CASE REPORT

Warfarin-induced skin necrosis diagnosed on clinical grounds and treated with maggot debridement therapy

Anna Louise Biscoe,¹ Alison Bedlow²

¹Warwick Medical School, Warwick University, Coventry, UK

²Department of Dermatology, South Warwickshire NHS Foundation Trust, Warwick, UK

Correspondence to

Anna Louise Biscoe,
A.Biscoe@warwick.ac.uk

SUMMARY

A patient with a history of deep vein thrombosis presented with painful bruising and blistering on his left leg 7–10 days after warfarin treatment. A complicated 2-month treatment followed, where vasculitis was originally diagnosed from histological findings before the final diagnosis of warfarin-induced skin necrosis (WISN) was made on clinical grounds. Warfarin was stopped, reversed and low molecular weight heparin started but, the lesions had progressed to full thickness necrosis. This was originally treated with conventional surgical debridement before introducing maggot debridement therapy (MDT) in an effort to try to salvage the limb.

symptoms. Also systemic steroids that had been given for vasculitis (the initial diagnosis) were not improving the condition and were therefore reduced.

In addition several surgical debridements were conducted and negative pressure wound (V.A.C) therapies applied. However, in this case there was still a question as to whether the leg was graftable. As such maggot debridement therapy (MDT) was used in addition to try and maintain the viability of the limb, which research has shown to be effective in limb salvage in 40–50% of cases.⁵ Therefore, this case attempts to illustrate the difficulty in diagnosing and treating WISN and the need for further research to aid the compilation of guidelines.

BACKGROUND

Warfarin-induced skin necrosis (WISN) is a rare but recognised complication of warfarin treatment with literature estimating WISN to cause complications in between 0.01% and 0.1% of patients on warfarin.^{1 2} WISN is thought to be due to the paradoxical prothrombotic state that arises from warfarin therapy as a result of an initial relative decrease in vitamin K-dependent clotting factors (eg, protein C).³ This imbalance can cause microthrombi which interrupt blood flow to the skin and cause necrosis. Protein C, S and antithrombin III deficiencies³ are, in fact, considered risk factors for WISN, but not all with these deficiencies will develop WISN.

Despite the high number of people on warfarin therapy there are no clear guidelines for diagnosis or treatment of WISN. A number of papers have attempted to provide guidance on both clinical and histological diagnoses agreeing that diagnosis should be based on clinical findings with support of histological evidence where possible.^{1 3 4} In accordance with these papers, this case illustrates the importance of a clinical diagnosis of WISN, as in this case a primarily histological-based diagnosis and treatment resulted in further complications.

There are also no official guidelines on the best way to treat WISN. However, current research agrees that after diagnosis quick withdrawal and reversal of warfarin will reduce morbidity. In addition they found aggressive wound care and surgical debridement along with supportive antibiotic therapy to be effective, whereas, systemic corticosteroids and vasodilators have not been found to improve outcomes.³ In line with these findings this case illustrates that when WISN was suspected and warfarin reversal was administered along with antibiotics there was no further progression of

CASE PRESENTATION

A 74-year-old man with history of deep vein thrombosis (DVT) who had been warfarinised on a previous occasion was treated for reoccurrence of DVT in his left calf treated with warfarin. After 7–10 days he developed painful bruises and blistered areas around his left foot and heel, which progressed proximally and began to affect the right lower leg as well. Warfarin was stopped, which stopped progression of the lesion but, haemorrhagic bullae had developed at sites of existing skin lesions.

He was reviewed by the dermatologist as an outpatient (figure 1) who took a biopsy but was later readmitted to hospital with

- ▶ A necrotic lesion—2 cm diameter on lateral aspect of lower right leg (stitches from biopsy still present).
- ▶ 0.5 cm lesion between first and second metatarsal on right foot.
- ▶ Five reddish lesions over right leg and calf.
- ▶ Several purple lesions over left foot with breakdown of skin and some ulcers.
- ▶ Large dry ulcer over left heel.

At this stage histology reported necrotising small vein vasculitis. Warfarin was cautiously restarted and he was treated with prednisolone (60 mg once a day orally). The patient's condition was still improving even after restarting warfarin and when he was discharged.

The patient attended outpatient rheumatology clinic where he was seen concurrently by the rheumatologist and the haematologist. There were no new lesion sites but he had developed ulcers which appeared infected and was started on

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Figure 1 Patient's left leg and foot at presentation to the dermatology.

co-amoxycylav 625 mg thrice a day and metronidazole 400 mg thrice a day and swab taken for microscopy, culture and sensitivity. Microscopy, culture and sensitivity reported *Staphylococcus aureus* and *Staphylococcus pseudomonas* and hence his antibiotic therapy was altered to flucloxacilin orally 500 mg four times a day by his general practitioner (GP).

Approximately 2 months after the initial examination for DVT the patient was finally referred to A&E via his GP, querying cellulitis with worsening left leg and foot lesions and ulcers with extensive exudate (figure 2). The patient also felt feverish although he was not recording the temperature and his daughter reported mild confusion. On examination the left leg showed

Figure 2 Patient's left leg and foot at final admission.

