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Fournier's Gangrene in a Patient With CKD Without Diabetes Possibly Related to Sodium-Glucose Cotransporter 2 Inhibitor Therapy

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INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2)-inhibitors reduce the risk of adverse cardiovascular and kidney outcomes in patients with diabetes mellitus, chronic heart failure, or chronic kidney disease (CKD).[1,2] Beneficial effects were proven in ample randomized controlled trials (RCTs) in patients with or without type 2 diabetes, making SGLT2-inhibitors game-changers not only in diabetes, but also in CKD and chronic heart failure. SGLT2-inhibitors have robust benefits for reducing cardiovascular death and hospitalization for heart failure.[2] RCTs also support their use for modifying risk of CKD progression irrespective of the patient's diabetes status, primary kidney disease, or kidney function. The benefits of therapy outweigh any serious side effects.[1,2]

SGLT2-inhibitors increase the excretion of glucose through the urine; thus, the commonly associated adverse effects include increased risks of mycotic genital and urinary tract infections. In 2018, 5 years after approval of the first SGLT2-inhibitor, the US Food and Drug Administration issued a warning that 12 cases of necrotizing fasciitis (Fournier's gangrene), a life-threatening infection mostly caused by aerobic and anaerobic bacteria have been reported in patients with type 2 diabetes.[3]

Our patient with CKD but without diabetes mellitus presented with Fournier's gangrene on SGLT2-inhibitor treatment.[3,4] To date, with more than 90,000 patients under SGLT2-inhibitor therapy investigated in RCTs, according to the pharmacovigilance departments of AstraZeneca and Boehringer Ingelheim, this is the first report of a Fournier's gangrene on SGLT2-inhibitor treatment in a patient with CKD without diabetes. Key teaching points of this case are presented in Table 1.

CASE PRESENTATION

A physician in his sixth decade presented to the emergency unit with a mild inflammation and livid discoloration of the skin of his scrotum that had developed the same day over the course of a few hours. As a doctor himself, he was worried about the possible suspected diagnosis of early Fournier's gangrene related to the use of a SGLT2-inhibitor, which he started 23 months before this event because of CKD due to Alport syndrome. After starting SGLT2-inhibitor therapy, the patient living with Alport syndrome was followed-up with prospectively (European Alport

Table 1. Teaching points

We report a first case of a Fournier's gangrene as suspected unexpected serious adverse reaction in a patient with CKD without diabetes under SGLT2-inhibitor therapy.
As a key consideration, this case illustrates that good patient education and patient's awareness prevented worse outcome in this life-threatening case of Fournier's gangrene.
This case establishes an important precedent, but we encourage the publication of other cases, to guide possible preventive measures in such instances. After all, numbers of similar cases might increase, given the very remarkably increasing numbers of patients with CKD receiving SGLT2-inhibitors.

CKD, chronic kidney disease; SGLT2, sodium-glucose cotransporter 2.

