Multiple arterial and venous thromboses due to protein S deficiency - a case report

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Article Info

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Received : 30 December 2021
Accepted : 31 March 2022
Available Online : 15 May 2022

ISSN: 2224-7750 (Online)
2074-2908 (Print)

DOI: https://doi.org/10.3329/bsmmuj.v15i2.60869

Keywords: Arterial and venous thromboses, Protein S deficiency, Diffuse parenchymal lung disease, central retinal artery occlusion

Cite this article:
Paul SK, Rahman MA, Ahmed S, Chakrabortty R, Majumder S, Hamza M. Multiple arterial and venous thromboses due to Protein S deficiency- a case report. Bangabandhu Sheikh Mujib Med Univ J. 2022; 15(2): 132-137.

Available at:
www.banglajol.info

A Journal of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

Case Presentation

Dr. Susanta Kumar Paul (Resident): A 64-year-old, hypertensive, ex-smoker patient was admitted to our emergency department because of exertional dyspnea and dry cough for six months and left-sided leg swelling for three months. He had no history of fever, hemoptysis, chest pain, joint pain, or features suggestive of venous thromboembolism. On examination, exercise-induced desaturation (oxygen saturation was 84.0-88.0% during walking and became 96.0-97.0% with rest) and swollen left lower limb with engorged superficial veins were present. Hyperpigmentation, trophic skin changes, calf muscle tenderness, and carotid or abdominal bruit were absent. Bilateral vesicular breath sound with prolonged expiration and scattered crepitations was found on chest auscultation.

Laboratory and radiological investigations showed (Table-I) raised D-dimer with normal renal and liver functions, while complete blood count showed normal hemoglobin with neutrophilic leucocytosis and high ESR. High-resolution computed tomography (HRCT) of the chest revealed ground-glass opacities with septal thickening and a few fibrotic bands in different segments of both lung fields, predominantly in peripheral regions (Figure-1).

RT-PCR for Covid-19 infection, troponin I, NT-pro BNP, and color doppler echocardiography were normal. Doppler ultrasound of leg vein showed chronic thrombus with partial recanalization in the left common femoral vein cranial to the saphenofemoral junction.

Provisional diagnosis

Diffuse parenchymal lung disease with pulmonary embolism with deep vein thrombosis (DVT) of the left leg

Diffuse parenchymal lung disease with venous-thromboembolism

Dr. Susanta Kumar Paul (Resident): Diffuse parenchymal lung diseases (DPLDs) are a heterogeneous group of disorders that share common clinical physiological and radiological characteristics affecting the pulmonary parenchyma (interstitium) and/or alveolar lumen resulting in high mortality rates. DPLDs are classified into idiopathic interstitial pneumonia, granulomatous DPLD (e.g., sarcoidosis), DPLD of known cause (e.g., Drugs or association with connective tissue disease), and other forms of DPLD (e.g., lymphangioleiomyomatosis, histiocytosis X, etc.). The main representative group of idiopathic interstitial pneumonia is idiopathic pulmonary fibrosis (IPF), a chronic and progressive disease characterized by deposition of extracellular matrix followed by remodeling of the lung associated with the histological and radiological pattern of usual interstitial pneumonia (UIP).[1] The patient often presents with a dry distressing cough with insidious progressive breathlessness. Physical examination reveals the presence of fine end-inspiratory crackles and in many cases, digital clubbing develops. The typical radiological findings include ground glass and reticulonodular shadowing in the earlier stage with progression to honeycomb cysts and traction bronchiectasis. Lung function tests show a restrictive ventilatory defect with small lung volumes and reduced gas transfer factor.

