Fournier’s gangrene with dapagliflozin in a rural hospital: a case report

Ali Elbeddini 1,2, Yasamin Tayefehchamani,3 Michelle Davey,1 Jodi Gallinger,4 Naushin Hooda,5 Ahmed Aly,1 Dawn Erickson,6 Stephanie Lee1

SUMMARY
Sodium-glucose cotransporter 2 (SGLT2) inhibitors, which are used for treatment of type 2 diabetes, are associated with risk of urogenital infections. FDA issued a black box warning about multiple case reports of Fournier’s gangrene (FG) observed in patients taking SGLT2 inhibitors. FG is a type of necrotising fasciitis that occurs in the anogenital area. We report a case of a 71-year-old woman with type 2 diabetes on dapagliflozin, presenting with foul-smelling discharge and a large abscess in the perianal area. Her risk factors for FG included her advanced age, obesity, diabetes and trauma to the site. During her stay, dapagliflozin was discontinued and she received procedural debridement, wound care and broad-spectrum intravenous antibiotics. Due to possible association between FG and SGLT2 inhibitors, patients presenting with signs and symptoms of FG who are taking SGLT2 inhibitors should be examined for infection in the urogenital area and treated promptly.

BACKGROUND
Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor used to lower blood glucose in adults with type 2 diabetes. In addition to their ability to lower blood glucose, SGLT2 inhibitors have beneficial effects on blood pressure and weight loss and have a low risk of hypoglycaemia. Emerging evidence has also demonstrated the benefits of SGLT2 inhibitors in cardiovascular disease, chronic kidney disease and heart failure (EMPA-REG [empagliflozin], CANVAS [canagliflozin] and DECLARE TIMI-58 [dapagliflozin], respectively).1–3 This class of antihyperglycaemic medications reduces blood glucose by increasing glucose excretion in the urine. Because of this glycosuric effect, bacterial growth resulting in genitourinary infections are commonly reported adverse effects of SGLT2 inhibitors.1–3 However, many prescribers continue to select dapagliflozin for its positive renal outcomes and cardiac benefits after carefully weighing it against the risk of urogenital infection and diabetic ketoacidosis.1,3

Concerns that SGLT2 inhibitors may be associated with more serious infections emerged after the FDA issued a black box warning in 2018.4 This warning described twelve cases of Fournier’s gangrene (FG) that occurred in patients taking the SGLT2 inhibitors dapagliflozin, canagliflozin and empagliflozin.5 FG, also known as necrotising fasciitis of the perineum, is a rare, rapidly progressing and potentially fatal urological emergency. Because FG is usually polymicrobial, treatment requires urgent surgical debridement and administration of broad-spectrum antimicrobials.2 Prior to this, the FDA had issued a black box warning for canagliflozin regarding leg and foot amputation risk which was removed in 2020, but remained described in the “Warnings and Precautions” section of the prescribing information.6

Risk factors for FG include diabetes, local trauma, male gender, obesity, older age, immunosuppression, HIV infection, end-stage renal or liver failure, smoking and alcohol abuse.7 The level of blood glucose control is important as uncontrolled diabetes has been linked to more severe infections requiring greater interventions and worse outcomes. Interestingly, although male gender is a risk factor for the development of FG, cases of FG occurring in patients taking SGLT2 inhibitors have been observed in males and females at similar frequencies.1,4

We present a case of FG that developed in a patient taking dapagliflozin. The patient was treated with multiple debridement procedures and broad-spectrum antibiotics. Other case reports have described the development of FG associated with SGLT2 inhibitors.8–11 However, this is the first case
Case report portraying a female patient who developed FG while taking dapagliflozin.

CASE PRESENTATION
A 71-year-old female patient presented to the emergency department (ED) of a rural hospital in Ontario, Canada after a fall in her bathroom. The patient's medical history was significant for type 2 diabetes treated with glimepiride, dapagliflozin and linagliptin; hypertension treated with trandolapril, amlodipine and bisoprolol; and hypercholesteremia treated with rosuvastatin. The patient has been taking dapaglifozin for 5 years and has been diabetic for 8 years. She was not complaining of pain but had experienced some discomfort for a few days. On examination by the medical team, an extensive abscess was observed in the perianal area with 5 cm of necrotic tissue and foul-smelling discharge (figure 1). This was located in right ischiorectal fossa and was evaluated to be an advanced infection. She was given a single intravenous dose of 3.375 g piperacillin–tazobactam in the ED and admitted for emergency surgery and debridement. The procedures included incision, drainage and debridement of the right ischiorectal fossa abscess.

