Unexpected outcome (positive or negative) including adverse drug reactions

Anticoagulant-induced priapism progressing to penile gangrene: a devastating complication!

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Summary

A 35-year-old man developed priapism with the use of low-molecular-weight heparin and warfarin following repair of left brachial artery sustained after gunshot injury. Priapism progressed to penile gangrene despite decompression and distal shunt procedure leading to total penectomy and perineal urethrostomy. We describe the mechanism of anticoagulant (heparin and warfarin)-induced penile gangrene and the possible methods to avert such a devastating complication.

BACKGROUND

Anticoagulants (like warfarin and low-molecular-weight heparin) are commonly used for the treatment of arterial and venous thrombosis to prevent clot propagation. They are also used to prevent thromboembolism in patients with thrombophilia, atrial fibrillation, mechanical heart valves and after high-risk surgery. In the setting of vascular thrombosis, both heparin and warfarin are initiated with warfarin being continued till the desired time. Strict monitoring is required to prevent overdose and avert unusual complications such as bleeding and rarely priapism. It is also known that both of them cause priapism individually.^{1 2} When used in combination it is difficult to pinpoint to the perpetrator of priapism. Priapism progressing to penile gangrene secondary to use of anticoagulant is still rare with only few cases being reported in the literature. Herein we report an unusual complication of penile gangrene after the use of anticoagulants.

CASE PRESENTATION

A 35-year-old man, non-diabetic, non-hypertensive, married, having two children with normal erectile function, presented 4 h after sustaining gunshot injury to the left side of chest and left upper limb (figure 1). There were no injuries to the external genitalia. On evaluation, he had left pneumo-haemothorax which was relieved with insertion of intercostal chest tube and left upper limb ischaemia due to laceration of the brachial artery with thrombosis (confirmed by colour Doppler of left upper limb). His preoperative haematological parameters showed haemoglobin 13.2 gm/dl, total white blood cell (WBC) count 8200 cells/cmm³ and a normal differential WBC count. Platelet counts were 3 80 000 cells/cmm³. Coagulation parameters were within normal range (bleeding time 4 min, coagulation time 6 min 10 s and international normalised ratio (INR) 1.0). He underwent embolectomy with repair of the brachial artery using saphenous vein graft. Postoperatively, injection dalteparin (fragmin) 5000 IU subcutaneous (SC) twice daily along with oral warfarin 5 mg twice daily was started.

On the third postoperative day, the patient complained of penile pain with persistent erection of 12 h. Colour Doppler of penis showed low arterial flow and absence of venous flow. Coagulation parameters showed prothrombin time was 137 s (control: 14 s) and INR of 9.8. In view of raised INR, anticoagulants were stopped immediately. Aspiration of cavernosal blood revealed dark, unclotted blood and analysis of cavernosal blood aspirate was consistent with ischaemic priapism. Coagulation parameters were corrected with transfusion of fresh frozen plasma and injection vitamin K given for 3 days, and the INR reached 1.2 the next day. Priapism was initially managed with repeated irrigation and aspiration followed by creation of distal cavernoglanular shunt (Winter shunt). Partial detumescence was achieved. But, 48 h from the onset of priapism, the glans started developing gangrene.

The patient was later referred to us after 7 days from the onset of priapism, dry gangrene had progressed till the peno-scrotal junction (figure 2). The urinary bladder continued to be drained by previously placed perurethral

Figure 1 Chest x-ray showing pellets from gunshot injury causing left hemopneumothorax.

Figure 2 Penile gangrene till the peno-scrotal junction.

Foley catheter. Haematological work-up ruled out sickle cell disease or haematological malignancy. His platelet counts were marginally low (150 000 cells/cmm).

After counselling, informed consent was taken to perform total penectomy as enough penile stump could not be saved so as to enable him void in a standing position. Intraoperatively, there was dry gangrene till the peno-scrotal junction with thrombus extending proximally into the corpora cavernosal till the crural bifurcation. Corpus spongiosum was also thrombosed till the bulb of the penis.

TREATMENT

Total penectomy with perineal urethrostomy was performed after taking informed consent from the patient

(figure 3). The left upper limb could not be salvaged and developed gangrene for which a mid-forearm amputation was done.

OUTCOME AND FOLLOW-UP

Postoperatively, the wound remained healthy and he is voiding well at 6 months of follow-up.

