CASE REPORT

Anticoagulation therapy for thromboembolism prevention: a case of warfarin-induced skin necrosis in the setting of protein C deficiency

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SUMMARY

Patients with protein C deficiency are at increased risk for thrombotic diseases. Non-vitamin K antagonist anticoagulant options should be considered in patients with warfarin-induced skin necrosis (WISN) in the setting of protein C. We report a 41-year-old African American male patient with WISN and protein C deficiency who was treated with rivaroxaban followed by dabigatran. After 1 month on rivaroxaban, he began experiencing blood in his stools, unrelenting pain in his lower extremities, found it difficult to obtain medication despite having insurance and as a result did not maintain compliance. He was then assessed at the hospital, symptomatically treated and discharged on dabigatran. After 6 weeks, he reported symptomatic relief and less side effects. This case involved a head-to-head clinical comparison of rivaroxaban and dabigatran as alternatives to warfarin anticoagulation therapy.

BACKGROUND

Protein C is a major component of anticoagulation in the human body. Circulating in the bloodstream, it functions by inactivating factors Va and VIIIa, thus inhibiting blood coagulation. Conversely, a deficiency in protein C—an autosomal-dominant disease—increases the risk of developing abnormal coagulopathies. The loss of protein C increases the likelihood of acquiring both venous and arterial thrombi that typically presents with venous thromboembolism, purpura fulminans and disseminated intravascular coagulation. Warfarin, a vitamin K antagonist, is used to reduce the risk of blood clots and thromboembolisms. However, a very rare side effect of warfarin is skin necrosis. To this end, the use of alternative anticoagulants for preventing thromboembolic disease should be considered in patients with warfarin-induced skin necrosis (WISN) in the setting of protein C deficiency. This article involved a clinical comparison of rivaroxaban and dabigatran as alternatives to warfarin therapy.

CASE PRESENTATION

A 41-year-old African American male with an extensive medical history of deep vein thrombosis (DVT) and one episode of pulmonary embolism (PE), presented with swollen and tender legs. Five years prior, he was diagnosed with protein C deficiency after experiencing a PE. The activity of protein C

was 12% of normal. Gene sequencing to identify the mutation was not performed, and his family history did not reveal any symptoms of hypercoagulopathies. At age 37, he received placement of a Greenfield filter to prevent further complications of DVT. He was prescribed warfarin but was non-compliant due to experiencing small skin lesions.

At his current admission, his international normalized ratio (INR) was 0.90, and he was restarted on warfarin to maintain an INR of 2–3. At day 4, he developed worsening painful subcutaneous necrosis throughout his legs. The clinical history of our patient with protein C deficiency combined with recurrent skin lesions was highly suggestive of WISN. Warfarin was immediately stopped, and novel anticoagulants were considered.

We first prescribed rivaroxaban (Xarelto), and after 2 weeks, our patient reported that the painful skin lesions showed very minor improvement. However, after 1 month, he stopped using rivaroxaban due to complications of blood in his stools, continued pain in his lower extremities and difficulty obtaining medication due to cost despite having government insurance. He was without anticoagulation for 1 week when he was readmitted to our facility due to pain on standing, walking and knee flexion. On physical exam, the medial side of both legs showed skin necrosis and ulcerations, with more prominence on the left side (figure 1). His INR level was at 0.99. Venous and arterial Doppler studies showed signs of post-phlebitis changes from old thrombi, but no significant plaque or stenosis. He was treated with enoxaparin, as well as symptomatic relief of the pain with morphine and antibiotics for superficial infections. Following symptomatic improvement, he was discharged 7 days later with a prescription of dabigatran (Pradaxa), which was available with his insurance.

At 6 weeks' follow-up, he reported that the pain and skin lesions had ameliorated while taking dabigatran. He reported notable improvement in his leg pain, and physical examination showed an overall decrease in the size of inflammatory lesions. Compared with his previous treatment with rivaroxaban, he noted that his symptoms recovered faster with dabigatran. Furthermore, he was compliant with dabigatran because it improved his quality of life, was able to return to work and was more economically feasible for him.