An association between IPF and the risk of thromboembolic events has been documented, but the exact cause is unknown. However, reduced mobility due to breathlessness, fatigue, and stiffness of joints may predispose to venous thromboembolism (VTE). Moreover, a higher prevalence of pulmonary hypertension (PH) among these patients leads to increased vascular resistance

and blood stagnation; consequently, angiogenic chemokines increase subsequently, and aberrant angiogenesis and endothelial abnormalities occur.[2] Another explanation is that IPF is a prothrombotic condition evidenced by the presence of thrombin concentration in the bronchoalveolar lavage of fibrotic lung disease patients, which acts as a potent inducer of different fibrogenic cytokines. In situ thrombosis in pulmonary arteries or the vascular beds are also responsible for deep vein thrombosis and pulmonary embolism.

A study conducted by Navaratnam et al showed that patients with IPF have almost five times higher risk of venous thromboembolism and are associated with higher mortality.[3] According to Dalleywater et al., the prevalence of pulmonary embolism and deep vein thrombosis in IPF patients has been 2.4% and 1.1%, respectively.[4] A meta-analysis by Boonpheng et al. showed that the pooled risk ratio of VTE in IPF was 2.1, two-fold higher than normal healthy subjects.[5] Concerning diagnosis, PE should be suspected when there is an acute deterioration, excluding imaging features in high resolution computed tomography (HRCT) or finding from serial pulmonary function tests suggesting progression of interstitial lung disease.

Differential diagnosis

Post-Covid Fibrosis with Venous-thromboembolism

Dr. Shamim Ahmed (Associate professor): After the identification of the first case of coronavirus disease (COVID-19) at Wuhan, China in 2019, it is now still responsible for the global pandemic. COVID-19 disease involves not only the lung but also affects the heart, liver, and kidneys, leading to death. Most recent data showed that COVID-19 disease is responsible for coagulopathy. The association of deep vein thrombosis (DVT) with pulmonary embolism (PE) in COVID-19 patients is poorly understood. So far, no placebo-controlled randomized trials have been conducted, so it is difficult to establish the true risk of venous thromboembolism in COVID-19 patients.

Several observational studies showed that venous thromboembolism (VTE) is surprisingly high in COVID-19 patients, even patients treated with standard therapy and pharmacological thromboprophylaxis. Eleven studies were conducted to assess the incidence of venous thromboembolic events in patients with COVID-19 in ICU and general wards, which showed that the overall incidence of VTE ranged from 4.0-42.0%. A meta-analysis by Lua et al. reported the pooled incidence rate of VTE of 21% among hospitalized patients.[6] Different factors are responsible for thrombosis in COVID-19 disease, among them hypercoagulable state, endothelial injuries, immobility, and decreased venous blood flow is common.[7]

Diagnosis of PE in COVID-19 patients is challenging because symptoms and signs can overlap with COVID-19 infection or its associated complications such as myocarditis, acute respiratory distress syndrome (ARDS), or pleural effusion. The presence of one or more predisposing factors for VTE and risk score assessment by the Wells score or the Geneva clinical prediction score may be useful to avoid unnecessary tests.

The diagnostic approach of PE is different between stable and unstable patients. The hemodynamically unstable patient requires CTPA but mobilizing critically ill patients outside the ICU for CTPA may be troublesome and there has a risk of contamination. Stable patients with suspected PE are initially evaluated with a D-dimer test if there is a low or intermediate risk of VTE. But many COVID-19 infection patients may have high levels of D-dimer due to other causes- inflammation, disseminated intravascular coagulation, old age, and infection suggesting the need for CTPA to initially rule-out test for pulmonary embolism.[8] Transthoracic echo may indicate RV overload and/or dysfunction or even a right-sided thrombus.[9]

Dr Susanta Kumar Paul (Resident): During the hospital course, the patient developed sudden visual loss of the right eye, followed by the left eye with weakness, tingling, and numbness of both lower limbs. On examination of the eye, the visual acuity of the right eye was non-perception of light and 6/60 in the left eye. Pupillary light reflex was absent in the right eye and brisk in the left eye. Ocular motility was full in all gazes. Fundoscopic examination indicated right retinal whitening with hemorrhage and cotton wool spots compatible with central retinal artery occlusion (CRAO). The left eye was normal.