DISCUSSION

Priapism by definition is full or partial erection that continues more than 4 h beyond sexual stimulation and orgasm or is unrelated to sexual stimulation.¹ Priapism is mainly of three types namely ischaemic, non-ischaemic and stuttering priapism. Ischaemic priapism is a surgical

Figure 3 Total penectomy with perineal urethrostomy.

emergency. Treatment when delayed beyond 48–72 h may help to resolve erection but invariably results in erectile dysfunction. Rarely, priapism may result in partial or total penile gangrene.²

Penile gangrene is a rare complication of priapism.² It may be dry or infective with the latter being more common. The various causes of penile gangrene are listed (box 1). To date, only 16 cases of penile gangrene secondary to priapism have been reported in the literature. In an excellent review of 14 cases of partial or total penile gangrene following priapism by Khoriaty *et al*,² age of the patients varied from 14 to 60 years, the duration of time to develop gangrene from the onset of priapism varied from 13 h to 15 days. The aetiology were idiopathic (6/14), sickle cell disease (5/14), traumatic (1/14), urethral carcinoma (1/14) and unknown in one patient. The other two cases reported in the literature were as a result of thrombotic thrombocytopenic purpura³ and the other due to metastasis into the penis from a primary bladder malignancy.⁴ All patients had undergone intervention to relieve priapism in the form of aspiration and irrigation or creation of distal shunt prior to development of gangrene. The extent of gangrene varied from foreskin to entire penis. The authors have proposed that local infection, pressure dressing, presence of urethral catheter, oedema along with ischaemia of corpus spongiosum contributed to penile necrosis and avoidance of these factors is helpful in preventing penile gangrene.

In our case, the time from the onset of priapism to development of gangrene was 3 days. Although a perurethral Foley catheter was used to drain bladder, there was no associated infection and no pressure dressing were applied to the penis. There was no apparent cause of gangrene except for the use of anticoagulants. The use of warfarin in high dose and sudden withdrawal of fragmin resulted in ischaemic priapism due to thrombosis of venous outflow from the penis (confirmed by colour Doppler of penis). Persistence of priapism along with thrombosis of arteries led to precipitation of gangrene.

Heparin-induced priapism is rare with fewer than 20 cases being reported so far.¹⁰ The pathophysiological mechanism of priapism following use of heparin is that it induces the development of antiplatelet-antibodies that

may lead to the aggregation of thrombocytes and thus alter the penile blood flow leading to low-flow priapism.¹¹ Also, heparin when stopped abruptly results in rebound hypercoagulable state resulting thrombosis of corpora cavernosa as well as corpus spongiosum.¹²

Penile gangrene has been noted only with the use of subcutaneous low-molecular-weight heparin (LMWH, Enoxaparin sodium, Clexane, Sanofi, Surrey) when used at the dose of 50 mg twice daily.¹³ Although priapism has been noted with the use of intravenous and intracavernosal unfractionated heparin, penile gangrene has not been noted with the use of unfractionated heparin in the literature.^{1–11} However, we suggest that similar precautions should be taken with the use of both LMWH and unfractionated heparin.

The proposed mechanism of warfarin-induced skin necrosis is due to the lowering of the natural anticoagulant protein C (half-life: 9 h) which leads to a hypercoagulable state in the first few days of warfarin initiation, before lowering of prothrombin (half-life: 60 h) which leads to protective anticoagulation.^{14–16} High warfarin loading doses and premature heparin discontinuation predispose to the development of warfarin-induced skin necrosis.

As both heparin and warfarin are known to produce priapism, we suggest that patients taking anticoagulants should be alerted to the peril signs of priapism. Similarly, the effect of warfarin should be monitored by daily until INR is in therapeutic range twice at least 24 h apart and then twice a week for 2 weeks, then once a month until the therapy is complete.¹⁷

It is also important to note that the key factors determining successful surgical reversal of ischaemic priapism are evacuation of thrombus, re-establishment of cavernous inflow and patency of shunt.¹ So when the distal shunt failed in the first instance as in our case, proximal shunt should be performed promptly to relieve priapism and possibly development of gangrene.

