

Warfarin-Induced Skin Necrosis Due to Protein C Deficiency in a Dialysis Patient

Diyaliz Hastasında Protein C Eksikliğine Bağlı Warfarin-İlişkili Deri Nekrozu

ABSTRACT

Protein-C (PC) is a vitamin-K-dependent anticoagulant proenzyme produced by the liver. PC deficiency may cause both venous and arterial thromboses. In patients with PC deficiency, warfarin further decreases PC activity and causes thrombosis of skin arterioles leading to skin necrosis.

A 59-year-old female was admitted with dyspnea, cough, hoarseness and edema in her neck and arms. She had chronic kidney disease for 20 years. She had been on hemodialysis for 8 years but had been switched to peritoneal dialysis due to vascular access problems caused by multiple venous thromboses. With a pre-diagnosis of Superior Vena Cava (SVC) syndrome, cavography was performed and near-total occlusion of the SVC was detected. Balloon dilatation was performed and warfarin 5 mg and enoxoparin 40 mg were started. Within a day, necrotic and well-demarcated lesions 4x5 cm in size appeared on the arm. Warfarin was stopped and enoxoparin was continued. After 2 weeks, plasma PC activity was found to be significantly low (40% of normal). The diagnosis of "warfarin-induced skin necrosis in a patient with PC deficiency" was established. Skin lesions promptly and completely recovered after the treatment.

PC deficiency should be considered in dialysis patients with multiple thromboses, vascular access problems and warfarin-induced skin necrosis.

KEY WORDS: Protein-C deficiency, Warfarin-induced skin necrosis, Dialysis, Superior vena cava syndrome

ÖZ

Protein-C (PC), karaciğer tarafından üretilen, vitamin-K'ya bağımlı antikoagülan bir pro-enzimdir. PC eksikliği hem venöz hem arteriyel trombozlara neden olabilir. Warfarin, PC eksikliği olan hastalarda PC seviyesini daha da düşürerek, derideki arteriollerde trombozlara yol açar ve deri nekrozlarına sebep olur.

Elli dokuz yaşında kadın hasta nefes darlığı, öksürtük, ses kısıklığı, boyunda ve kollarda şişlik nedeniyle başvurdu. Yirmi yıldır kronik böbrek yetersizliği tanısı olan hasta 8 yıl hemodiyalize girmiş fakat birden çok vasküler trombozları olması nedeniyle damar giriş yolu problemi dolayısıyla periton diyalizine geçilmiş. Superior vena kava (SVK) sendromu ön tanısıyla yapılan venokavografisinde SVK proksimalinde tama yakın tromboz saptandı. Balon anjiyoplasti yapılarak stenoz genişletildi. Warfarin 5 mg ve enoksaparin 40 mg bid tedavisi başlandı. Bir gün sonra, sol kolda 4x5 cm keskin sınırlı, çevresi eritemli, ağrılı, hemorajik büllöz nekrotik lezyon gelişti. Warfarin tedavisi hemen kesildi, enoksaparine devam edildi. İki hafta sonra yapılan tetkiklerde plazma PC aktivitesi düşük bulundu (normalin %40'ı). "PC eksikliği olan hastada warfarine bağlı deri nekrozu" tanısı kondu. Tedavi sonucunda hastanın deri lezyonları tamamen geriledi.

PC eksikliği, birden çok trombozu ve damar giriş yolu problemleri olan ve warfarine bağlı deri nekrozları gelişen diyaliz hastalarında mutlaka akla gelmelidir.

ANAHTAR SÖZCÜKLER: Protein C eksikliği, Warfarinle ilişkili deri nekrozu, Diyaliz, Superior vena kava sendromu

Abdullah ÖZKÖK¹
Hande ÖZPORTAKAL¹
Murat AŞIK²
Serçin ÖZKÖK²
Özlem ALKAN¹
Memduha BOYRAZ¹
Gökhan GÖNENLİ³
Banu ŞAHİN YILDIZ¹
Kübra AYDIN BAHAT¹
Ali Rıza ODABAŞ¹

- 1 Istanbul Medeniyet University, Goztepe Training and Research Hospital, Department of Nephrology, Istanbul, Turkey
- 2 Istanbul Medeniyet University, Goztepe Training and Research Hospital, Department of Radiology, Istanbul, Turkey
- 3 Koc University, School of Medicine, Department of Internal Medicine, Istanbul, Turkey



