Fournier’s Gangrene Therapy in Gynecological Patients

Subjects: Obstetrics & Gynaecology

Contributor: ADRIANA SERRANO OLAVE, Jesus Jimenez Lopez, Ana Isabel Bueno Moral, Ernesto González-Mesa

Fournier’s gangrene (FG) is a serious pathology of the soft tissues and fascia of the perineum and genital region with a high morbidity and mortality rate. In recent years, the SGLT-2 inhibitor oral antidiabetic has been related to this entity. According to the new warnings from the main drug agencies, a compilation of cases has been initiated to establish or deny a possible causal relationship. Most of these cases have been reported in men. However, it is important not to underestimate this entity in the gynecological field, since it is extremely serious and requires intense and rapid aggressive treatment based on surgery and empiric antibiotherapy. Later, some cares are needed to involve surgical reconstruction of the defects introduced by debridement. As a result of the low incidence of FG, clinical trials’ data may be insufficient to robustly assess this issue because of the limited numbers of participants. Real-world evidence may help to clarify the association between SGLT2i and FG.

Keywords: gangrene ; SGLT-2 inhibitor ; diabetes ; genital lump ; gas ; emphysema ; surgery

1. Introduction

Fournier’s gangrene (FG) was described by Jean Alfred Fournier in 1883. Alfred, a French dermatologist and venereologist, described this acute-onset as a rapidly progressing perineal disease in previously healthy young men [1]. This condition is a rare, life-threatening bacterial necrotizing infection of the perineum. The main risk factors for Fournier’s gangrene are diabetes, obesity, immunosuppression (such as HIV), alcoholism, smoking, male sex, and the use of cytotoxic drugs [2]. Although many of the associated comorbid risk factors are common diseases, FG is rare. The published literature on its incidence in men and women is quite limited. Therefore, analysis from the US Inpatient Database of 593 civilian hospitals in 13 states in 2001 and 21 states in 2004 report that Fournier’s gangrene occurs in 1.6 of every 100,000 males per year, primarily between 50 and 79 years (3.3 of every 100,000). Nevertheless, the small number of Fournier’s gangrene cases in women precludes any meaningful incidence analysis [3][4]. The infection is usually polymicrobial due to an aerobic and an anaerobic bacteria. Traditionally, the diagnosis of this entity was made by clinical examination. Thus, the most common symptoms are scrotal edema, local pain, hyperemia, pruritus, crepitus (between 19% and 64% of cases), fever, and the presence of foul-smelling secretions. Due to a progressive increase in imaging studies, the diagnosis of this entity has become more common, computed tomography (CT) of the abdomen and pelvis being the most appropriate scan. It accurately evaluates the extent of the necrosis, including the possible dissemination to the retroperitoneum [5]. The treatment is aggressive combining surgical debridement and broad-spectrum antibiotics. Reported mortality rates range from 3% to 45%, especially associated with comorbidities such as those previously mentioned [6].

In August 2018, the US Food and Drug Administration (FDA) issued a warning that Sodium glucose co-transporter 2 inhibitors (SGLT2i) may cause FG [7]. The underlying physiopathological mechanisms are not fully clear, but there appears to be greater endothelial damage at the microvascular level. Later, in January 2019, the Spanish Society of Gynecology & Obstetrics (SEGO), the European Medicines Agency (EMA) and the Spanish Agency for Medicines and Health Products (AEMPS) published a statement mentioning the risk of FG in women treated with SGLT 2 inhibitors [8]. SGLT2i are relatively new antihyperglycemic agents that have become popular in the treatment of diabetes due to their favorable cardiac and renal outcomes. The EMA in 2012 and the FDA in 2013 approved these drugs for patients with type 2 diabetes (T2DM) as an adjunct to diet and exercise to improve glycemic control; including canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin [7][9]. The SGLT2 cotransporter is located almost exclusively in the kidney and it is responsible for the reabsorption of 90% filtered glucose by the glomerulus. Thus, its inhibition improves insulin resistance and decreases glycosylated hemoglobin (HbA1c) values. By inhibiting the reabsorption of glucose and sodium from the renal tubule, SGLT2i stimulates glycosuria and natriuresis, reducing blood glucose, body weight and blood pressure [9]. Nevertheless, this mechanism is independent of insulin, and therefore it makes an interesting drug in combined therapies [10]. The most common adverse reactions are mild genital and urinary tract infections [1]. In contrast, there are studies where the risk of serious and non-serious UTI events among patients treated with SGLT-2 inhibitors was similar to that of

those treated with other antidiabetics [11]. Additionally, more serious and life-threatening side effects have been found including ketoacidosis, acute kidney injury, increased amputation rates, and Fournier's gangrene [8][9][10].

