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Warfarin associated venous limb gangrene in cancer-related DVT (case report)

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ABSTRACT

INTRODUCTION: Warfarin anticoagulation of oncologic patients with DVT may paradoxically progress to phlegmasia cerulea dolens and limb gangrene, due to cancer-associated disseminated intravascular coagulation. This case report, written in line with the SCARE criteria, endorses venous thrombectomy in selected patients to attempt limb salvage. A young woman's warfarin associated acute ileofemoral phlegmasia that developed over cervical cancer radiation therapy induced DVT, was successfully resolved by clot removal. Extracting venous thrombus at the onset, while still as unorganized masses, preserves ambulation and prevents post-thrombotic syndrome development, an improvement of quality of life especially significant for oncologic patients with limited life-expectancy.

PRESENTATION OF CASE: A 34 years old female, with history of stage 3 cervical cancer following radiation therapy, was admitted in regards to left lower limb painful pitting oedema with cramps. Doppler scan revealed a left ileofemoral DVT. She was set on LMWH, but on fourth day of warfarin co-administration, phlegmasia cerulea dolens developed. An emergency venous thrombectomy with fasciotomy was performed. Postoperatively, dry foot gangrene developed, which dictated transmetatarsal amputation. The patient was discharged after 2 months of inpatient treatment, preserving ambulation.

DISCUSSION: Venous thrombectomy (with fasciotomy) in oncologic phlegmasia, ± serial debridement, becomes an attractive opportunity for limb salvage when feasible at acute presentation, available in a limited resource setting.

CONCLUSION: Due to severe procoagulant/anticoagulant balance disturbances in cancer patients' warfarin-bridged for DVT, phlegmasia onset should not defer surgical approach, unless a rapid response to conservative treatment.

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1. Introduction

Venous gangrene following administration of warfarin in oncologic patients with DVT is a known possible limb and life-threatening complication, considered in actual antithrombotic therapy guidelines, although with little awareness from general surgeons [1]. This type of gangrene typically occurs only after LMWH discontinuation, and warfarin commencement or continua-

tion, in the DVT affected limb, despite no arterial flow disturbance, confirmed by Doppler-identifiable pedal pulses [2].

2. Case report

A 34 years old female, Caucasian, non-smoker, was referred to general surgery department of a clinical hospital, with a 2 days onset of left lower limb pain and swelling, muscle cramps. She had a half-year history of cervical cancer (T₃N₀M₀, stage 3). Five days prior to symptoms onset, she completed the 3rd cycle of radiotherapy, that provide a 5-year survival rate of 57%. Physical exam was unremarkable, except a BMI 17.4 and the local status: severe pitting left thigh and ankle edema, tender on palpation, with positive Hommans and Moses signs. Doppler-duplex scan showed significant occlusive thrombotic masses, with a non-floating apex in the left common iliac vein, spreading retrograde into the internal and external iliac veins, common femoral vein, deep and superficial femoral veins, popliteal vein, anterior and posterior tibial veins, peroneal vein, including the great saphenous vein. A left DVT (LET

Abbreviations: DVT, deep vein thrombosis; LMWH, low molecular weight heparin; LET, lower extremity thrombosis (Classification); NSAID, non steroidal anti-inflammatory drug; INR, international normalized ratio; FFP, fresh frozen plasma; VKA, vitamin K antagonists; ICU, intensive care unit.