Received : 10.03.2017

Accepted : 17.06.2017

Correspondence Address:

Abdullah ÖZKÖK
 Istanbul Medeniyet Üniversitesi,
 Göztepe Eğitim ve Araştırma Hastanesi,
 Nefroloji Bölümü, Istanbul, Turkey
 Phone : +90 216 570 92 97
 E-mail : abduallahozkok@yahoo.com

INTRODUCTION

Protein C (PC) is a vitamin-K dependent anticoagulant proenzyme that is produced in the liver. PC deficiency may cause both venous and arterial thromboses and specific entities such as neonatal purpura fulminans and warfarin-induced skin necrosis. PC deficiency may be hereditary or acquired (1). Warfarin further decreases the already low activity of protein C and it causes multiple thromboses of skin arterioles leading to hemorrhagic and necrotic skin lesions (2). Patients with chronic kidney disease (CKD) are known to have a high risk of thrombosis but the exact pathophysiological mechanisms are not known. However, recent studies have suggested a contribution of acquired PC deficiency to the thrombophilia observed in dialysis patients (3,4). Herein, we present a dialysis patient with superior vena cava (SVC) syndrome and protein C deficiency who developed warfarin-induced skin lesions.

CASE REPORT

A 59-year-old female was admitted with dyspnea, cough, hoarseness and edema in her neck and arms. She had CKD due to chronic pyelonephritis for 20 years. She had been on hemodialysis treatment for 8 years but she had recently been switched to peritoneal dialysis due to vascular access problems caused by multiple venous thromboses. On physical examination, venous distention of the neck and chest wall was found. The chest X-ray revealed minimal pleural effusion on the left side. Baseline biochemical parameters are presented in Table I. With a pre-diagnosis of SVC syndrome, cavography was performed by the interventional radiology department



Figure 1: Near-total occlusion of the superior vena cava on angiography.



Figure 2: Warfarin-induced necrotic and hemorrhagic skin lesions in the left arm.

Table I: Results of the baseline biochemical parameters.

Parameters	Values	Reference Values
Creatinine (mg/dL)	8.23	(0.7-1.4)
Uric Acid (mg/dL)	5.9	(2.6-6)
Urea (mg/dL)	101	(21-43)
Calcium (mg/dL)	10	(8.5-10.5)
Phosphorus (mg/dL)	4.8	(2.7-4.5)
Parathormone (pg/mL)	391	(15-68)
ALP (U/L)	151	(30-135)
ALT (U/L)	8	(5-45)
LDH (U/L)	159	(0-247)
GGT (U/L)	58	(5-85)
T. Cholesterol (mg/dL)	145	(130-200)
Triglyceride (mg/dL)	70	(<30)
Total protein (g/dL)	7.1	(6.0-8.0)
Albumin (g/dL)	3.3	(3.2-5.5)
ESR (mm/h)	45	(0-20)
CRP (mg/dL)	4.5	(0-0.8)
WBC(μ L)	7800	(4000-11000)
Hb (g/dL)	12.1	(12-18)
Platelet (μ L)	214000	(150000-500000)
PT (sec)	14.1	(11.5-15.5)
INR	1.07	(0.8-1.25)
aPTT (sec)	21.1	(25.6-35.2)

ALP: Alkaline phosphatase, **ALT:** Alanine aminotransferase, **LDH:** Lactate dehydrogenase, **GGT:** Gamma-glutamyl transferase, **T. Cholesterol:** Total cholesterol, **ESR:** Erythrocyte sedimentation rate, **CRP:** C-reactive protein, **WBC:** White blood cell, **Hb:** Hemoglobin, **PT:** Prothrombin time, **INR:** International normalized ratio, **aPTT:** Activated partial thromboplastin time.

and revealed near-total occlusion of the proximal part of SVC (Figure 1). Balloon dilatation was performed to the proximal part of SVC and warfarin 5 mg and low-molecular-weight heparin (enoxoparin 40 mg bid) were started simultaneously. Within 24 hours of these treatments, necrotic, hemorrhagic, painful and well-demarcated lesions 4x5 cm in size appeared on the left arm (Figure 2). Warfarin was immediately stopped and enoxoparin was continued. Local supportive treatments and sterile dressings were used for the lesions. After 2 weeks of discontinuation of warfarin, tests for protein C, S and anti-thrombin-3 activities were performed and plasma protein C activity was found to be significantly low (40% of normal). The diagnosis of “warfarin-induced skin necrosis in a patient with PC deficiency” was established. At follow-up, the skin lesions promptly recovered completely.