Fundal photography revealed retinal whitening with hemorrhage in the right eye and cotton wool spots in the left eye (Figure-2). Fluorescence angiography showed delayed retinal arterial and arterio-venous filling in the right eye feature suggestive of central retinal artery occlusion. Left eye optic disc was pale and normal arterio-venous filling (Figure-3). Neurological examination of the lower limb revealed right foot drop with power 4/5, and jerks were diminished with planter equivocal. Touch and pain sensation was diminished in glove stocking pattern with intact vibration and position sense.

Magnetic Resonance Imaging (MRI) of the brain and nerve conduction study (NCS) of the lower limb was used to evaluate neurological problems. MRI of the brain showed subacute cerebral infraction (Figure-4) and severe motor and sensory neuropathy of the lower limb. Computed tomography pulmonary angiography (CTPA), MRV of the brain, and serum B12 and B9 level was unremarkable.

Dr Rajashish Chakrabortty (Associate Professor): As the patient has both arterial (Central retinal artery occlusion and cerebral ischaemic stroke) and venous thrombosis (DVT), anticoagulant deficiency might be a cause.

Dr Susanta Kumar Paul (Resident) : For further evaluation of deep vein thrombosis, ischemic cerebral infarction, and central retinal artery occlusion, the coagulation profile of the patient was done. The coagulation profile is shown in Table-I. The

Table-I

Laboratory and radiological investigations

Investigations	Findings	Reference value
Hemoglobin (g/dL)	10.8	13-17
ESR(mm in1st hour)	81	0-10
White cell count(/cmm)	12,100	4,000-11,000
Neutrophils (%)	88%	40-80
Lymphocytes (%)	9%	20-40
serum creatinine (mg/dl)	0.9	0.6-1.3
SGPT(ALT) U/L	74	Upto 45
troponin I(ng/mL)	0.01	0.00-0.10
NT-pro-BNP(pg/mL)	215	<75years old: 0-300
HbA1c %	6.1	4.5-6.3
D-dimer (µgFEU/mL)	3.697	0-0.5
Sputum culture & sensitivity	No growth of specific species	
High-resolution chest tomography (HRCT) of chest	Ground glass opacities with septal thickening and a few fibrotic bands are noted in different segments of both lung fields predominantly in peripheral regions.	
RT-PCR for Covid-19	Negative	
Color Doppler echocardiography	No RWMA at rest, left ventricular ejection fraction 62%.	
Doppler ultrasound B-mode	Chronic thrombus with partial recanalization in the left common femoral vein cranial to the saphenofemoral junction.	
Protein S	15%	90-130%
Protein C	70%	70-130%
Anti-thrombin III	130%	80-120%
Serum Homocysteine	14.1	5.46-16.20µmol/L
JAK2 V617F mutation	negative	
IgG	12.3	7.67-15.90g/l
IgM	0.304	0.37-2.86g/l
IgA	0.623	0.61-3.56g/l
C3	0.776	0.9-1.8g/l
C4	0.303	0.1-0.4 g/l
Protein electrophoresis	Alpha-2 region raised	
Coomb's test (Direct&indirect)	Negative	
APTT	30	20-40 Seconds
Fibrinogen	421	200-400 mg/L
cANCA	Negative	
pANCA	Negative	

