ELSEVIER

https://www.jhltopen.org/

Fournier's gangrene in recent transplant recipient on empagliflozin

Lisa M. Raven, MBBS, FRACP,[a,b,c,*] Jacob Y. Cao, BSc, MBBS,[c,d] Peter S. Macdonald, MBBS, MD, PhD, FRACP,[c,d,e] Andrew Jabbour, BSc (Med), MBBS (Hons), PhD, FRACP,[c,d,e] and Jerry R. Greenfield, MBBS (Hons 1), PhD, FRACP[a,b,c]

[a]*Department of Diabetes and Endocrinology, St Vincent's Hospital, Sydney, Australia;*
[b]*Clinical Diabetes, Appetite and Metabolism Laboratory, Garvan Institute of Medical Research, Sydney, Australia;*
[c]*School of Clinical Medicine, St Vincent's Campus, Faculty of Medicine and Health, University of New South Wales, Sydney, Australia;*
[d]*Department of Heart and Lung Transplantation, St Vincent's Hospital, Sydney, Australia;*
[e]*Victor Chang Cardiac Research Institute, Sydney, Australia.*

KEYWORDS:
SGLT2;
sodium glucose co-transporter 2;
empagliflozin;
cardiac transplant;
Fournier's gangrene

A 51-year-old man with recent orthotopic heart transplant 5 months earlier, presented to clinic with presyncope and 1 week history of diarrhea, including an episode of fecal incontinence.

On examination, the patient was hypotensive, blood pressure 80/50 mm Hg; tachycardic, heart rate 141 beats per minute; and febrile, temperature 38.5°C. There was no obvious focal source of infection on examination.

Laboratory investigations showed a new neutropenia, white blood count 1.2×10^9/liter (reference range 4.0-11.0), neutrophils 1.0×10^9/liter (reference range 2.0-7.5), and c-reactive protein 397 mg/liter (reference range < 5.0). Blood, urine, and fecal culture were negative. Ceftriaxone, azithromycin, and gentamicin were commenced empirically.

Computer tomography scan the following day revealed gas locules within the subcutaneous soft tissue around the anal area (Figure 1A) and Fournier's gangrene was suspected which required urgent surgical debridement (Figure 1B). Vancomycin, clindamycin, and cefepime were commenced. Tissue culture grew *Enterococcus faecalis* and *Escherichia coli*. In total, 7 debridement procedures were needed and fecal diversion with colostomy was required.

Post-transplant diabetes mellitus had been diagnosed 3 months earlier with HbA1c 7.0% (53 mmol/mol) and fasting glucose 18.7 mmol/liter. Insulin isophane, insulin aspart, and empagliflozin 10 mg had been commenced at diagnosis of diabetes, followed by metformin 500 mg daily. Insulin was weaned prior to presentation with Fournier's gangrene based on glucose levels < 10 mmol/liter. Immunosuppression included everolimus (commenced 1 month prior to presentation with Fournier's gangrene), tacrolimus, mycophenolate, and prednisolone (8 mg at time of presentation).

*Corresponding author: Lisa M. Raven MBBS, FRACP, St Vincent's Hospital Sydney, 390 Victoria Street, Darlinghurst, NSW 2010, Australia.
E-mail address: lisa.raven@svha.org.au.

