Fournier's gangrene under SGLT-2 inhibitor therapy: A literature review and case report

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A B S T R A C T

INTRODUCTION: Fournier’s gangrene is a rare, life-threatening necrotizing infection of the perineum. In 2018, the U.S. Food and Drug Administration (FDA) issued a warning regarding a possible connection between Fournier’s gangrene and new oral anti-diabetic drugs called SGLT-2 inhibitors. There are only a few published case reports of Fournier’s gangrene in patients treated with SGLT-2 inhibitors and a total of 55 patients reported by the FDA to date.

PRESENTATION OF CASE: We report a case of Fournier’s gangrene in a patient with multiple risk factors, including diabetes type 2, smoking, obesity and immunosuppression.

DISCUSSION: Further studies are needed to determine whether or not it is the SGLT-2 inhibitor itself that increases the risk of Fournier’s gangrene, or the fact that the patients receiving this kind of drug is a subgroup of patients with multiple risk factors.

CONCLUSION: New oral anti-diabetic drugs, SGLT-2 inhibitors, may be associated with Fournier’s gangrene. Surgeons should become suspicious when patients with diabetes present with perineal symptoms.

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1. Introduction

Fournier’s gangrene is a rare, life-threatening necrotizing infection of the perineum. The main risk factors for Fournier’s gangrene, that should raise a higher level of suspicion, are diabetes, obesity, immunosuppression and smoking. These are conditions leading to compromised host immunity, all of which create an environment that is favorable for establishing infection. The principle for treatment is urgent patient resuscitation, broad-spectrum antibiotic therapy and immediate surgical debridement, to reduce the systemic toxicity and stop the rapid infectious progress [1].

In 2018, the U.S. Food and Drug Administration (FDA) issued a warning regarding a possible connection between Fournier’s gangrene and new oral anti-diabetic drugs called SGLT-2 inhibitors. There are only a few published case reports of Fournier’s gangrene in patients treated with SGLT-2 inhibitors and a total of 55 patients reported by the FDA to date.

We have done a literature review and found a total number of 8 cases of Fournier’s gangrene in patients with SGLT-2 inhibitors including our case, which are summarized in this article along with reporting our new case. Previous case reports have been published in journals of Medicine and Diabetes. It is important also for surgeons to be aware of this possible connection. This project has been reported in line with the SCARE criteria [2].

2. Case report

In January 2020, a 52-year-old female presented at the emergency department with three days of fever and increased swelling and pain in the gluteal region.

The patient had a past medical history of type 2 diabetes, for which she had been taking the SGLT-2 inhibitor dapagliflozin for 1.5 years, in addition to the previous regimen with insulin. She also had obesity, BMI 42, hypertension, asthma and hepatitis B. She was smoking 20 cigarettes per day. The patient was substituted with prednisolone regularly, 15 mg per day, due to previous adrenalec- tomy, and had also undergone hemithyroidectomy due to thyroid cancer. She was considered a patient with severe systemic disease, ASA 3. There was no previous history of genital or urinary tract infections.

The patient presented with fever and pain in the gluteal region for three days, however she had not taken any extra doses of prednisolone. At presentation, the patient was not clinically distressed, and she was stable. The patient’s body temperature was 38.0 °C. The plasma glucose level was significantly elevated, 26.3 mmol/L. Test of long-term glucose level, HBA1c, was not performed.

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Physical examination revealed an abscess, the size of a tennis ball, 5 cm from anus on the left side of the gluteal region. It was indurated, inflamed and warm with pus discharge from a minor opening. The right side of the gluteal region was unaffected.

Treatment with intravenous fluid, broad-spectrum antibiotics (4 g piperacillin with 0.5 g tazobactam) and intravenous cortisone was rapidly initiated. All oral medication was ceased on admission due to preoperative fasting. No radiologic investigation was carried out. It was clinically considered as a perianal abscess. The patient was in a stable condition and was prepared for surgical incision later the same night.

Eight hours after arrival, the patient was on the table for surgical exploration under general anesthesia. The procedure was performed by a surgical resident accompanied by a specialist in general surgery. Large amounts of pus and odorous necrotic material were released during debridation. The tissue was falling apart upon touch, and the cavity reached almost the way to the rectal wall. The cavity was irrigated with saline solution and filled with absorbent dressing (Aquacel®). It was described as an abscess; neither a typical perianal nor a typical pilonidal abscess.

The patient was discharged on day 2, with a plan for daily intermittent irrigation and change of absorbent dressing at the local health care centre, and future follow-up at the colorectal unit.

However, the patient returned to the emergency department on day 3, again with high fever of 39 °C. Laboratory tests showed elevated inflammatory markers with a high white blood cell count on 19 × 10^9/L and C-reactive protein of 227 mg/L. The pain now included the contralateral side of the gluteal region. Pus was emerging from the opening and there was increased redness and swelling on both sides.

The patient went through a second surgical exploration during the night. The second procedure was performed by a surgical resident accompanied by a specialist in general surgery. The adipose tissue was grey and watery. All tissue that was considered to be nonvital was excised. Penrose drains were inserted through multiple openings. It was described as a large horseshoe abscess with rapid progression.