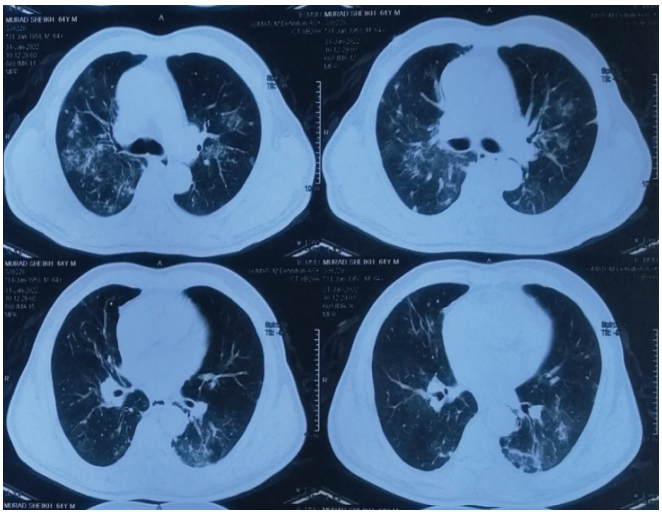

Figure-1: HRCT scan of the chest: Bilateral pulmonary inflammatory lesion

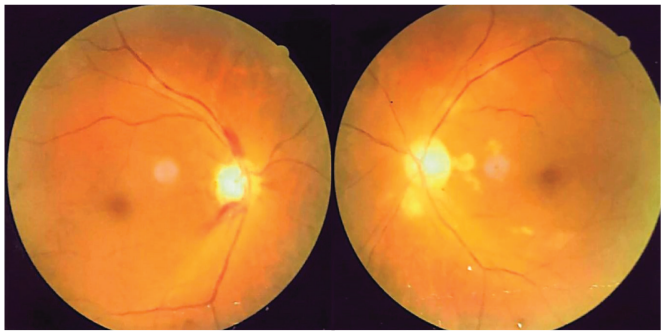

Figure-2: Fundoscopy: Pale optic disc, hemorrhage in the right eye, and exudates of the left eye

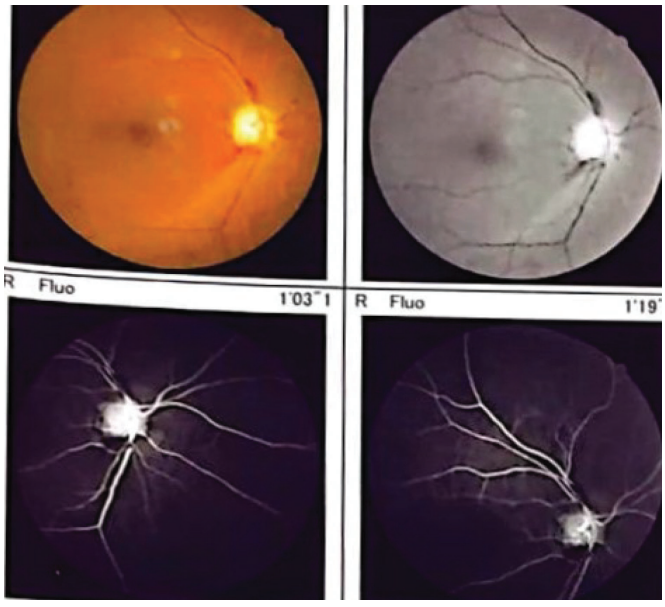

Figure-3 (a): Fluorescence angiography showing delayed retinal artery and arteriovenous filling of the right eye