DISCUSSION

PC is a vitamin K-dependent protein synthesized in the liver. PC circulates in the blood as a zymogen and when activated, act as an anticoagulant serine protease enzyme that inhibits the coagulation cascade by degrading F5a and F8a with the help of its cofactor protein S (5).

PC deficiency is associated with a tendency to thromboembolism including deep vein thrombosis, pulmonary embolism, arterial thrombosis, stroke, neonatal purpura fulminans, fetal loss and warfarin-induced skin necrosis. PC deficiency may be hereditary or acquired. Hereditary PC deficiency is an autosomal dominant disease. More than 160 mutations have been described in the gene for PC located on chromosome 2 (2q1314) (1,6). The prevalence of inherited PC deficiency in the general population is 0.2-0.5% but the prevalence is higher (2-5%) in patients with venous thromboembolism (7-9).

Acquired PC deficiency may also occur in various clinical situations such as liver diseases, hepatic congestion, disseminated intravascular coagulation, acute infections, trauma, CKD, certain malignancies, vitamin K deficiency, use of vitamin K antagonists and rarely the presence of acquired inhibitor autoantibody against PC (10-14).

Warfarin-induced skin necrosis is one of the specific clinical manifestations of PC deficiency. PC has a half-life of 6 hours, which is significantly shorter than that of other vitamin K-dependent coagulation factors. Thus, during the initial phase of treatment with warfarin, a transient hypercoagulable state occurs due to earlier inhibition of PC, leading to vascular occlusion and skin necrosis. Prompt discontinuation of warfarin and administration of low-molecular-weight heparin should be the first steps for the treatment of warfarin-induced skin necrosis. Other treatment modalities may include protein C concentrate and fresh frozen plasma (15).

Patients with CKD are known to have a tendency for thrombosis but the exact pathophysiological mechanisms are not known (3,4). In the prospective study by Ghisdal et al (3), 310 dialysis patients were screened for 7 thrombophilic factors before kidney transplantation and 1 month after the transplantation. One month after transplantation, the prevalence of thrombophilic factors was significantly decreased from 74.4 to 44.7%. Specifically, prevalence of PC deficiency was found to significantly decrease from 12.1% to 1.9%. However, the incidence of cardiovascular or thromboembolic events 1 year after transplantation was similar between the patients with and without thrombophilia. In summary, in this study, thrombophilic factors were found to be highly prevalent in dialysis patients and furthermore most thrombophilic factors were corrected 1 month after transplantation. In another study, frequency of thrombophilic factors including PC deficiency was higher in hemodialysis patients with vascular access thrombosis (VAT) compared to that of patients without VAT (4). Similar to the previous study, all thrombophilic factors including PC deficiency were resolved after transplantation.

Before warfarin administration, our patient had multiple VAT ultimately leading to the SVC syndrome. The exact etiology of multiple VAT is not known but acquired thrombophilic factors such as PC deficiency may contribute to this exaggerated tendency to thrombosis.

In the differential diagnosis of necrotic skin lesions, leukocytoclastic vasculitis, cholesterol embolization syndrome, cryoglobulinemic vasculitis and calciphylaxis should also be considered. Calciphylaxis, also known as calcific uremic arteriopathy, is mostly associated with hyperparathyroidism and high calcium-phosphorus product in patients with end-stage renal disease. However, calciphylaxis cases have also been reported in the absence of hyperparathyroidism and renal dysfunction (16-18). In our case, lack of significant hyperparathyroidism, normal serum calcium and phosphorus levels, prompt recovery of necrotic lesions and documentation of decreased protein C enzyme activity were considered to be in favor of the diagnosis of “warfarin-induced skin necrosis and PC deficiency” rather than calciphylaxis. The pathogenesis of most of these diseases is not well known and they may share common pathophysiological pathways. It may therefore be challenging and difficult to establish an exact diagnosis in such cases.