INVESTIGATIONS
At presentation, her blood pressure was 139/69 mmHg, her heart rate was 118 bpm and her temperature was 36.2°C (97.2°F). Her HbA1c was 11.7% (104 mmol/mol IFCC) and her random blood plasma glucose was 25.4 mmol/L. She presented with leucocytosis and neutrophilia with a white blood cell count of 33.2×10⁹/L and a neutrophil count of 29×10⁹/L. Her potassium level stayed around 3.4 mEq/L during the admission and the platelet reported at 95×10⁹/L. Her serum creatinine was 209 μmol/L (Cockcroft-Gault eGFR of 22 mL/min/1.73 m²). Her urinalysis was positive for glucose, ketones, blood and protein, and negative for leukocytes and nitrates. Her high serum creatinine and proteinuria may have been an indication for chronic kidney disease secondary to uncontrolled diabetes; however, more serum creatinine measurements were required to definitively describe her kidney status.

TREATMENT
On day 2 of admission, she was started on intravenous vancomycin 2 g, intravenous piperacillin–tazobactam and intravenous clindamycin. Based on the therapeutic drug monitoring and trough levels, vancomycin was put on hold after 2 days. She received operations on days 3 and 6 (figures 2 and 3), which included debridement, rigid sigmoidoscopy and perianal ring block. On day 8 of admission, she received another debridement of the wound and dressing change. During her stay at the hospital, her blood pressure medications were continued as normal, except for trandolapril which was substituted for perindopril due to availability on hospital formulary. Her blood pressure remained consistent until day 5, at which time it increased and remained elevated for a few days thereafter. Her dose of perindopril was subsequently increased, and she also received hydralazine on day 8 of admission. To compensate for dapagliflozin being discontinued, the doses for her other diabetes medications were increased. She was also initiated on insulin glargine 10 U with breakfast and insulin aspart three times daily on a low–moderate sliding scale. Her random blood glucose measurement was lowered to 18.6 mmol/L on day 2 and 6.7 mmol/L by day 5 of admission. The random blood glucose values remained stable and within target range between 5 and 6 mmol/L until discharge.

Her dressings were changed daily after each bowel movement and as needed. An obstetric bed was used to assist dressing changes and she was referred to a dietician to optimise her diet for diabetes management and promote wound healing.

Figure 2  Operative procedures on fifth day of admission.

Figure 3  Debridement on day 7 of admission.

Figure 4  Blood test results over the duration of stay at the hospital.

Figure 5  Neutrophil count over the duration of stay at the hospital.
The perineum swab collected on admission revealed rare polymorphonuclear leucocytes, rare epithelial cells, many Gram-positive cocci, many Gram-negative bacilli and a few Gram-positive bacilli. It showed heavy growth of *Streptococcus anginosus* susceptible to penicillin and clindamycin. Clindamycin and piperacillin–tazobactam were continued for 7 days. The blood culture and the urine culture tests came back as negative.

**OUTCOME AND FOLLOW-UP**

Our patient had uncontrolled diabetes and experienced trauma to the perianal area after sustaining a fall. Other risk factors in this patient included obesity and older age. The uncontrolled diabetes potentially prolonged the healing process and treatment of the infection. However, by day 8 of the admission, white blood cell average was $9 \times 10^9\text{/L}$ and neutrophil average was $6 \times 10^9\text{/L}$ (figures 4 and 5). After 14 days of hospitalisation, the patient was discharged with controlled blood glucose under insulin administration, and a clean and odourless wound.

Given that her serum creatinine was high throughout her stay at the hospital and protein was observed in her urine, she may have been suffering from stage G4 (severe) diabetic kidney disease with microalbuminuria, which is common among...
patients with uncontrolled diabetes. This requires multiple dose adjustments to chronic medications that are cleared renally on discharge. Other important pieces of information that should be shared on discharge include diabetes education and demonstrating insulin use techniques.