The following morning, on day 4, a third surgical exploration was performed by a specialist in colorectal surgery along with a specialist in general surgery. It revealed that the infectious progress had continued with even more necrosis of the underlying tissue, now reaching along the wall of the rectum. The condition had progressed into fulminant Fournier’s gangrene. Considering the devastating consequences of gangrene left untreated, a more radical debridement was performed at this stage. More adipose tissue was debrided, along with muscular tissue that could not be spared.

It was then noted that the patient was treated with oral dapagliflozin, a SGLT-2 inhibitor, which was discontinued permanently.

The patient was transferred to a center with the capacity of hyperbaric oxygen therapy, although this was never carried out. Broad-spectrum antibiotics were changed from piperacillin and tazobactam to meropenem and clindamycin. A fourth surgical exploration on day 5 showed that the area was still inflamed, but there were no further signs of necrosis, and no need for further debridement or hyperbaric oxygen therapy. On day 6, a sigmoid colostomy was made, to enhance the healing process due to the proximity to the anus.

Bacterial analysis from cultures obtained during surgeries showed a combination of aerobic and anaerobic pathogens, not further specified. Tests for group A streptococci were negative. The blood cultures remained negative for bacteria.

The patient was discharged on day 18. Two months later, the healing process was still ongoing, and the wound was tended to by home health care on a daily basis. Five months later, the wounds were fully healed with new skin covering the area.

3. Discussion

The case was reported to the Swedish Medical Products Agency as the first case of Fournier’s gangrene in association with dapagliflozin in Sweden. From the surgical perspective, it is important to be aware of the possible connection between Fournier’s gangrene and new oral anti-diabetic drugs called SGLT-2 inhibitors.

The treatment of Fournier’s gangrene relies on instant identification of suspected cases, followed by immediate surgical debridation and broad-spectrum antibiotics. Bare removal of the drug itself is not enough to stop the gangrene. However, it is important that the surgeon identifies that the patient is treated with a SGLT-2 inhibitor, promptly ceases the therapy and reports this as an adverse event.

A literature review was performed, including previous case reports of Fournier’s gangrene in patients treated with SGLT-2 inhibitors. An overview of these previous cases along with this case is presented in Table 1. The first case was presented in 2016. The age of patients range from 39 to 72 years of age. Five of eight cases were patients treated with dapagliflozin. The remaining three patients were treated with other types of SGLT-2 inhibitors; empagliflozin and canagliflozin. The time between drug initiation and onset of symptoms ranged from 10 days to 6 years. Three cases presented within months and three cases presented within years. Body mass index (BMI) was not stated in three cases. However, in all the five cases where BMI was presented, it was above 30. In fact, in three of these cases BMI was above 40 and in one case as high as 62. In one of the cases where BMI was not stated, obesity was listed as a comorbidity. Obesity and smoking seem to be common comorbidities. Length of hospital stay varied between 12 and 51 days. Two patients required treatment at the intensive care unit.

In summary, the patient presented in this case had characteristics similar to the previous cases presented in the literature, with obesity, smoking and a long hospital stay appearing to be the most striking similarities.

Further studies are required to determine whether it is in fact the SGLT-2 inhibitor itself that causes the gangrene, or if it is the subgroup of patients receiving this kind of anti-diabetic drug that constitutes the risk.

### Table 1

| Publ | Age | Drug name | Drug initiation | HbA1c | BMI | Comorbidities | Length of hospital stay | ICU | Reference |
|------|-----|-----------|-----------------|-------|-----|---------------|------------------------|-----|-----------|
| 2016 | 67  | dapagliflozin | 3 weeks | 10.8% | n.a. | Obesity | 51 | n.a. | Chi et al. [3] |
| 2017 | 41  | empagliflozin | 7 months | 11.2% | 38 | Obesity, smoking | 15 | n.a. | Kumar et al. [4] |
| 2018 | 60  | dapagliflozin | 4 months | n.a. | n.a. | n.a. | 12 | n.a. | Omer et al. [5] |
| 2019 | 64  | dapagliflozin | 6 months | 7.4% | 33 | Obesity, ex-smoking | 30 | n.a. | Onder et al. [6] |
| 2019 | 57  | empagliflozin | 10 days | n.a. | 62 | Obesity | 30 | n.a. | Elshimy et al. [7] |
| 2019 | 39  | dapagliflozin | 4 years | 10.0% | 49 | Obesity, smoking, hypertension | 27 | 18 | Rodler et al. [8] |
| 2020 | 72  | canagliflozin | 6 years | 7.5% | n.a. | Previous prostate cancer | 30 | n.a. | Elbeddini et al. [9] |
| 2020 | 52  | dapagliflozin | 1.5 years | n.a. | 42 | Obesity, smoking, hypertension | 18 | 0 | This paper |
4. Conclusion

New oral anti-diabetic drugs, SGLT-2 inhibitors, may be associated with Fournier’s gangrene. Previous case reports have been published in journals of Medicine and Diabetes. Even though surgeons generally are not particularly interested in diabetic medication, it is important even for surgeons to become suspicious when patients with diabetes present with perineal symptoms.

Declaration of Competing Interest

None.

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None.

Ethical approval

No ethical approval was required.

Consent

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

Author contribution

Lisa Ellegård – data collection, literature review, writing the paper.
Mattias Prytz – editing the paper.

Registration of research studies

Not applicable.

Guarantor

Mattias Prytz.

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