In conclusion, protein C deficiency should be considered in patients with multiple thrombosis and warfarin-induced skin necrosis. CKD patients are known to have tendency of thrombosis however the etiology of this thrombophilic state is not currently known. Further studies that address the possible contribution of acquired protein C deficiency to thrombophilia observed in CKD patients are needed.

REFERENCES

1. Reitsma PH: Protein C deficiency: From gene defects to disease. *Thromb Haemost* 1997;78:344-350
2. Nazarian RM, Van Cott EM, Zembowicz A, Duncan LM: Warfarin-induced skin necrosis. *J Am Acad Dermatol* 2009;61:325-332
3. Ghisdal L, Broeders N, Wissing KM, Mena JM, Lemy A, Wijns W, Pradier O, Donckier V, Racapé J, Vereerstraeten P, Abramowicz D: Thrombophilic factors in Stage V chronic kidney disease patients are largely corrected by renal transplantation. *Nephrol Dial Transplant* 2011;26:2700-2705
4. Nampoory MR, Das KC, Johnny KV, Al-Hilali N, Abraham M, Easow S, Saed T, Al-Muzeirei IA, Sugathan TN, Al Mousawi M: Hypercoagulability, a serious problem in patients with ESRD on maintenance hemodialysis, and its correction after kidney transplantation. *Am J Kidney Dis* 2003;42:797-805
5. Dahlbäck B, Villoutreix BO: Regulation of blood coagulation by the protein C anticoagulant pathway: Novel insights into structure-function relationships and molecular recognition. *Arterioscler Thromb Vasc Biol* 2005;25:1311-1320
6. Foster DC, Yoshitake S, Davie EW: The nucleotide sequence of the gene for human protein C. *Proc Natl Acad Sci U S A* 1985;82:4673-4677
7. Tait RC, Walker ID, Reitsma PH, Islam SI, McCall F, Poort SR, Conkie JA, Bertina RM: Prevalence of protein C deficiency in the healthy population. *Thromb Haemost* 1995;73:87-93
8. Mateo J, Oliver A, Borrell M, Sala N, Fontcuberta J: Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism results of the Spanish Multicentric Study on Thrombophilia (EMETStudy). *Thromb Haemost* 1997;77:444-451
9. Heijboer H, Brandjes DP, Büller HR, Sturk A, ten Cate JW: Deficiencies of coagulation inhibiting and fibrinolytic proteins in outpatients with deep vein thrombosis. *N Engl J Med* 1990;323:1512-1516
10. Griffin JH, Mosher DF, Zimmerman TS, Kleiss AJ: Protein C, an antithrombotic protein, is reduced in hospitalized patients with intravascular coagulation. *Blood* 1982;60:261-264
11. Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M, Mannuccio Mannucci P: Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. *Hepatology* 2005;41:553-558
12. Angchaisuksiri P: Coagulopathy in malaria. *Thromb Res* 2014;133:5-9
13. Warkentin TE, Cook RJ, Sarode R, Sloane DA, Crowther MA: Warfarin induced venous limb ischemia/gangrene complicating cancer: A novel and clinically distinct syndrome. *Blood* 2015;126:486-493
14. Mitchell CA, Rowell JA, Hau L, Young JP, Salem HH: A fatal thrombotic disorder associated with an acquired inhibitor of protein C. *N Engl J Med* 1987;317:1638-1642
15. Schramm W, Spannagl M, Bauer KA, Rosenberg RD, Birkner B, Linnau Y, Schwarz HP: Treatment of coumarin induced skin necrosis with a monoclonal antibody purified protein C concentrate. *Arch Dermatol* 1993;129:753-756
16. Hayashi M, Takamatsu I, Kanno Y, Yoshida T, Abe T, Sato Y; Japanese Calciphylaxis Study Group: A case-control study of calciphylaxis in Japanese end-stage renal disease patients. *Nephrol Dial Transplant* 2012;27:1580-1584
17. Brandenburg VM, Kramann R, Specht P, Ketteler M: Calciphylaxis in CKD and beyond. *Nephrol Dial Transplant* 2012;27:1314-1318
18. Saifan C, Saad M, El-Charabaty E, El-Sayegh S: Warfarin-induced calciphylaxis: A case report and review of literature. *Int J Gen Med* 2013;6:665-669