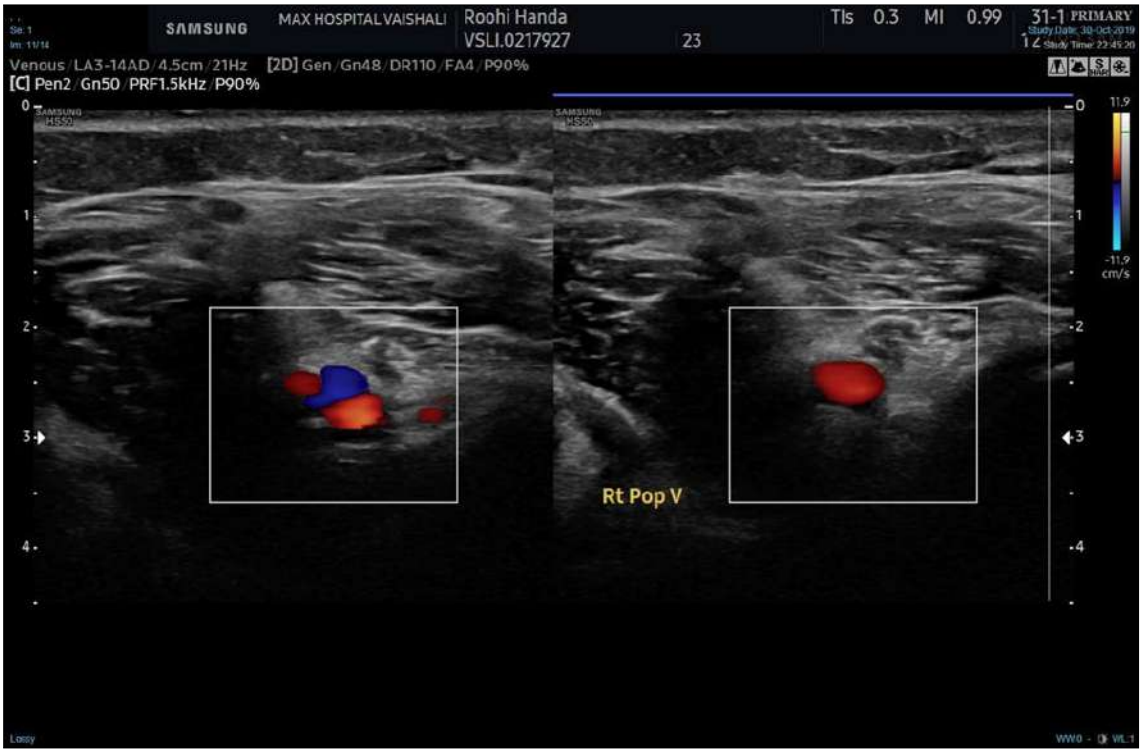

Fig 7: Venous doppler of lower limb revealed deep vein thrombosis involving right popliteal veins with extension into short saphenous vein