2. Insightful Analysis

Since the issuance of the health alert by the FDA in 2018 and later by the SEGO, EMA and AEMPS in 2019, FG cases under SGLT2 Inhibitors therapy have increased [12][13]. There is a bias called notoriety bias. It is a selection of bias in which a case has a higher probability of being reported if the subject is exposed to the factor studied, which is known or thought to cause the event of interest [14]. Therefore, it could partly explain the increased FG reporting numbers after the warning of different drugs agencies. Although, most cases have been suffered by men, from the Gynecology and Obstetrics service of the Malaga Regional Hospital. The researchers would like to reflect the non-negligible number of female cases. One of the reasons for the relatively lower appearance of FG in women could be related to the better drainage of the perineal region by vaginal secretions. Another reason could be confusing in the initial diagnosis regarding other infections of the genital area.

Among patients with remarkable characteristics, the researchers believe that advanced age possibly exerts a negative influence on prognosis. Regarding medical history, in all cases there was obesity, long poorly controlled type 2 diabetes mellitus and tobacco (smoker or ex-smoker). Median female body mass index (BMI) was 38, which implies that the comorbidities of the patients reported must be considered [10]. In other published articles, it was described that the average age of presentation of FG is 50–60 years. Among other risk factors are, as in the researchers' cases, diabetes mellitus, obesity and alcoholism [15][16][17]. In addition, it seems that the female sex is an added risk factor for mortality [16] as well as tobacco and obesity seem to play a role in enhancing the adverse effects of diabetes and the risk of FG. All patients shared a poorly adjusted DM2 at the time of diagnosis with blood glucose levels above 180 mg/dl [18]. Hb1Ac analysis could refine the diabetes in a severe scale. The patients all presented high values (9%, 8% and 7.2%, respectively), which may reflect an incomplete diabetic control. The measurement of glycated Hb is a laboratory test widely used in diabetes to know if the patient's control over the disease has been good during the last three or four months (although there are doctors who only consider the last two months). Surgical history does not seem relevant.

Regarding treatment, all patients were taking a compound of Metformin and SGTL-2 inhibitor (Dapagliflozin, Canagliflozin and Empagliflozin). Another noteworthy fact is that no case of Fournier's gangrene involved ertugliflozin, which could be due to its shorter time to market. The mean was about 20 months, although more cases are needed to estimate a statistically significant minimum treatment time. The underlying mechanism is unknown. Elevated blood glucose levels (above 180 mg/dl) and additional SGLT2 therapy can lead to a state of glycosuria, favoring urinary tract infections. This is associated with local immunodeficiency and deficient microvascularity (T2DM and other comorbidities) which may promote FG in certain patients [19].

Three patients went to the Emergency Department due to a painful genital lump. In addition, fever was present in all cases. The most common anatomic region of gangrene involvement was the labia followed by perineum and gluteus/buttocks. Blood tests were unremarkable except for leukocytosis with neutrophilia, which were elevated in CRP. In any case, coagulation or hepatorenal function was altered. In general, CT allowed the confirmation of the clinical suspicion in the three patients, revealing gas in the soft tissues. Thus, the characteristic image showed air inside tissues, emphysema and subcutaneous edema, in the most severe cases passing through the muscle and bordering on large vessels. However, it is often enough for diagnosis. Usually, the most frequent isolated aerobe is Escherichia coli and the anaerobe Bacteroides fragilis [18]. Nevertheless, in the research, B. fragilis was only related to one case and E. coli was not found. In 6 out of 10 cases, the infection is polymicrobial, which means the use of several antibiotics initially, with subsequent modification of the schedule based on culture findings [19]. All blood cultures were negative.