- ▶ Extensive blistering to dorsum of foot and lateral mid leg which were filled with clear fluid.
- ▶ Toe-to-knee hot inflamed/blistered skin.
- ▶ Haemorrhagic bullae.
- ▶ Oedema

It was noted that

- ▶ The plantar surface was spared.
- ▶ The foot was well-perfused.
- ▶ Capillary refill time was <2 s.
- ▶ Popliteal pulse present.
- ▶ Patient was afebrile.

INVESTIGATIONS

- ▶ Imaging for underlying malignancy was unremarkable
- ▶ Doppler ultrasound showed no DVT
- ▶ Blood tests for all causes of vasculitis were negative:
- ▶ Negative antineutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA), cryogloblins, JAK2, paroxysmal nocturnal haemoglobinuria (PNH), anticardiolipin and antiphospholipid abs.
- ▶ Hepatitis B/C and HIV1 and HIV2 virology were negative.
- ▶ Normal full blood count (FBC), complement, immunoglobulins (to rule out myeloma due to spinal fractures on x-ray).

Follow-up biopsy showed widespread vascular endothelial swelling, occasional superficial and deeper small vessel thrombosis—minimal mural fibrinoid changes. There were widespread

vascular and perivascular interstitial and subcutaneous inflammatory infiltrates including focal abscess formation. It was noted that there was a thrombotic element to the lesions but that the inflammatory infiltrate was not a typical feature of warfarin necrosis.

DIFFERENTIAL DIAGNOSIS

In addition to the difficulties in diagnosing warfarin-induced necrosis one also has to bear in mind that incorrect treatment or treatment of alternate diagnoses could lead to worsening of the condition. Further differentials for this case include

- ▶ Venous/arterial ischaemia
- ▶ Necrotising fasciitis/infection
- ▶ Vasculitis

In this case treatment for vasculitis and reinstatement of warfarin, although indicated by the histological findings and the patient's previously uneventful warfarinisation, may have led to progression of the condition. The difficulty facing the clinician in this case is very clear when you consider that while swift and specific treatment is required for WISN and many of the other differentials listed below (particularly heparin induced thrombocytopenia and thrombosis and necrotising fasciitis) there are no specific criteria to diagnose the condition and incorrect treatment often leads to a decline in the patient's symptoms.

Other common differentials for WISN:

- ▶ Cholesterol embolism
- ▶ Pyoderma gangrenosum
- ▶ Cellulitis
- ▶ Fournier's gangrene
- ▶ Cryofibrinogenemia
- ▶ Disseminated intravascular coagulopathy
- ▶ Purpura fulminans
- ▶ Heparin induced thrombocytopenia and thrombosis, as heparin and warfarin treatments are commonly given concurrently

TREATMENT

After final admission of flucloxacillin 1 g four times a day intravenously and clindamycin 600 mg four times a day intravenously were started. Warfarin was stopped and anticoagulation was continued with low-molecular-weight (LMW) heparin. Steroid dose was reduced at 10 mg/day and vitamin K was administered. Pain was brought under control using pregabalin. Tissue viability and amputation was in question, however, the foot remained well perfused and started to improve.

Plastics review noted that all weight-bearing areas of foot were spared but it was not graftable at that time. Tissue viability and amputation was therefore in question, however, the foot remained well perfused and the foot was debrided surgically and negative pressure dressings applied. After several surgical debridements the foot was still not graftable and maggot larvae were ordered for MDT and were applied for 7 days.

MDT is the medical use of live maggots (ie, fly larvae) for the management of non-healing wounds, by clearing out the necrotic tissue. The disinfected fly larvae are applied to the wound within special dressings to prevent them from migrating. The maggots feed using extracorporeal digestion which serves to clear the necrotic tissue in the wound: The larvae secretes proteolytic enzymes onto the tissue in the wound to liquefy the necrotic tissue and absorb the liquefied result after a few days. In this way a large number of small maggots consume necrotic tissue more precisely than is possible in a normal surgical operation.

Not all fly larvae can be used for MDT. In this case Calliphoridae or 'blow flies' of the species *Phaenicia sericata* were used. As with all medicinal maggots these were sterilised to prevent secondary infection from microbes carried by the maggots and were grown in a laboratory setting.

Postmaggot debridement Manuka honey dressing was applied and the limb was kept elevated. Finally VAC (registered trademark for pressure wound therapy) therapy was applied in the hope that skin grafting would be possible in the future.

OUTCOME AND FOLLOW-UP

The patient was treated as above and after continued review by the plastics team, grafting was successfully carried out and amputation was avoided. The patient is now stable.

DISCUSSION

A number of papers have attempted to outline the clinical features which could be used for the diagnosis of WISN and are compiled below in box 1.

In this case clinical diagnosis was made based on the temporal relation with warfarin administration and the development of macroscopically characteristic lesions on the patient's limbs that is, development of petechiae and ecchymoses followed by haemorrhagic skin bullae. In addition once warfarin was stopped the condition improved or ceased to worsen on two occasions and when restarted there was deterioration which further supported the clinical suspicion for WISN. While no thrombophilias were identified on investigation the absence of such conditions in no means rules out the possibility of WISN. The only clinical feature against a diagnosis of WISN is that the patient had been previously treated with warfarin for a prior DVT with no adverse side effects. However, this could be due to the administration of antibiotics which can interfere with the vitamin K gut flora and may have exacerbated the condition.³

Papers have also cited a number of histological features that are characteristic of WISN and that could be used to support the clinical diagnosis. These are outlined in box 2.