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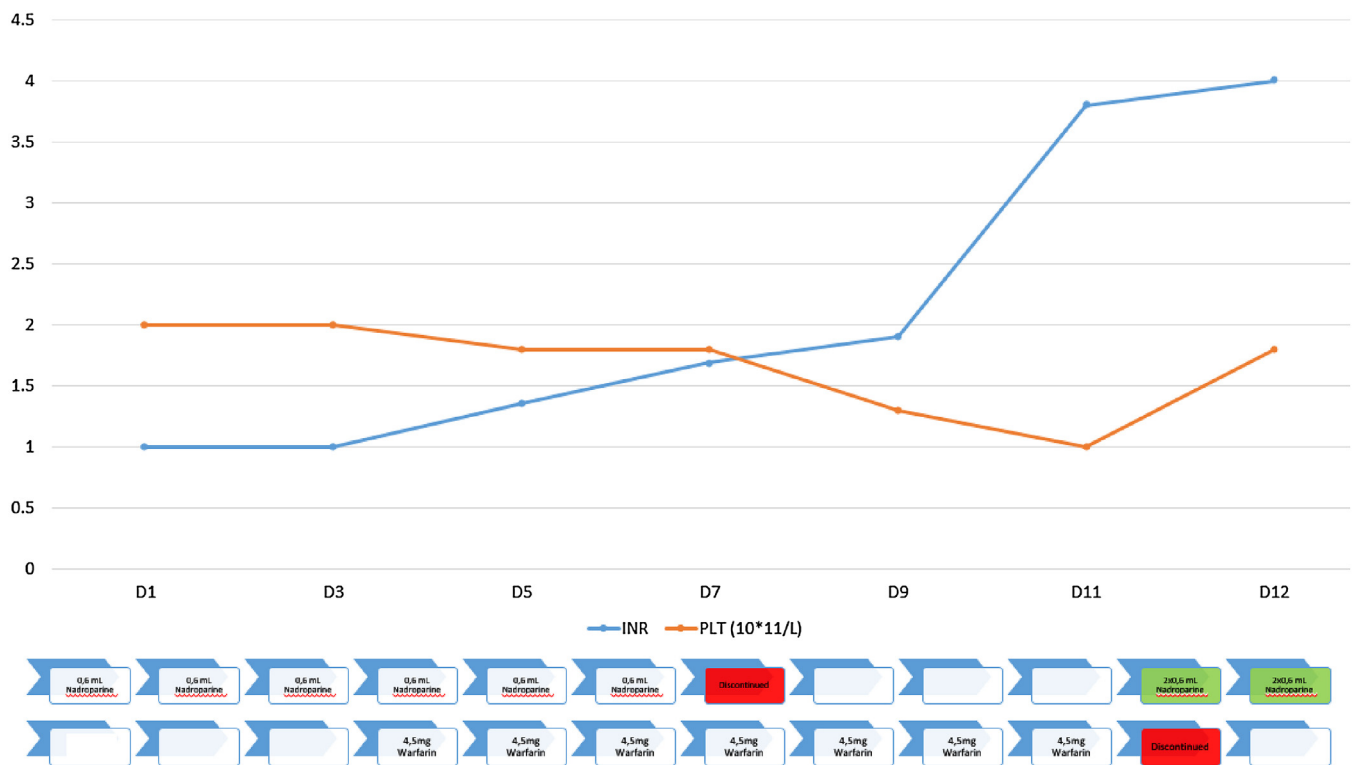


Fig. 1. Fall of platelets (PLT) after LMWH discontinued, with a sudden rise at reintroduction; supratherapeutic INR associated with low platelets at the phlegmasia onset (day 11).

class III) [5] was established, and the patient started on 0.6 mL of daily nadroparin, an NSAID, and elastic bandage with moderate compression applied over the left lower limb (Fig. 1).

At the 4th day, 4.5 mg of warfarin begun to be co-administered, and on the 8th day, after 4 days on VKA, nadroparin was discontinued. Four days afterwards, a sudden painful cyanosis of foot and ankle developed, with Doppler probe detectable pulse on posterior tibial and dorsalis pedis arteries (Fig. 2).

Considering the supratherapeutic INR and decline of platelets count, the diagnosis of warfarin-associated phlegmasia cerulea dolens was established, and warfarin discontinued, the patient being started on 0.6 mL nadroparin twice daily. Due to lack of improvement, on the next day she was taken into the operation room, where a venous ileo-femoral thrombectomy with 3-compartment left leg fasciotomy have been performed, under general anesthesia. The operating team consisted of two highly competent consultant vascular surgeons, with significant experience in peripheral arterial and venous interventions, and a first-year resident. By groin approach, using Fogarty thrombembolectomy catheters 5F, 8F a significant quantity of unorganized thrombotic masses were retrogradely extracted from the external iliac vein, common femoral vein, antegradely from the greater saphenous vein, and by means of infrapopliteal access – retrogradely from the superficial femoral vein (Fig. 3). Longitudinal venotomy sites were closed with Polypropylene 5-0 (Prolene blue monofilament, Ethicon) continuous suture. The operation lasted 140 min, with an estimated 500 mL intraoperative blood loss.

The patient was transferred to ICU for surveillance, and the outcome has been daily assessed by the operating surgeon. Anticoagulation proved to be enough for pulmonary embolism prevention, with no cava-filter or balloon applied. On the third postoperative day, hemorrhagic bullae developed over the foot (reperfusion injury), and 2 weeks afterwards, when demarcation occurred, a transmetatarsal amputation has been performed

for left foot dry gangrene (grade IIIA complication according to Clavien-Dindo Classification) [10]. Over the next 10 days, wound debridement and necrectomy was repeatedly performed, followed by skin grafting (Fig. 4).

She was discharged home after 2 months of inpatient treatment, preserving ambulation. The anticoagulation was maintained with therapeutic doses of LMWH, prescribed for at least 6 months. Unfortunately, the patient died 4 months later, because of cervical cancer advancement with brain and lungs metastases.

3. Discussion

Patients with malignancy who develop phlegmasia cerulea dolens/venous gangrene over the DVT-affected limb are known to exhibit some peculiarities: rise of platelets on LMWH, falling off after its' discontinuation; and a supratherapeutic INR secondary to warfarin [2]. The pathogenesis is linked to tumor cell release of microparticles that activate thrombin, even when vitamin K-dependent procoagulants are decreased [3]. Thrombin generation associated with warfarin-induced decrease in protein C and S, induce a cancer-associated disseminated intravascular coagulation, which contributes to a profound disturbance in pro-coagulant/anticoagulant balance and consumptive coagulopathy [3,4].