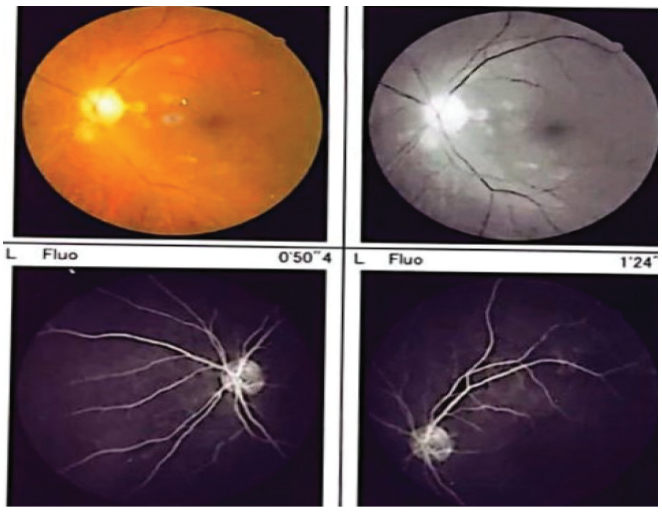

Figure-3 (b): Fluorescence angiography showing pale disc in the left eye

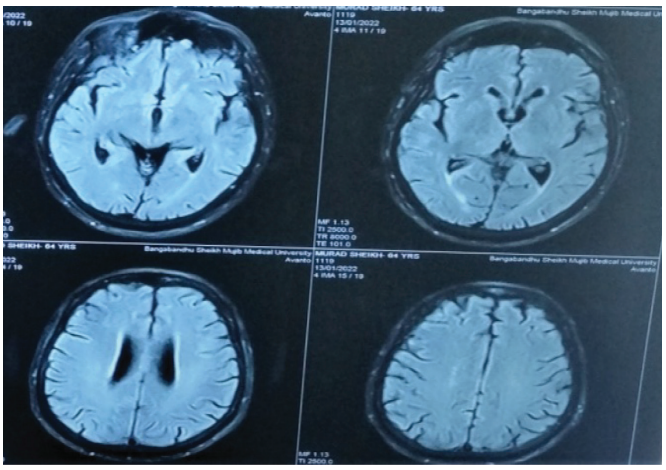

Figure-4. MRI of the brain(T2 FLAIR) showing hyperintense signal change at the left parietal region

coagulation profile showed a significant reduction of Protein S with normal protein C, anti-thrombin III, and homocysteine levels. JAK-2 mutation, protein electrophoresis, serum immunoglobulin, cANCA, and pANCA were also normal.

Final diagnosis

Dr. Rajashish's diagnosis: Central retinal artery occlusion, ischemic cerebral infarction, and deep vein thrombosis of the left femoral vein due to protein S deficiency.

Discussion

Professor Dr Mohammed Atiqur Rahman: Protein S (PS) is a vitamin K-dependent natural anticoagulant and acts as a

cofactor to facilitate the action of activated protein C on its substances, activated factor V, and activated factor VIII. Hereditary deficiency of Protein S is well documented for causing venous thromboembolism, but the pathogenesis of arterial thrombosis due to Protein S deficiency is much less recognized.[10]

Protein S deficiency is an autosomal disorder that mostly occurs in the heterozygous and occasionally homozygous state. The heterozygous condition occurs in about 2% of patients with venous thromboembolism. Rarely PS deficiency occurs as a homozygous state during the neonatal or infant period manifesting as purpura fulminans.[11]

At first, Girolami et al reported that both venous and arterial thrombosis might occur in a thrombophilic state.[12] A systematic analysis of literary case reports of Protein S deficiency conducted by Hasan et al showed that different circulation and regions in the body could be affected by Protein S deficiency, the most common being cerebral and peripheral followed by coronary circulation.[13] The deficiency of Protein S is a cause of otherwise unexplained strokes in young patients.[14] Retinal artery occasion is an ocular emergency. Generalized atheromatous change associated with diabetes mellitus, hypertension, or embolism from atherosclerotic plaques of the carotid arteries or cardiac thrombi is the main cause. It is rare in young. The average age of onset is between 60-70 years.[15] Studies showed that protein C deficiency, antithrombin III, factor V Leiden mutation, increased Factor V, lipoprotein A are responsible for retinal artery thrombosis.[16] Protein S deficiency is a very rare cause of retinal artery occlusion. The clinical manifestations of Protein S deficiency are venous thromboembolism, arterial thrombosis, and recurrent pregnancy loss.[17]

Dr Rajashish Chakrabortty (Associate professor): Different authors in different countries reported the association between Protein S deficiency and thromboembolic disorders. However, there is a controversial association between Protein S deficiency and arterial thrombosis. Many case reports and small case series explain Protein S deficiency is one factor in patients with arterial thrombosis, most commonly stroke at a young age.[18,19] However, prospective and cohort studies did not support the evidence that Protein S deficiency increases the risk of arterial thrombosis.