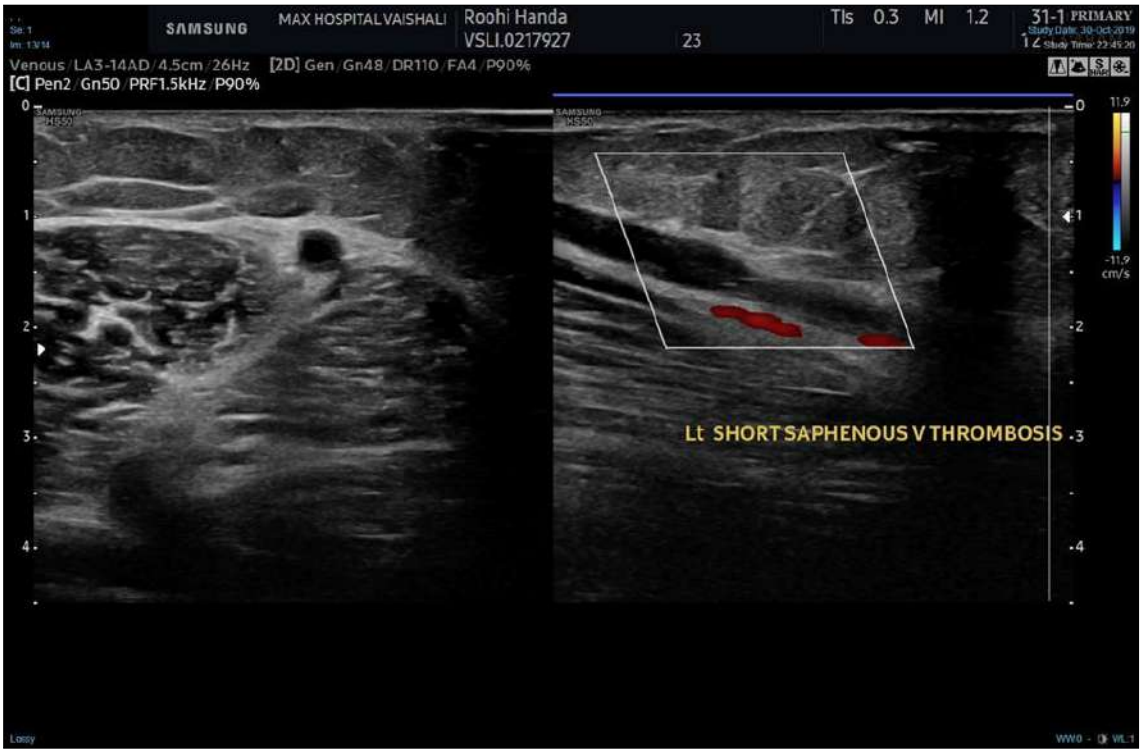

Fig 8: Venous doppler of lower limb revealed deep vein thrombosis involving left common, external iliac, common, superficial and deep femoral and popliteal veins with extension into short saphenous vein