DISCUSSION
FG is a life-threatening and rapidly progressing necrotising fasciitis of polymicrobial aetiology involving the perineal and genital areas. We have herein presented a case of management of FG including sequential aggressive debridement procedures and broad-spectrum antibiotic therapy. Although more commonly described in the literature for men, this is the first published report, to our knowledge, of FG occurring in a woman on a SGLT2 inhibitor.

FG shows vast heterogeneity in clinical presentation from innocuous cellulitis adjacent to the portal of entry or source of infection, to severe pain, oedema and systemic features. The patient’s chief complaint included discomfort in the perianal area; a large abscess with foul-smelling discharge in the absence of fever was further discovered on physical examination; however, this was not described by the patient as a primary concern. Interestingly, this presentation differs from the FDA warning detailing this was not described by the patient as a primary concern. Interestingly, this presentation differs from the FDA warning detailing this was not described by the patient as a primary concern. Interestingly, this presentation differs from the FDA warning detailing this was not described by the patient as a primary concern. Interestingly, this presentation differs from the FDA warning detailing this was not described by the patient as a primary concern. Interestingly, this presentation differs from the FDA warning detailing this was not described by the patient as a primary concern. Interestingly, this presentation differs from the FDA warning detailed the symptoms of FG which include symptoms of tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, with an elevated temperature over 100.4°F. Crepitus of the inflamed tissues is also a common feature due to the presence of gas-forming organisms, although was not present in the evaluated patient. Imaging techniques such as CT scans can be used to confirm diagnosis; however, this was not required in the present case. Laboratory investigations were significant for leucocytosis and neutrophilia with a white blood cell count of 33.2 × 10^9/L and neutrophil count of 29 × 10^9/L, which is consistent with other case reports in the literature that also describe leucocytosis, thrombocytopenia, electrolyte derangements and elevated inflammatory markers. The location of FG occurred in the perianal area, but commonly originates from the gastrointestinal tract, genitourinary tract and the skin.

Comorbid systemic disorders and additional risk factors are being identified in patients with FG, with diabetes mellitus and alcohol misuse being among the most common concern in 20%–70% and 25%–50% of patients, respectively. Other risk factors described in the literature include immunosuppression, chemotherapy, chronic corticosteroid use, liver disease and kidney disease. The patient described had multiple risk factors for the development of FG including uncontrolled diabetes, possible poor kidney function and use of a SGLT2 inhibitor. FG is usually secondary to infections with local trauma, operative procedures or urinary tract disease as these events provide portals of entry for bacteria causing FG; however, a minority of cases remain idiopathic. In the present patient, an event, namely a fall, was implicated in the development of FG thereby allowing identification of the source of infection.

Management of FG included urgent debridement of the necrotic tissue, followed by broad-spectrum antibiotics. The Infectious Disease Society of America recommends that empiric antimicrobial therapies for FG cover aerobic and anaerobic bacteria, including methicillin-resistant Staphylococcus aureus (MRSA). Common pathogens are those found on the skin including Staphylococcus and Streptococcus species as well as genitourinary bacteria like Escherichia coli and Bacteroides species. Empiric antimicrobial therapy should include vancomycin or linezolid to cover MRSA plus either piperacillin–tazobactam, a carbapenem,

Learning points
▶ The causal relationship between Fournier’s gangrene (FG) and sodium-glucose cotransporter 2 inhibitors have not been extensively demonstrated.
▶ Given the emergency nature of FG, prompt diagnosis and treatment of this condition is really important.
▶ Many physicians choose dapagliflozin for its positive renal outcome or cardiac benefits, but the benefits should be weighed against the risk of urogenital infection and diabetic ketoacidosis.

Acknowledgements The authors would like to thank the pharmacy and nursing team at Winchester District Memorial Hospital for their support during the process and collecting the data.

