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 Lee 1

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 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.4 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.5

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

Figure 1 Necrotising tissue observed in examination.
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 leucocytes 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.
Table 1 Published case reports on Fournier’s gangrene in patients on SGLT2 inhibitors

<table>
<thead>
<tr>
<th>Case report</th>
<th>Kumar et al9</th>
<th>Onder et al10</th>
<th>Nagano et al15</th>
<th>Rodler et al14</th>
<th>Elbeddini et al8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41</td>
<td>64</td>
<td>34</td>
<td>39</td>
<td>72</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>SGLT2</td>
<td>Empagliflozin (14 months ago)</td>
<td>Dapagliflozin (6 months ago)</td>
<td>Empagliflozin (~5 months ago)</td>
<td>Dapagliflozin (4 years)</td>
<td>Canagliflozin (6 years)</td>
</tr>
<tr>
<td>Other diabetes</td>
<td>Metformin</td>
<td>Metformin</td>
<td>Metformin</td>
<td>Metformin</td>
<td>Metformin</td>
</tr>
<tr>
<td>medications</td>
<td>Type 2 diabetes</td>
<td>Type 2 diabetes</td>
<td>Type 2 diabetes</td>
<td>Type 2 diabetes</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Sex</td>
<td>Sex</td>
<td>Sex</td>
<td>Sex</td>
<td>Sex</td>
</tr>
<tr>
<td></td>
<td>Current smoker</td>
<td>Recurrent fungal infection</td>
<td>Urinary catheterisation/operative procedures</td>
<td>Recurrent fungal infection</td>
<td>Recurrent fungal infection</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td>Scrotal swelling, history of multiple episodes of genital thrush</td>
<td>Scrotal pain, swelling and redness that had progressed over a period of 3 days</td>
<td>Pain and swelling in the perineum</td>
<td>Fever (1 week), swelling and pain in groin and testicles with pus discharge</td>
<td>Severe abdominal pain, nausea</td>
</tr>
<tr>
<td>Blood glucose levels</td>
<td>Plasma glucose on presentation was 19.9 mmol/L HbA1c 8.8%</td>
<td>Plasma glucose on presentation was 14.4 mmol/L HbA1c 7.4%</td>
<td>Plasma glucose was 6.1 mmol/L at presentations HbA1c 6.5%</td>
<td>Plasma glucose on presentation was 16.8 mmol/L HbA1c 10%</td>
<td>HbA1c 7.5%</td>
</tr>
<tr>
<td>Perineal examination</td>
<td>Grossly swollen and indurated scrotum with bilateral inguinal lymphadenopathy</td>
<td>Tender and indurated scrotum and bilateral inguinal lymphadenopathy</td>
<td>Skin redness, induration, swelling and tenderness observed in the perineum, scrotum and left inguinal region</td>
<td>Swelling in right groin, intense smell</td>
<td>Red, tender scrotum with peeling skin, indurated perineum</td>
</tr>
<tr>
<td>Imaging</td>
<td>CT revealed features consistent with Fournier’s gangrene (FG)</td>
<td>CT scan of the lower abdomen and pelvis revealed findings consistent with FG</td>
<td>Ultrasound revealed normally perfused testicles and several abscesses in the groin</td>
<td>CT scan positive for gas-forming infection in ischioanal fossa and suspicious for perianal fistula</td>
<td></td>
</tr>
<tr>
<td>Wound management</td>
<td>Emergency exploration, debridement, application of vacuum dressing</td>
<td>Debridement Excision of necrotic tissues and abscess pouches in the left gluteal region, scrotum and lower abdomen Placement of colostomy</td>
<td>Surgical incision, and debridement and drainage</td>
<td>Removal of necrotic tissue and further debridement procedures</td>
<td>Loop sigmoid colostomy, multiple debridement procedures, negative pressure dressing and rectal tube</td>
</tr>
<tr>
<td>Culture results</td>
<td>Operative cultures: heavy polymicrobial growth of Streptococcus anginosus, mixed anaerobes and Gram-negative bacilli</td>
<td>Information not available</td>
<td>Methicillin-resistant Staphylococcus aureus</td>
<td>Day 3: culture of smears from the groin and scrotum were positive for Peptostreptococcus anaerobius Subsequent cultures: positive for Candida albicans</td>
<td>Bacteroides ovatus, Prevotella dentium and Actinomyces species</td>
</tr>
<tr>
<td>Antimicrobial use</td>
<td>2-week course of intravenous antibiotics (amoxicillin, gentamicin and vancomycin, changed to intravenous meropenem), discharged home with oral antibiotics</td>
<td>4-week course of intravenous antibiotics (ceftriaxone 1 g twice a day and meronidazole 500 mg three times a day)</td>
<td>3-week course of intravenous antibiotics (meropenem and clindamycin which was changed to vancomycin after MRSA was cultured)</td>
<td>3-week course of intravenous antimicrobials (gentamicin and piperacillin–tazobactam started in ED was changed to linezolid, meropenem and nystatin on day 2; linezolid stopped after 3 days and meropenem and nystatin changed to fluconazole on day 11)</td>
<td>8 days of intravenous antibiotics (meropenem, vancomycin, clindamycin), step down to 6 days of oral antibiotics (sulfamethoxazole–trimethoprim, ciprofloxacin and metronidazole)</td>
</tr>
<tr>
<td>Medication management</td>
<td>Discontinue empagliflozin</td>
<td>Discontinue dapagliflozin</td>
<td>Sitagliptin restarted 9 days after surgery Metformin started 21 days after surgery Insulin initiated according to sliding scale</td>
<td>Dapagliflozin discontinued Basal-bolus insulin from admission to day 19 Metformin and sitagliptin restarted on day 23 of admission</td>
<td>Canagliflozin discontinued; remaining home medications continued as before</td>
</tr>
</tbody>
</table>

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 9×10⁹/L and neutrophil average was 6×10⁹/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 the symptoms of FG which include symptoms of tenderness, redness, or swelling of the genitals or the area from the genitals to the perianal area; a large abscess with foul-smelling discharge.

Leucocytosis and neutrophilia with a white blood cell count of 33.2×10⁹/L and neutrophil count of 29×10⁹/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.

Comorbidity 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, or the combination of ceftriaxone and metronidazole for broad-spectrum coverage. If streptococcal species are suspected, a penicillin plus clindamycin should be used. Since this case was believed to be a polymicrobial necrotising fasciitis, vancomycin, piperacillin and clindamycin were initiated and then intravenous antibiotics were tailored once swab culture came positive with heavy growth of S. anginosus. Vancomycin was kept on hold and the patient continued on piperacillin and clindamycin. This combination is important as clindamycin reduces the virulence of streptococcal species and improves outcome regardless of resistance. A beta-lactam is added to clindamycin because of concerns regarding resistance to clindamycin.

There is not enough evidence to propose a causal relationship between FG and use of SGLT2 inhibitors. However, between March 2013 and January 2019, fifty-five cases of FG were reported to the FDA in patients on SGLT2 inhibitors. Out of the 35, 16 cases were linked to dapagliflozin, 18 linked to empagliflozin and 21 linked to canagliflozin. A recent case report published by Elbeddini et al presented a case of an elderly male patient on canagliflozin who developed FG. Other published case reports, all males, are described in detail in table 1. In the present study, however, we presented an elderly female patient on dapagliflozin who developed FG in the perianal area but did not present to the ED with classical symptoms of FG.

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. Drafting the thoughts and ideas. 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. AG: conception and design, acquisition of data or analysis and interpretation of data. Critical revision and editing. YT: conception and design, acquisition of data or analysis and interpretation of data. Critical revision and editing.
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