Mutations in the PROS1 gene cause protein S deficiency. According to the etiology, PS deficiency is classified into congenital and acquired. The congenital PS deficiency is classified into three forms (type I , type II , and type III) based on the antigen level of total, free and functional activity of Protein S.[20] Acquired PS deficiencies are related to several diseases, which include chronic liver disease disseminated intravascular coagulation, pregnancy, HIV, varicella, systemic lupus erythematosus, sickle cell disease, and drugs (oral warfarin, contraceptive pills, and estrogen therapy).[21] The exact prevalence of Protein S deficiency in the Bangladeshi population is unknown. Dykes et al have determined the prevalence of Protein S deficiency to be between 0.03% and 0.13% in the general population in a study involving 3,788 Scottish volunteers.[22] The estimated prevalence in the Japanese population is 1.0-2.0%. The PS deficiency is 5-10 times higher in Japanese people compared to Caucasians. The factor Leiden mutation is common in white populations. This mutation is rare and has never been found in Japanese and Asian populations. The occurrence of thrombophilic disorder is equal between males and females.[10]

There are many case reports of retinal artery thrombosis or branch retinal artery thrombosis due to protein C deficiency.[23] This case is unique because most of the case reports showed that Protein S deficiency is associated with venous and cerebral thrombosis followed by coronary circulation. However, retinal artery thrombosis due to Protein S deficiency is very rare.

Dr Fahmida (Resident): How will you diagnose protein S deficiency?

Dr Shuvo (Medical officer): Diagnosis of protein S deficiency depends on measurement of free protein S assay followed by protein S activity and exclusion of secondary cause of protein S deficiency.

Dr Hamza (Resident): What is the confirmatory test for protein S deficiency?

Dr Shamim Ahmed (Associate professor): Molecular genetic testing can confirm the diagnosis by detecting the variation in the PROS1gene which is responsible for protein S deficiency.

Dr Sanjoy (Resident): What is the treatment of protein S deficiency?

Professor Dr Mohammed Atiqur Rahman: There is no specific treatment for the patient with protein s deficiency. Anticoagulation is used to treat and prevent the recurrence of DVT or pulmonary embolism. Heparin is the drug of choice. Direct oral anticoagulant(Rivaroxaban, apixaban, dabigatran) can be used. Patients with protein S deficiency without a history of DVT or pulmonary embolism usually don't require any treatment except at times during surgery, pregnancy, immobilization, or trauma. Genetic counseling may be beneficial for the affected individuals and their families.

Dr. Abir (Resident): How long anticoagulants should be continued?

Dr. Rajashish Chakrabortty (Associate professor): Patients with symptomatic DVT or PE anticoagulants should be continued for life long.

Dr. Dip Jyoti (Resident): What is the life expectancy of a patient with protein S deficiency?

Dr Shamim Ahmed (Associate professor): There is no available data regarding the life expectancy of a patient with protein S deficiency, and it depends on the severity of the symptoms.

Though Patient with protein S deficiency has a risk of developing DVT or PE 2 to 11times in comparison with those without deficiency. Sometimes many people will never develop a complication.