Truthfully, the initial treatment algorithm in the three patients was quickly applied through empirical antibiotic therapy and surgical debridement. There is no consensus in the literature on the optimum antimicrobial treatment for FG. The three patients, as the Infectious Diseases Society of America (DSA) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) recommend, received a broad-spectrum treatment based on the use of a Carbapenem, a Cephalosporin or a beta-lactam/beta-lactamase inhibitor (Meropenem in all cases) plus Vancomycin or Daptomycin for methicillin-resistant Staphylococcus aureus (MRSA) coverage, and Clindamycin for its antitoxin activity against Streptococci or Staphylococci [18]. Subsequently, antibiotics were regulated according to antibiograms. Outcome was truly negative, with only one survivor. It is unclear whether patients could be started on SGLT2 inhibitors again after complete remission, although the researchers prefer not to restart it [11]. Likewise, in all cases, they needed several surgeries, most of them up to four interventions. The length average of staying was two months. The oldest patient died 48 h after the surgery. Despite all the efforts and the rapid response, the outcome was fatal in two of the patients and the survivor

presented high comorbidity. Answering the question of whether the female gender is a risk factor for mortality in patients with FG, it is associated with a higher incidence of inflammation of the retroperitoneal space and the abdominal cavity. The differences between the male and female genital anatomy could be the reason for the rapid spread of the infection to the retroperitoneum and the fatal outcome in women [19][20][21], although more studies are needed to back it up.

3. Conclusions

Based on the recent warnings from the FDA, SEGO, EMA and AEMPS and the drastic growing popularity of therapy with SGLT2 inhibitors, especially rising quickly worldwide along with the increased needs of diabetic patients with heart disease and obesity, it is important to consider the possible and fatal adverse effects [6][12]. Likewise, genital infections in patients with risk factors such as aforementioned T2DM and tobacco should alert the medical community to rule out FG [12]. Furthermore, it is suggestive to request HbA1c at diagnosis in order to estimate the risk of glycosuria due to SGLT2i and poor diabetic control with FG. It is necessary realizing more scientific analysis between the onset time of FG associated with SGTL-2 inhibitors, as well as studies to generate evidence for a causal connection or improve treatment algorithms for patients with FG [9]. This class of drug has only been on the market for the last nine years, hence the information of its true risk and side effects is limited. Finally, the researchers encourage doctors to voluntarily report all adverse drug effects in order to conduct post-marketing studies to determine the true risk of SGLT2i in diary clinical practice [8].

