Late onset Warfarin induced skin necrosis in human immunodeficiency virus infected patient with pulmonary tuberculosis

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Abstract

The incidence of Warfarin-induced skin necrosis (WISN) is very low 0.01-0.10%. The majority of the WISN cases appear between day 3 and 6 of onset of Warfarin therapy. The cases of late onset WISN are rarely seen. We report a case of late onset WISN in a young human immunodeficiency virus positive female patient with thrombotic pulmonary embolism and reactivation of pulmonary tuberculosis.

Key words: Human immunodeficiency virus, late onset, skin necrosis, Warfarin

INTRODUCTION

Warfarin is a widely used anticoagulant or blood-thinner. Warfarin-induced skin necrosis (WISN) affects one in every 10,000 patients who are on Warfarin. The incidence of Warfarin-induced skin necrosis is only 0.01-0.10% of patients on Warfarin. WISN is a rare but potentially fatal complication of Warfarin therapy in which there is paradoxical blood clotting. Blood clots block the blood vessels and cause necrosis.

The majority of cases appear between day 3 and 6 of therapy. Late onset Warfarin-induced skin necrosis occurs occasionally from 15 days to 15 years after onset of therapy.

The initial treatment remains supportive and conservative. Although, discontinuation of Warfarin has not been shown to alter the outcome it is generally recommended. Heparin should be started in high-doses and vitamin K and fresh frozen plasma (FFP) should be administered to restore protein C and S levels.

CASE REPORT

A 29-year-old female patient, referred from general medicine department was presented with asymptomatic purplish and black colored skin lesions over the face (around lips) and extremities since past 15 days. Patient was a known and treated case of pulmonary tuberculosis and had taken complete anti-tubercular treatment 2 years back. Three months back, before the development of skin lesions, patient came to our hospital with complains of continuous cough and heaviness in chest. 2 D echo was carried out, which showed blocking in left pulmonary artery due to thrombus with right ventricular enlargement. Patient was put-on oral Warfarin 2.5 mg once daily to dissolve the thrombus. At that time her sputum was negative for acid fast bacilli (AFB). Two and half months later the patient came back with worsening of her chest complaints and on investigation she was found to have reactivation of pulmonary...
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tuberculosis (sputum positive for AFB). She also had the above mentioned skin lesions for which she was referred to skin out patient department (OPD). General examination revealed her poor general condition with multiple purple to black ecchymotic patches around mouth, upper, and lower extremities [Figures 1 and 2]. Skin over right knee revealed black eschar surrounded by ecchymotic patch and erythema [Figure 3]. She also had resolving grouped vesicular lesions involving right L3, 4 dermatome, and clinically, suggestive of Herpes zoster. Routine investigations were within normal limits. Prothrombin time international normalized ratio (PTINR) of patient was carried out, which initially was not recordable as it was very high. We advised enzyme linked immune sorbent assay (ELISA) for human immunodeficiency virus (HIV) antibodies taking in to consideration her reactivation of pulmonary tuberculosis, drug reaction, and herpes zoster. ELISA for HIV antibodies was reactive. Then the patient was admitted in medicine ward. Oral Warfarin was stopped and she was given two units of FFP on two alternate days. After giving one FFP, PTINR came down to 4 min, however, the patient died on the 4th day of admission.

DISCUSSION

Warfarin works by inactivating vitamin K-dependent clotting factors II, VII, IX, and X. At the same time, vitamin K-dependent proteins C and S are inactivated these are natural anticoagulants. Half of the activated protein C disappears within 6 h due to its half-life. So, protein C runs out during the first few days of Warfarin therapy, before Factor X and II disappear, which have half-lives of 2-5 days. In some circumstances, this leads to excessive clotting. Skin necrosis affects areas of the body with a high-fat content, such as breasts, thighs, buttocks, and abdomen. The trunk, extremities and face can also be involved. The first sign is usually a purplish bruise-like rash, which over a few days becomes bluish-black with a red rim followed by skin necrosis.

Infection with the HIV is a type of hypercoagulable state associated with a variety of acquired coagulopathies that increase the incidence of venous and arterial thrombosis, including antiphospholipid-anticardoplipin antibodies, increased platelet activation, lupus anticoagulant, elevated plasma factor VII activity, activated protein C resistance, protein C deficiency, and protein S deficiency. There is a paucity of data on the incidence of clinical thrombosis in HIV-infected individuals with protein S deficiency. Previous literature studies have reported thrombotic events in 1.52-18% of HIV-infected patients with protein S deficiency. The pathogenesis of this HIV-related protein S deficiency is poorly understood. Sorice et al. screened for specific anti-protein S antibodies using immunoblotting and showed an overall positivity of 28.6% in HIV-seropositive patients, with a higher prevalence in symptomatic than in asymptomatic patients.