Box 1 Aetiology of penile gangrene^{1–8}

1. Dry gangrene
 - A. Calciphylaxis due to secondary hyperparathyroidism from End Stage Renal Disease⁵ and chronic renal failure⁹
 - B. Penile strangulation from constricting devices⁶
 - C. Priapism²
 - D. Anticoagulant therapy—heparin, warfarin¹
 - E. Injection of heroin into femoral vessels⁷
 - F. Metastasis to penis⁴
 - G. Thrombotic thrombocytopenic purpura³
 - H. Sickle cell disease²
2. Wet (infective) gangrene.
 - A. Fournier gangrene—idiopathic/genitor-urinary procedures⁸

Learning points

In patients on anticoagulants

- ▶ Unopposed warfarin administration should be avoided and adequate levels of an alternative anticoagulant should be ensured prior to treatment with warfarin.
- ▶ Excessive levels of warfarin anticoagulation should be avoided in order to prevent a precipitous decrease in protein C levels.
- ▶ Low-molecular-weight heparin should not be discontinued suddenly so as avoid reflex hypercoagulable state.
- ▶ Ischaemic priapism need to be treated aggressively with irrigation and aspiration followed up with shunting procedures (distal shunting if unsuccessful is followed up with proximal shunting).

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Broderick GA.** Priapism. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, eds. *Campbell-Walsh urology*, vol 1. Philadelphia: Saunders, 2012: 749–69.
2. **Khoriaty N,** Schick E. Penile gangrene: an unusual complication of priapism (How to avoid it?). *Urology* 1980;**16**:280–3.
3. **Kwork B,** Varol C. Priapism and penile gangrene due to thrombotic thrombocytopenic purpura. *Urology* 2010;**75**:71–2.
4. **Ajape AA,** Bello A. Penile gangrene: an unusual complication of priapism in a patient with bladder carcinoma. *J Surg Case Rep* 2011;**3**:37–9.
5. **Halachmi S,** Storch S. Penile gangrene due to severe vascular calcification. *IMAJ* 2006;**8**:888–9.
6. **Labanaris AP,** Zugor V, Smiszek R, *et al.* Dry gangrene of the penis induced by a bullring for sexual stimulation purposes. *Sci World J* 2008:896–900.
7. **Somers WJ,** Lowe FC. Localized gangrene of the scrotum and penis: a complication of heroin injection into the femoral vessels. *J Urol* 1986;**136**:111–13.
8. **Singh V,** Sinha RJ, Sankhwar SN. Penile gangrene: a devastating and lethal entity. *Saudi J Kidney Dis Transpl* 2011;**22**:359–61.
9. **Stein M,** Anderson C, Ricciardi R, *et al.* Penile gangrene associated with chronic renal failure: report of 7 cases and review of the literature. *J Urol* 1994;**152**:2014–16.
10. **Lin PH,** Bush RL, Lumsden AB. Low molecular weight heparin induced priapism. *J Urol* 2004;**172**:263.
11. **Bschleipfer TH,** Hauck EW, Diemer TH, *et al.* Heparin-induced priapism. *Int J Impot Res* 2001;**13**:357.
12. **Mustard JF,** Murphy EA, Downie HG, *et al.* Heparin and thrombus formation: early suppression and late enhancement. *Br J Haematol* 1963;**9**:548–51.
13. **Chang IH,** Ha MS, Chi BH, *et al.* *J Korean Med Sci* 2010;**25**:1390–3.
14. **McGehee WG,** Klotz TA, Epstein DJ, *et al.* Coumarin necrosis associated with hereditary protein C deficiency. *Ann Intern Med* 1984;**101**:59–60.
15. **Koner O,** Tekin S, Soybir N, *et al.* Cardiac operation in a patient with combined homozygous protein C and protein S deficiency. *J Cardiothorac Vasc Anesth* 2000;**14**:188–90.
16. **Moll S.** Warfarin-induced skin necrosis. *Br J Haematol* 2004;**126**:628.
17. **UAB coagulation service.** Test interpretation and therapy. *Anticoagulant therapy monitoring. (Internet).* http://peir.path.uab.edu/coag/article_221.shtmls (accessed 25 July 2012).

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Nagathan DS, Pahwa HS, Kumar A, Goel A. Anticoagulant-induced priapism progressing to penile gangrene: a devastating complication!. *BMJ Case Reports* 2012;10.1136/bcr-2012-007073, Published XXX

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