https://doi.org/10.1016/j.jhlto.2024.100060

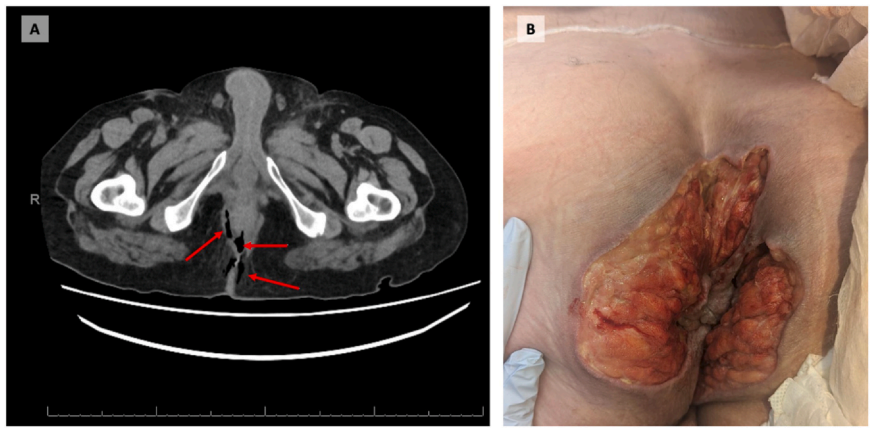

Figure 1 Fournier's gangrene in a transplant recipient on empagliflozin. (A) Computer tomography scan showing gas locules within the subcutaneous soft tissue around the anal area. (B) Peri-anal area postsurgical debridement.

This is the first reported case of Fournier's gangrene with sodium glucose co-transporter 2 (SGLT2) inhibitor use in a solid organ transplant recipient. Fournier's gangrene is a rare but reported adverse event associated with SGLT2 inhibitor use.[1] Fournier's gangrene is characterized by necrotizing fasciitis around the genital and/or perianal regions and requires surgical debridement. The incidence of Fournier's gangrene is estimated to be 1.6/100,000 in males in America, with limited ability to estimate in females.[2] Diabetes itself is associated with increased risk of Fournier's gangrene.[3–5] There are case reports of Fournier's gangrene associated with alternative diabetes medications, other than SGLT2 inhibitors.[1,5] Immunosuppression and corticosteroid use, such as that required in organ transplant recipients, are also risk factors for Fournier's gangrene.[3,4] The most common pathogens are polymicrobial organisms, *E. coli* and *Streptococcus*.[4] The exact mechanism of the development of Fournier's gangrene is unknown. It is postulated that small abrasions may facilitate entry of pathogens into the soft tissue and these pathogens release collagenase enzymes causing tissue damage with rapid spread. Diabetes and the use of SGLT2 inhibitors cause glucosuria which creates a favorable environment for bacterial and fungal infections. However, the causal relationship between SGLT2 inhibitors and Fournier's gangrene is questionable.[5]

In summary, patients who are immunosuppressed and have diabetes may be at higher risk of developing Fournier's gangrene with SGLT2 inhibitor use due to concomitant risk factors. With increasing therapeutic indications, pharmacovigilance of this rare event, particularly in those on immunosuppression is required.

Author contributions

L.M.R. and J.R.G. were involved in the writing of the original draft and review; J.Y.C., P.S.M., and A.J. were involved in the writing, review, and editing.

Disclosure statement

This report did not receive any funding. The authors have no conflicts of interest to declare. L.M.R. is supported by a Scholarship (107026) from the National Heart Foundation of Australia.

Patient Consent

The authors declare that appropriate patient consent was received for publicaton of this case report.

References

1. Bersoff-Matcha SJ, Chamberlain C, Cao C, Kortepeter C, Chong WH. Fournier gangrene associated with sodium–glucose cotransporter-2 inhibitors. Ann Intern Med 2019;170:764-9.
2. Sorensen MD, Krieger JN, Rivara FP, et al. Fournier's gangrene: population based epidemiology and outcomes. J Urol 2009;181:2120-6.
3. Nisbet AA, Thompson IM. Impact of diabetes mellitus on the presentation and outcomes of Fournier's gangrene. Urology 2002;60:775-9.
4. Tang LM, Su YJ, Lai YC. The evaluation of microbiology and prognosis of fournier's gangrene in past five years. SpringerPlus 2015;4:14.
5. Taylor L, Asmar O, Mandal A, Tridente A, Hardy K, Shokrollahi K. Perspectives from a regional plastic surgery centre on evidence for the purported link between SGLT2 inhibitors and Fournier's gangrene. Front Surg 2021;8:754101.