Typically, WISN is reported in middle-aged obese women receiving Warfarin treatment for pulmonary embolism, deep venous thrombosis, myocardial infarction, or valvular heart surgery. Our patient was moderately built young female and was put-on oral Warfarin by physician for thrombotic pulmonary embolism.

The lesions associated with Warfarin-induced skin necrosis are characteristically noted during the 1st week of therapy, commonly appearing between days 3 and 6 of treatment. However, rare cases in which the skin lesions appeared months after beginning therapy, as in our case, have been reported. It is suspected that late-onset Warfarin-induced necrosis is a result of poor compliance with Warfarin dosage schedules, with the patient stopping and subsequently restarting the
medication without heparin coverage.\textsuperscript{[11-13]} Heparin was not given in our case.

Our case was a case of pulmonary tuberculosis with HIV infection and one of the contributing factors for skin necrosis could be hypercoagulability secondary to HIV and tuberculosis.

Bhaijee \textit{et al.}\textsuperscript{[14]} in their case series mentioned that the occurrence of 6 WISN cases in a 40-month period may be attributed to hypercoagulability, secondary to HIV-1 and tuberculosis.

In our case, the diagnosis of WISN was made clinically, as patient had ecchymotic patches and necrotic eschar, which was supported by impaired PTINR. Patient had not taken any other drug apart from Warfarin during past 3 months. Skin biopsy can aid in diagnosis and it usually reveals clotting within blood vessels in the skin without any inflammation. Blood tests for protein C and protein S levels are important to assess the likely pre-disposing causes.

Because of her rapidly deteriorating clinical condition, additional laboratory studies were not performed.

Allowed to run its natural course, WISN is associated with significant morbidity and deaths have been reported in severe cases.\textsuperscript{[2,6,3,9]}

In our case, Warfarin was stopped immediately and patient was given two FFP but in spite of this the patient died, which could be due to associated pulmonary tuberculosis and HIV infection.

The incidence of WISN is very low 0.01-0.10%. In that the cases of late onset WISN is rarely seen. We report a case of late onset WISN in HIV positive patient with thrombotic pulmonary embolism and reactivation of pulmonary tuberculosis.

**REFERENCES**

1. Koch-Weser J. Coumarin necrosis. Ann Intern Med 1968;68:1365-7.
2. DeFranzo AJ, Marasco P, Argenta LC. Warfarin-induced necrosis of the skin. Ann Plast Surg 1995;34:203-8.
3. Chan YC, Valenti D, Mansfield AO, Stansby G. Warfarin induced skin necrosis. Br J Surg 2000;87:266-72.
4. Bissuel F, Berruyer M, Cause X, Dechavanne M, Trepo C. Acquired protein S deficiency: Correlation with advanced disease in HIV-1-infected patients. J Acquir Immune Defic Syndr 1992;5:484-9.
5. Majluf-Cruz A, Silva-Estrada M, Sánchez-Barboza R, Montiel-Manzano G, Treviño-Pérez S, Santoscoy-Gómez M, \textit{et al.} Venous thrombosis among patients with AIDS. Clin Appl Thromb Hemost 2004;10:19-25.
6. Hassell KL, Kressin DC, Neumann A, Ellison R, Marlar RA. Correlation of antiphospholipid antibodies and protein S deficiency with thrombosis in HIV-infected men. Blood Coagul Fibrinolysis 1994;5:455-62.
7. Sorice M, Griggi T, Ancieri P, Circella A, d’Agostino F, Ranieri M, \textit{et al.} Protein S and HIV infection. The role of anticardiolipin and anti-protein S antibodies. Thromb Res 1994;73:165-75.
8. Parsi K, Younger I, Gallo J. Warfarin-induced skin necrosis associated with acquired protein C deficiency. Australas J Dermatol 2003;44:57-61.
9. Ad-El DD, Meirovitz A, Weinberg A, Kogan L, Arieli D, Neuman A, \textit{et al.} Warfarin skin necrosis: Local and systemic factors. Br J Plast Surg 2000;53:624-6.
10. Franson TR, Rose HD, Spivey MR, Maroney J, Libnoch JA. Late-onset, Warfarin-caused necrosis occurring in a patient with infectious mononucleosis. Arch Dermatol 1984;120:927-31.
11. Essex DW, Wynn SS, Jin DK. Late-onset Warfarin-induced skin necrosis: Case report and review of the literature. Am J Hematol 1998;57:233-7.
12. Koduri PR, Parveez R. Lack of compliance and late-onset Warfarin-induced skin necrosis. Am J Hematol 1999;61:218-9.
13. Scarff CE, Baker C, Hill P, Foley P. Late-onset warfarin necrosis. Australas J Dermatol 2002;43:202-6.
14. Bhaijee F, Wainwright H, Meintjes G, Wilkinson RJ, Todd G, De Vries E, \textit{et al.} Warfarin-induced skin necrosis in HIV-1-infected patients with tuberculosis and venous thrombosis. S Afr Med J 2010;100:372-7.

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