Although, endothelial damage related to radiation therapy could be the causative factor for DVT onset, the progression of thrombosis to venous gangrene seems secondary to warfarin intake, this mechanism being rather consistent with a specific disease course and laboratory profile. She developed a sudden bluish discoloration only at 11th day of treatment, when platelets count dropped to $100 \times 10^9/L$ and INR reached over therapeutic range – 3.8.

In comparison with other published case reports of cancer related venous gangrene [6,7,4], the onset in our patient installed at a younger age, after 50 being more common [6].



Fig. 2. Phlegmasia cerulea dolens onset, asymmetric severe limb edema with cyanosis of foot and leg.

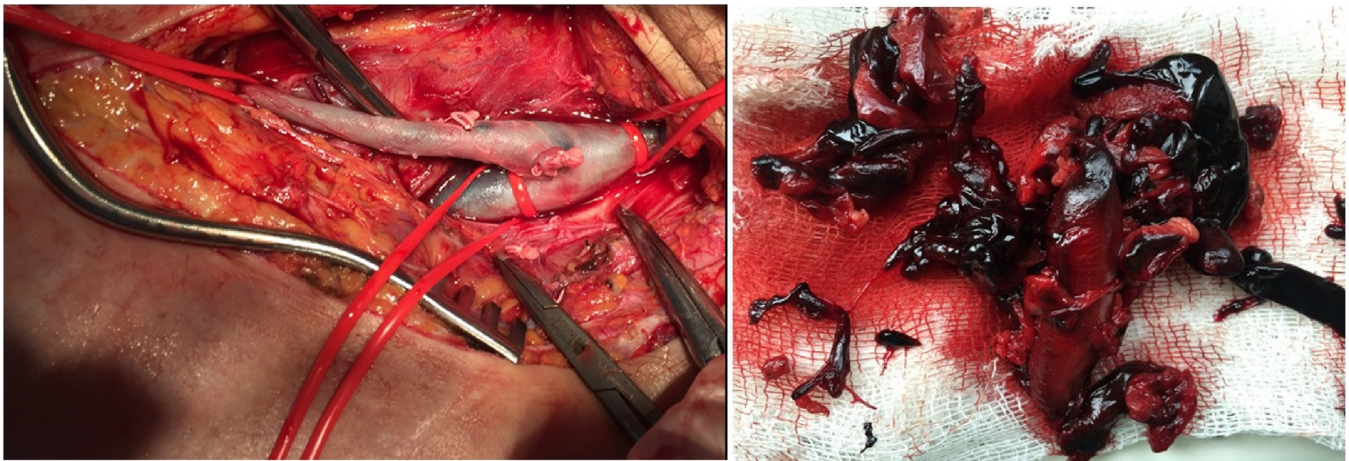


Fig. 3. Left inguinal exposure of common femoral vein and the thrombectomy-specimen of unorganized thrombotic masses.



Fig. 4. Post-operative course, 35th POD, before skin grafting.

Surgical thrombectomy $\pm$ distal arteriovenous fistula is rarely reported in cancer-related DVT progression to phlegmasia cerulea dolens cases, despite considered a safe method, that should be indicated in selected patients when conservative treatment does not prevent the development of an acute compartment syndrome with venous gangrene, and while there are contraindications to thrombolysis or in condition that thrombolytic therapy is not available [8,9].

Emergency management includes immediate warfarin discontinuation, FFP-reversal of VKA, heparin anticoagulation. Venous thrombectomy may be considered for limb salvage when an acute presentation compatible with an unorganized thrombus at Doppler scan. All compartment fasciotomy may improve arterial supply in phlegmasia cerulea dolens by relieving the excessive intracompartmental pressure. The patients without any diagnosis of neoplasia, undergoing the progression from DVT to warfarin-induced venous limb gangrene, should be investigated for cancer.

This case-experience, reported in line with the SCARE criteria [11], endorses successful experience of limb salvage, with minimal tissue loss. Operative venous thrombectomy in phlegmasia is currently more and more practiced, with substantially improved early and long term results [8,12]. Some limitations of the approach were lack of daily INR and platelets surveillance, lack of cava filter or cava-occlusion protection against pulmonary emboli, single case-experience of vein clot removal in oncologic setting. Due to patient death long term follow-up went impossible, which served a weakness for this case-report.

The primary take-away lesson is venous thrombectomy (with fasciotomy) in oncologic phlegmasia, $\pm$ serial debridement, remains an attractive opportunity for limb salvage when feasible at acute presentation.

4. Conclusion

Due to severe procoagulant/anticoagulant balance disturbances in cancer patients' warfarin-bridged for DVT, phlegmasia onset should not defer surgical approach, unless a rapid response to conservative treatment.

Conflict of interest statement

None declared.

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Ethical approval

None.

Consent

Written informed consent was obtained from the husband of the deceased patient, for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Cojocari Vladimir: study concept, data collection and interpretation, writing the paper, submitting the paper.

Casian Dumitru: data collection, chief operator in surgical intervention, writing & reviewing the paper.

Gutu Eugen: writing & reviewing the paper.

Guarantor

Cojocari Vladimir.

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