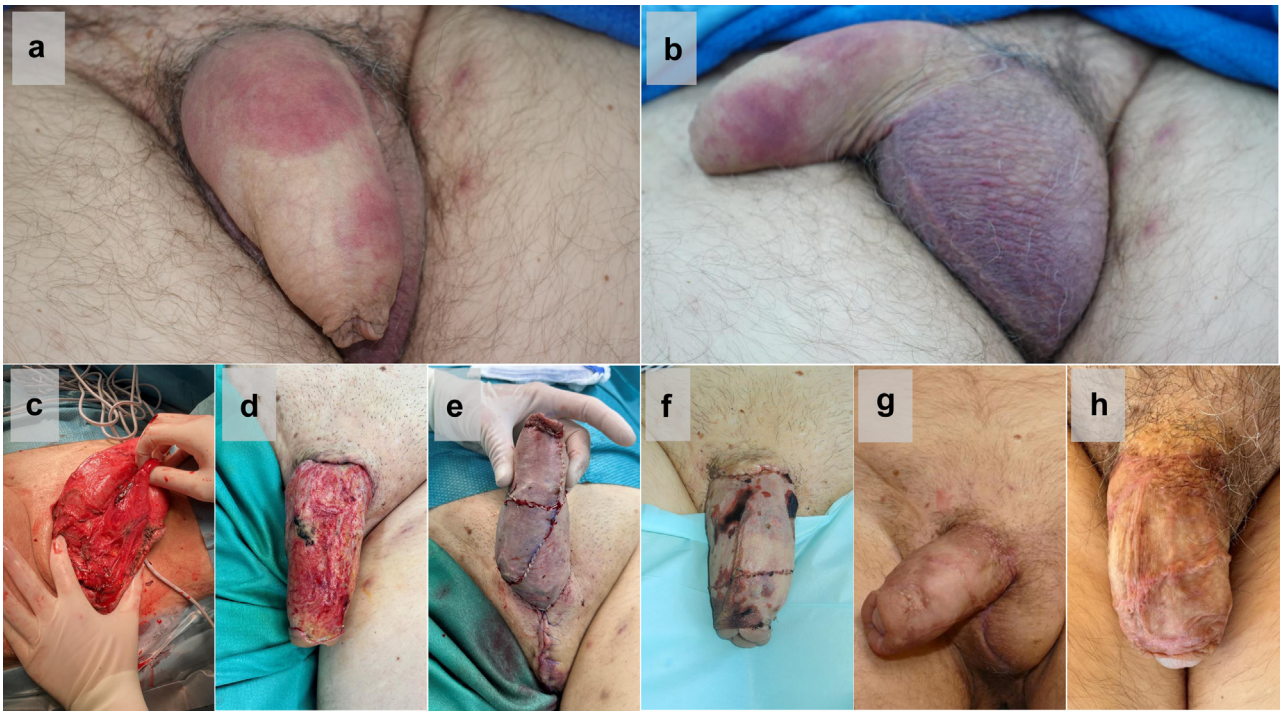

Figure 1. Course and surgical care of Fournier's gangrene in the patient. Gangrene of the (a) penile shaft and (b) scrotum within the first 2 hours of hospital admission. (c) The extent of the wound area was documented during the second look operation on day 3. On day 5, the penile shaft was covered by a split-thickness skin graft (d: before; e: after), which healed well (f) after 2 weeks, (g) after 2 months, and (h) after 4 months.

Therapy Registry, AZ 10/11/06; ClinicalTrials.gov identifier NCT 02378805).

Previous medical history included CKD, renal hypertension, dyslipoproteinemia, coronary artery disease with acute myocardial infarction, which resolved with a normal left ventricular function after application of a drug-eluting stent, an outlet stenosis of the truncus coeliacus due to ligamentum arcuatum syndrome, and inner-ear hearing impairment (due to Alport syndrome). Current medical therapy consisted of ramipril, atorvastatin, ezetimibe, aspirin, allopurinol, tamsulosin, cholecalciferol, and an SGLT2-inhibitor at standard oral dose of 10 mg/d. At yearly follow-ups, a normal HbA1c was documented. Baseline creatinine before the event was 1.6 mg/dl corresponding to an estimated glomerular filtration rate (CKD-Epidemiology Collaboration) of 46 ml/min, the albumin-to-creatinine ratio was 475 mg/g.

On hospital admission, there were no signs of systemic inflammation in the initial laboratory tests but only a suspicious area with subcutaneous blistering on the initial computer tomography. Clinically, however, the local infection progressed rapidly with penile to scrotal spread within 2 hours (Figure 1a and b) despite immediate start of vancomycin and piperacillin/tazobactam. Consequently, the patient underwent prompt surgically debridement of all suspicious and impaired lesions, followed by a second look debridement 48 hours later, where no significant novel necroses were detectable (Figure 1c). The intraoperative swab showed *Staphylococcus lugdunensis* treated antibiogram-compliant by linezolid and meropenem. Creatinine values increased to 4.5 mg/dl postoperatively but did not require kidney replacement therapy. The patient stayed at the intensive care unit for 1 week and kidney injury recovered to previous creatinine levels. Covering of the penile shaft was performed by a split-thickness skin graft with a satisfying surgical result (Figure 1d–g).

The patient was released after 18 days and slowly recovered in the following weeks with some sequelae (Figure 1h).

DISCUSSION

Fournier's gangrene can occur in patients who do not have diabetes; however, it is more common in patients with diabetes mellitus. In RCTs with canagliflozin, dapagliflozin and empagliflozin with more than 200,000 patient years-at-risk, the incidence rate of Fournier's gangrene was low with a rate of 15 per 100,000 patient-years; very notably, with higher incidences in the placebo group but verum group. Hazard ratios for Fournier's gangrene did not differ from other diabetes drugs.[5,6]

In our case, we interviewed the patient very extensively about his personal behavior, his intimate hygiene and risk factors. Remarkably, our patient, a nonsmoker with a normal body mass index and very

good personal hygiene, without diabetes and without local skin infection, had no common risk factors for developing Fournier's gangrene. In many countries, including Germany, there are no current regulatory and guideline recommendations about counseling for the side effect of Fournier's gangrene. The manufacturers are preparing a handout for patients treated with SGLT2-inhibitors to inform them about possible risks, signs of infection, and facts about better intimate care. In the UK, the UK Kidney Association guidelines' website provides an overview on the recommendations for physicians in the UK (https://guidelines.ukkidney.org/section-5-prescribing-sglt-2-inhibitors-safely/5g-mycotic-genital-infections-and-fourniers-gangrene/).

In our case, the use of a SGLT2-inhibitor might be related to the Fournier's gangrene or be a random coincidence. Future studies will elucidate the significance of this case with the background o exploding numbers of prescriptions for SGLT2-inhibitors worldwide.

In conclusion, in either case, our publication illustrates that good patient education and patient's awareness prevented worse outcome in this life-threatening case of Fournier's gangrene. When SGLT2-inhibitors are prescribed at an early stage of CKD in young patients, especially children, there should be a special focus on generating high level of evidence for efficacy and safety. This case, for example, has contributed to very strict hygiene rules and safety measures in the first RCT with a SGLT2-inhibitor in children with CKD, the DOUBLE PRO-TECT Alport trial (NCT05944016).

DISCLOSURE

OG received advisory fees from AstraZeneca, his employer received advisory fees from Boehringer Ingelheim. All the other authors report no conflict of interest related to this publication.

PATIENT CONSENT

The use of the photographs was consented, and the final version of this publication was read and approved by the patient, who is a doctor himself.

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The authors were all involved in caring for the patient, writing, reviewing, and revising the manuscript.

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