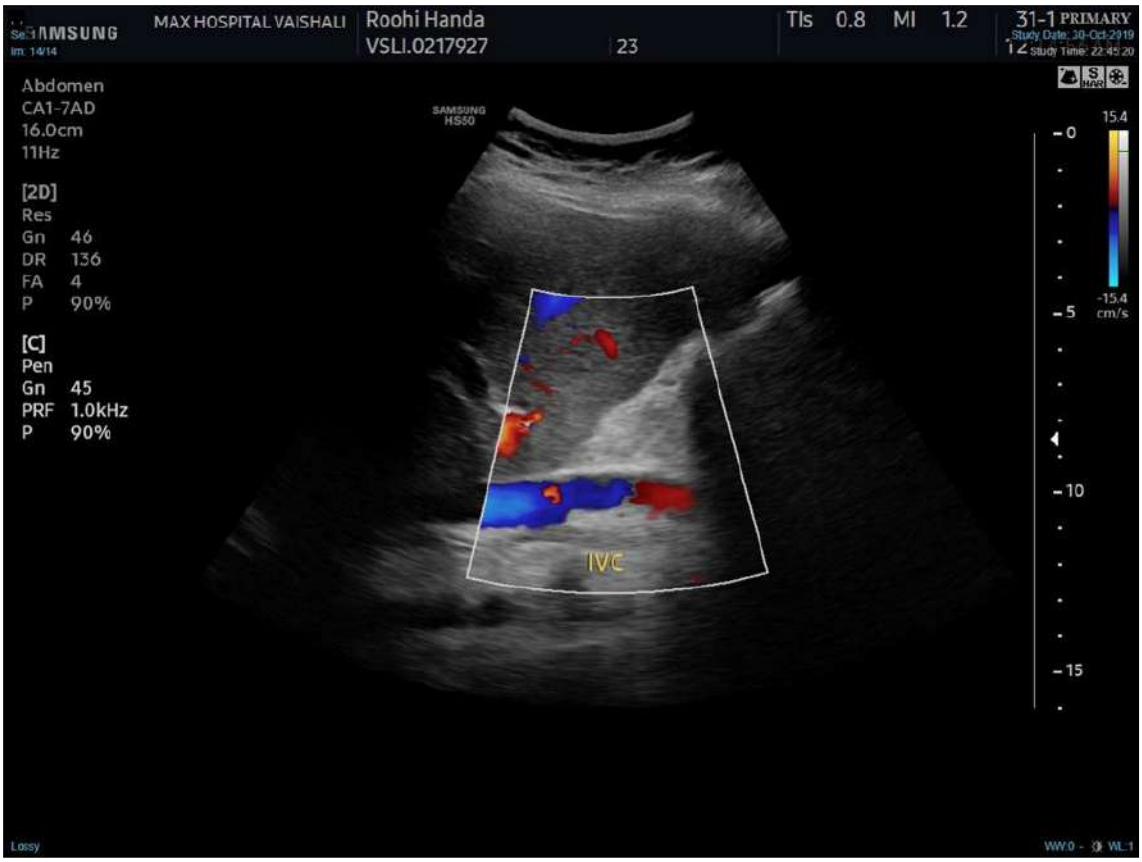

Fig 9: Venous doppler of lower limb revealed deep vein thrombosis involving left common, external iliac, common, superficial and deep femoral and popliteal veins with extension into short saphenous vein

Discussion

Protein S, a vitamin-K dependent glycoprotein is a cofactor for activated protein C reducing thrombin generation by inactivating procoagulant factor Va and VIIIa [1]. It also enhances fibrinolysis and inhibits prothrombin activation [2-6]. Protein S deficiency is an autosomal dominant inherited thrombophilia with increased risk of thromboembolism due to PROS1 gene mutation on chromosome 3 [7, 8, 9]. Inherited protein S deficiency is subdivided into three types: Type I - classic type includes reduced level of total and free protein S, with decreased protein S function, Type II - includes normal level of total and free protein S and reduced protein S function, Type III - quantitative defect including selective reduction in free protein S and its function [10]. In addition to PROS1 gene mutation reduced protein S level has been seen in pregnancy, oral hormonal contraceptive use, disseminated intravascular coagulation, acute thrombosis, HIV infection, nephrotic syndrome, liver disease. Incidence of protein S deficiency is 2-8% among patients with venous thromboembolism and 2013 MEGA study, frequency of protein S deficiency was 0.9% [11]. Protein S deficiency can manifest in varied manifestation including VTE, arterial thrombosis, neonatal purpura fulminans and obstetrical complications. VTE include DVT and pulmonary embolism. Median age of first thromboembolic event was 14.5 years and incidence of pulmonary embolism was 17% [12].

Protein S deficiency should be suspected in patient presenting with VTE in association with one or more of the following strong family history of VTE or deficiency, first VTE event before 50 years, VTE in unusual site such as portal mesenteric, cerebral vein and recurrent VTE. Certain diagnosis and documentation of protein S deficiency is most difficult among all hereditary thrombophilias. Free protein S level is the preferred approach for screening and test for true deficiency [13, 14]. Free Protein S level among asymptomatic or having first VTE in the absence of a strong family history, lower levels are more predictive for an increased risk of VTE [15].

Differential diagnosis of VTE including inherited thrombophilias (factor V Leiden mutation, protein C deficiency, antithrombin deficiency, prothrombin G20210A mutation) along with acquired risk factors (immobility, surgery, trauma, cancer, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, disseminated intravascular coagulation, and hormonal changes in pregnancy, oral contraceptives) should be evaluated and ruled out. Acute VTE is managed with anticoagulation for at least three to six months. Further continuation of anticoagulation depends on whether thrombosis is provoked or unprovoked along with other factors including recurrent thrombosis, life threatening thrombosis, thrombosis at unusual sites. If DOAC is chosen for long term prevention of recurrent VTE, higher dose regimen is used, as protein S deficiency is one of the more thrombophilic of the hereditary thrombophilias.

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