Contributors AE: conception and design, acquisition of data or analysis and interpretation of data. Drafting the article or revising it critically for important intellectual content. Final approval of the version published. Agreement to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved. Original manuscript conception and design. Original manuscript write-up. Acquisition of data. Literature search and analysis. Acquisition of patient consent. Analysis and interpretation of data. Critical revision and editing. YT: conception and design, acquisition of data or analysis and interpretation of data. Drafting the article or revising it critically for important intellectual content. Final approval of the version published. Agreement to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved. Original manuscript conception and design. Original manuscript write-up. Acquisition of data. Literature search and analysis. Acquisition of patient consent. Analysis and interpretation of data. Critical revision and editing. MD: conception and design, acquisition of data or analysis and interpretation of data. Drafting the article or revising it critically for important intellectual content. Final approval of the version published. Agreement to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved. MD: conception and design, acquisition of data or analysis and interpretation of data. Drafting the article or revising it critically for important intellectual content. Final approval of the version published. Agreement to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved.

The Infectious Disease Society of America recommends that empiric antimicrobial therapies for FG cover aerobic and anaerobic bacteria, including methicillin-resistant Staphylococcus aureus (MRSA). Common pathogens are those found on the skin including Staphylococcus and Streptococcus species as well as genitourinary bacteria like Escherichia coli and Bacteroides species. Empiric antimicrobial therapy should include vancomycin or linezolid to cover MRSA plus either piperacillin–tazobactam, a carbapenem,
article or revising it critically for important intellectual content. Final approval of the version published. Agreement to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved. DE: conception and design, acquisition of data or analysis and interpretation of data. Drafting the article or revising it critically for important intellectual content. Final approval of the version published. Agreement to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved. SL: conception and design, acquisition of data or analysis and interpretation of data. Drafting the article or revising it critically for important intellectual content. Final approval of the version published. Agreement to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD
Ali Elbeddini http://orcid.org/0000-0002-3339-6203

REFERENCES
1 Zinin B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med Overseas Ed 2015;373:2117–28.
2 Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–57.
3 Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med Overseas Ed 2019;380:347–57. doi:10.1056/NEJMoa1812389
4 Bersoff-Matcha SJ, Chamberlain C, Cao C, et al. Fournier gangrene associated with sodium-glucose cotransporter-2 inhibitors: a review of spontaneous postmarketing cases. Ann Intern Med 2019;170:764–9.
5 U.S. Food and Drug Administration. FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes, 2018. Available: https://www.fda.gov/drugs/safety-and-availability/fda-warns-about-rare-occurrences-serious-infection-genital-area-sglt2-inhibitors-diabetes
6 US Food and Drug Administration. FDA removes boxed warning for type 2 diabetes medicine canagliflozin, 2020. Available: <https://www.fda.gov/drugs/safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin> [Accessed 26 Oct 2020].
7 Singh A, Ahmed K, Aydin A, et al. Fournier’s gangrene. A clinical review. Arch Ital Urol Androl 2016;88:157–64.
8 Elbeddini A, Gallinger J, Davey M, et al. A case of Fournier’s gangrene in a patient taking canagliflozin for the treatment of type II diabetes mellitus. Am J Case Rep 2020;21:e92015–1.
9 Kumar S, Costello AI, Colman PG. Fournier’s gangrene in a man on empagliflozin for treatment of type 2 diabetes. Diabet Med 2017;34:1646–8.
10 Onder CE, Gursoy K, Kuskonmaz SM, et al. Fournier’s gangrene in a patient on dapagliflozin treatment for type 2 diabetes. J Diabetes 2019;11:348–50.
11 Sunumu V, Dapagliflozin_FB, Fiks B. Case report: fixed drug eruption caused by dapagliflozin. Case Rep Turk J Endocrinol Metab 2019;23:64–7.
12 Thwaiti A, Khan A, Malik A, et al. Fournier’s gangrene and its emergency management. Postgrad Med J 2006;82:516–9.
13 Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis [Internet] 2014;59:e10–52.
14 Andreadi E, Zürcher C, Tanutzer A, et al. Clindamycin affects group A Streptococcus virulence factors and improves clinical outcome. J Infect Dis 2017;215:269–77.
15 Nagano Y, Yakame NK, Aoki H, et al. Fournier’s gangrene in a patient with type 2 diabetes mellitus treated with empagliflozin: a case report. Drug Saf 2019;6:1–5.
16 Rodler S, Weig T, Finkenzeller C, et al. Fournier’s gangrene under sodium-glucose cotransporter 2 inhibitor therapy as a life-threatening adverse event: a case report and review of the literature. Curruse 2019;11:e5778.