References

1. Antoniou KM, Margaritopoulos GA, Tomassetti S, Bonella F, Costabel U, Poletti V. Interstitial lung disease. Eur Respir Rev. 2014 Mar;23(131):40–54.
2. Margaritopoulos GA, Kokosi MA, Wells AU. Diagnosing complications and co-morbidities of fibrotic interstitial lung disease. Expert Rev Respir Med. 2019 Jul;13(7):645–58.
3. Navaratnam V, Fogarty AW, McKeever T, Thompson N, Jenkins G, Johnson SR, et al. Presence of a prothrombotic state in people with idiopathic pulmonary fibrosis: a population-based case-control study. Thorax. 2014 Mar;69(3):207–15.
4. Dalleywater W, Powell HA, Fogarty AW, Hubbard RB, Navaratnam V. Venous thromboembolism in people with idiopathic pulmonary fibrosis: A population-based study. Eur Respir J. 2014 Dec;44(6):1714-5.
5. Boonpheng B, Ungprasert P. Risk of venous thromboembolism in patients with idiopathic pulmonary fibrosis: a systematic review and meta-analysis. Sarcoidosis, Vasc Diffus Lung Dis. 2018;35(2):109–14.
6. Lu Y-F, Pan L-Y, Zhang W-W, Cheng F, Hu S-S, Zhang X, et al. A meta-analysis of the incidence of venous thromboembolic events and impact of anticoagulation on mortality in patients with COVID-19. Int J Infect Dis. 2020 Nov;100:34–41.
7. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020 Apr;18(4):844–7.
8. Zuckier LS, Moadel RM, Haramati LB, Freeman LM. Diagnostic Evaluation of Pulmonary Embolism During the COVID-19 Pandemic. J Nucl Med. 2020 May;61(5):630-631.
9. Tal S, Spectre G, Kornowski R, Perl L. Venous Thromboembolism Complicated with COVID-19: What do we know so far? Acta Haematol. 2020;143(5):417–24.
10. Wagh SB, Anadure R, Dutta V, Sandhu MS, Trehan R. Isolated Protein S deficiency presenting as catastrophic systemic arterial and subsequently venous thrombosis. Australas Med J. 2012;5(8):424-8.
11. Brouwer J-LP, Lijfering WM, Ten Kate MK, Kluin-Nelemans HC, Veeger NJGM, van der Meer J. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of Protein S, protein C or antithrombin. Thromb Haemost. 2009; 101(1) : 93–9.
12. Girolami A, Simioni P, Lazzaro AR, Cordiano I. Severe arterial cerebral thrombosis in a patient with Protein S deficiency (moderately reduced total and markedly reduced free protein S): a family study. Thromb Haemost. 1989;61(1):144–7.
13. Hasan, P Mozazfia KT, Saleh MAD, Hasan D. A systematic analysis of literary case reports of protein S deficiency implicated in pathogenesis of arterial thrombosis. J Cardiol Cardiovascular Therap. 2017;6(2):112-121.
14. Wang Z-H, Zhao Z-J, Xu K, Sun G-B, Song L, Yin H-X, et al. Hereditary protein S deficiency leads to ischemic stroke. Mol Med Rep. 2015;12(3):3279–84.
15. Feltgen N, Schmidt D, Hansen L. [Occlusion of the retinal artery]. Ophthalmologe. 2003 Aug;100(8):651–7.
16. Kuhli-Hattenbach C, Hellstern P, Miesbach W, Kohnen T, Hattenbach L-O. Selective Thrombophilia Screening in Young Patients with Retinal Artery Occlusion. Ophthalmologica. 2016;235(4):189–94.
17. Edlich RF, Cross CL, Dahlstrom JJ, Long WB 3rd. Modern concepts of the diagnosis and treatment of purpura fulminans. J Environ Pathol Toxicol Oncol. 2008;27(3):191–6.
18. Hooda A, Khandelwal PD, Saxena P. Protein S deficiency: Recurrent ischemic stroke in young. Ann Indian Acad Neurol. 2009 Jul;12(3):183-4.
19. Soare AM, Popa C. Deficiencies of proteins C, S, and antithrombin and factor V Leiden and the risk of ischemic strokes. J Med Life. 2010;3(3):235–8.
20. Van Cott EM, Ledford-Kraemer M, Meijer P, Nichols WL, Johnson SM, Peerschke EIB et al. Protein S assays: An analysis of North American Specialized Coagulation Laboratory Association Proficiency Testing. Am J Clin Pathol. 2005;123(5):778–85.
21. Ten Kate MK, van der Meer J. Protein S deficiency: A clinical perspective. Haemophilia. 2008 Nov;14(6):1222–8.
22. Dykes AC, Walker ID, McMahon AD, Islam SI, Tait RC. A study of Protein S antigen levels in 3788 healthy volunteers: influence of age, sex and hormone use, and estimate for the prevalence of deficiency state. Br J Haematol. 2001 Jun;113(3):636–41.
23. Ghassemi F, Abdi F, Esfahani M. Ophthalmic manifestations of congenital protein C deficiency: A case report and mini-review. BMC Ophthalmol. 2020;20(1):282.