Box 1 Suggested clinical features for the diagnosis of warfarin-induced skin necrosis (WISN)

Suggested clinical features for the diagnosis of WISN

The temporal link with warfarin (times range from 3 to 10 days)^{1 2} and use in treatment for DVT or PE.

Appearance and location of the lesions:

- ▶ Lesions are normal located on the limbs, buttocks and thighs, penis (M) or breasts (F).^{1 2}
- ▶ Sudden development of paraesthesia, oedema, petechiae and ecchymoses progressing to full thickness necrosis and deep ulcers within 3–10 days after the initiation of warfarin therapy (WISN)^{1 3 4}
- ▶ After the first signs of skin lesions haemorrhagic bullae within the involved area may develop^{1 4}

Exclusions of other more common complications of warfarin therapy, for example, gangrene, decubitus ulcers, hematoma.^{1 7}

Patient phenotype

- ▶ More commonly female, obese and being treated for DVT or PE²
- ▶ Associated protein C, S or antithrombin III deficiencies^{2 8}
- ▶ Phospholipid antibodies⁷

Box 2 Suggested histological features for the diagnosis of warfarin-induced skin necrosis (WISN)

Suggested histological features for the diagnosis of WISN

Microthrombi and thrombi within the blood vessels of the dermis^{1 3 4} and subcutaneous tissue³

Fibrin deposits in the postcapillary venules and in superficial dermal vessels²

Red cell extravasation and endothelial cell damage.^{1 4}

There are not commonly signs of vasculitis³

In the case the histological investigation in part agrees with suggested features of WISN in showing of microthrombi and thrombi within the blood vessels as well as endothelial damage. However, there were also aspects which contradicted these recommendations in that there were signs of vasculitis and only minimal fibrinoid deposits.

Considering current research advocates a primarily clinical diagnosis of WISN and that in this case reversal of WISN and removal of warfarin prevented progression of symptoms despite mixed histological findings, the diagnosis of WISN seems a sensible conclusion. However, the mixed histology as well as the complications added by concurrent infection does serve to highlight the difficulty in confirming diagnosis of WISN and the need for more conclusive diagnostic criteria.

With regard to treatment for WISN there is general consensus that prompts warfarin withdrawal and reversal of warfarin with either vitamin K (as in this case) or fresh frozen plasma, which are effective in limiting the extent of WISN. Additionally, surgical debridement, where necessary to remove non-viable tissue and allow healing, is commonly used; however, there are limited studies on other methods of treatment. In this case a combination of surgical debridement, MDT and VAC dressing were used to try and maintain viability of the limb, the outcome of which can be seen in figure 3.

A number of studies have demonstrated the apparent improved outcomes of MDT compared with conventional techniques in non-healing diabetic ulcers, which found improved outcomes in the degree and speed of debridement as well as improved wound healing and reduced requirement for antibiotics.^{5 6} In addition, studies have demonstrated the efficacy of MDT. They showed that MDT used on wounds of any cause for limb salvage, as a last resort, saved 40–50% of limbs, usually with complete wound healing.^{5 6} However, it has been noted healing is optimised when maggot therapy is not delayed until infection or vascular compromise allow progression to limb-threatening levels. The reasons for such consistently high limb salvage rates is not confirmed, however, the following have been postulated; increased oxygen perfusion, rapid and luscious spread of granulation tissue, cellular proliferation fibroblast migration and matrix remodelling.⁵

In addition to improved medical outcomes MDT also has an economical advantage with maggots being a cheaper course of treatment. A conservative estimate of savings of £50 million annually in the UK was made based on the use of maggot therapy for 30% of non-healing diabetic ulcers.⁵ However, since medicinal maggots are highly perishable, they are susceptible to transportation problems and delays. Therefore, they must be shipped by overnight courier, and their arrival should be timed no more than 24 h before their application to the wound.

Figure 3 (A) Postmaggot debridement therapy and (B) VAC (registered trademark for pressure wound therapy) dressing.

Despite the possible logistical complication of MDT, evidence suggests that it should be considered in the treatment of WISN. In this case the combination of surgical and maggot debridement resulted in sufficient recovery for skin grafts to be applied and amputation to be avoided.

Learning points

- ▶ The diagnosis of warfarin-induced skin necrosis (WISN) is not simple and should be based primarily on clinical judgement with support of histological evidence where possible.
- ▶ If WISN is suspected prompt warfarin withdrawal and reversal is important to improve outcomes.
- ▶ Careful consideration of alternative diagnosis should be considered as treatment of alternative conditions can worsen outcomes
- ▶ Maggot debridement therapy (MDT) should be considered for the treatment for WISN.
- ▶ Previous warfarinisation and the absence of thrombophilias do not rule out a diagnosis of WISN.

Competing interests None.

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