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Figure 1 Warfarin-induced necrosis of the left medial leg.

DISCUSSION

Warfarin has been known to cause an acquired form of protein C deficiency by inhibiting synthesis of clotting factors II, VII, IX and X, as well as the regulatory factors proteins C and S.¹ A rare complication of warfarin therapy includes skin necrosis that affects 0.01%–0.1% of patients, with a female:male ratio of 1:4.^{2,3} Predisposing factors include obesity, perimenopausal

age, viral infections, hepatic disease and drug interactions. Deficiency of protein C, protein S or factor V Leiden, antithrombin III, hyperhomocysteinaemia and antiphospholipid antibodies are common underlying risk factors.

In most cases, the presentation of WISN occurs within hours to sometimes weeks after warfarin therapy. These lesions are more likely to occur in areas with subcutaneous fat,⁴ and as observed in our patient, necrosis occurred in the lower extremities. Ischaemia and necrosis of the skin are due to thrombus in capillaries, venules and deep veins within the dermis and subcutaneous layer, which is exaggerated following the initiation of warfarin anticoagulation therapy. While heparin offers resolution for acute symptoms of thrombosis, it may not be a suitable choice for long-term management. However, new case reports indicate that novel oral anticoagulants such as rivaroxaban and dabigatran may be suitable alternatives to warfarin in the setting of skin necrosis.^{3,5}

Our patient was initially trialled with rivaroxaban, a non-vitamin K antagonist. Martinelli *et al* reported its use in a 6-year old girl with WISN who also had protein S deficiency.⁵ They reported the treatment resulted in the disappearance of skin necrosis at 1 year of follow-up. Rivaroxaban was chosen by the authors due to its ability to inhibit both bound and free forms of Factor X.⁶ Furthermore, thrombin can activate protein C, and this natural anticoagulant interaction would not be interrupted with rivaroxaban^{6,7} (figure 2). Although our patient reported slight improvement of pain from skin necrosis, he did not comply to this treatment after 1 month when he began experiencing episodes of haematochezia and difficulty financing the medication.

As an alternative to rivaroxaban, dabigatran (Pradaxa) was started to manage his coagulation disorder. Herman *et al*³ reported the therapeutic used of dabigatran etexilate, a direct thrombin inhibitor, in a 21-year-old woman with WISN due to protein C deficiency. We followed their report, and applied the treatment to our patient. This anticoagulant was well tolerated, with no recurrent skin lesions when the patient was re-examined up to 6 months after initiating therapy. One of the potential side

Figure 2 Simplified coagulation cascade.

effects of dabigatran is prolonged bleeding time from overdose of medication; however, dabigatran toxicity can be reversed with a novel monoclonal antibody called idarucizumab, which was approved by the Food and Drug Administration in October 2015.

A commercial antidote for rivaroxaban is still not available, and factor Xa inhibitor antidotes such as Andexanet alfa are still under clinical development.⁸ In cases of rivaroxaban overdose, prothrombin complex concentrates can be used in its management.^{8,9} However, some studies indicated that administration of prothrombin complexes would not be required for asymptomatic overdose because the ceiling effect and short half-life rivaroxaban would limit the negative effects.¹⁰ In addition, recent years have led to analogues of factor Xa inhibitors such as apixaban. Overall, apixaban appears to be associated with a lower risk of bleeding than its

counterpart analogues¹¹ but has not been reported in setting of WISN.

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Competing interests None declared.

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Learning points

- Our patient was trialed with both rivaroxaban and dabigatran. Although both medications improved his symptoms, dabigatran was preferred due to less side effects, quicker improvement in pain and skin lesions and availability of a rescue drug.
- Currently, there are no guidelines for preventing thromboembolic disease in protein C-deficient patients with WISN. However, this case report highlights that the use of factor Xa and thrombin inhibitors such as rivaroxaban and dabigatran are viable options.
- Overall, the patient experienced faster symptomatic relief and less side effects with dabigatran compared with rivaroxaban. He experienced an overall improvement in his quality of life and, as a result, maintained compliance.

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