References

1. Bersoff-Matcha, S.J.; Chamberlain, C.; Cao, C.; Kortepeter, C.; Chong, W.H. Fournier gangrene associated with sodium-glucose cotransporter-2 inhibitors: A review of spontaneous postmarketing cases. Ann. Intern. Med. 2019, 170, 764–769.
2. Ellegård, L.; Prytz, M. Fournier's gangrene under SGLT-2 inhibitor therapy: A literature review and case report. Int. J. Surg. Case Rep. 2020, 77, 692–694.
3. Sorensen, M.D.; Krieger, J.N.; Rivara, F.P.; Broghammer, J.A.; Klein, M.B.; Mack, C.D.; Wessells, H. Fournier's gangrene: Population based epidemiology and outcomes. J. Urol. 2009, 181, 2120–2126.
4. Sorensen, M.D.; Krieger, J.N. Fournier's gangrene: Epidemiology and outcomes in the general US population. Urol. Int. 2016, 97, 249–259.
5. Chennamsetty, A.; Khourdaji, I.; Burks, F.; Killinger, K.A. Contemporary diagnosis and management of Fournier's gangrene. Ther. Adv. Urol. 2015, 7, 203–215.
6. Wang, T.; Patel, S.M.; Hickman, A.; Liu, X.; Jones, P.L.; Gantz, I.; Koro, C.E. SGLT2 Inhibitors and the Risk of Hospitalization for Fournier's Gangrene: A Nested Case-Control Study. Diabetes Ther. 2020, 11, 711–723.
7. Fadini, G.P.; Sarangdhar, M.; De Ponti, F.; Avogaro, A.; Raschi, E. Pharmacovigilance assessment of the association between Fournier's gangrene and other severe genital adverse events with SGLT-2 inhibitors. BMJ Open Diabetes Res. Care 2019, 7, e000725.
8. Anonymous. MHRA drug safety update: Risk of Fournier's gangrene with SGLT2 inhibitors for diabetes. Drug Ther. Bull. 2019, 57, 117.
9. Kasbawala, K.; Stamatiades, G.A.; Majumdar, S.K. Fournier's gangrene and diabetic ketoacidosis associated with Sodium glucose co-transporter 2 (SGLT2) inhibitors: Life-threatening complications. Am. J. Case Rep. 2020, 21, e921536.
10. Rodler, S.; Weig, T.; Finkenzeller, C.; Stief, C.; Staehler, M. Fournier´s gangrene under sodium-glucose cotransporter 2 inhibitor therapy as a life-threatening adverse event: A case report and review of the literature. Cureus 2019, 11, e5778.
11. Dave, C.V.; Schneeweiss, S.; Kim, D.; Fralick, M.; Tong, A.; Patorno, E. Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections: A Population-Based Cohort Study. Ann. Intern. Med. 2019, 171, 248–256.
12. Center for Drug Evaluation, & Research. Warning: Infection of Genital Area with SGLT2 Inhibitors for Diabetes; U.S. Food and Drug Administration: Silver Spring, MD, USA, 2018. Available online: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrences-serious-infection-genital-area-sglt2-inhibitors-diabetes (accessed on 9 February 2019).
13. Agencia Española de Medicamentos y Productos Sanitarios. Boletín Mensual de la AEMPS Sobre Medicamentos de uso Humano del mes de Enero de 2019—Agencia Española de Medicamentos y Productos Sanitarios. Available

online: https://www.aemps.gob.es/informa/boletines-aemps/boletinMensual/2019-boletinMensual/boletin-mensual-de-la-aemps-sobre-medicamentos-de-uso-humano-del-mes-de-enero-de-2019/ (accessed on 20 August 2019).

14. Hu, Y.; Bai, Z.; Tang, Y.; Liu, R.; Zhao, B.; Gong, J.; Mei, D. Fournier gangrene associated with sodium-glucose cotransporter-2 inhibitors: A pharmacovigilance study with data from the U.S. FDA adverse event reporting system. J. Diabetes Res. 2020, 2020, 3695101.
15. Beecroft, N.J.; Jaeger, C.D.; Rose, J.R.; Becerra CM, C.; Shah, N.C.; Palettas, M.S.; Lehman, A.; Posid, T.; Jenkins, L.C.; Baradaran, N. Fournier's Gangrene in females: Presentation and management at a tertiary center. Urology 2021, 151, 113–117.
16. Czymek, R.; Frank, P.; Limmer, S.; Schmidt, A.; Jungbluth, T.; Roblick, U.; Bürk, C.; Bruch, H.-P.; Kujath, P. Fournier's gangrene: Is the female gender a risk factor? Langenbecks Arch. Surg. 2010, 395, 173–180.
17. Hasdemir, A.O.; Büyükaşik, O.; Cöl, C. The clinical characteristics of female patients with Fournier's gangrene. Int. Urogynecol. J. Pelvic Floor Dysfunct. 2009, 20, 1439–1443.
18. Melgar Borrego, A.B.; López Moreda, M.; Martín Méndez, L.; Julián Viñals, R. Gangrena de Fournier. A propósito de un caso. Semergen 2006, 32, 464–467.
19. García Morúa, A.; Acuña López, J.A.; Gutiérrez García, J.D.; Martínez Montelongo, R.; Gómez Guerra, L.S. Gangrena de Fournier: Nuestra experiencia en 5 años, revisión de la literatura y valoración del índice de severidad de la Gangrena de Fournier. Arch. Esp. Urol. 2009, 62, 532–540.
20. Elbeddini, A.; Gallinger, J.; Davey, M.; Brassard, S.; Gazarin, M.; Plourde, F.; Aly, A. 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, e920115.
21. Muchuweti, D.; Muguti, E.; Mungazi, S.G. Spontaneous closure of an extensive postdebridement perineal wound in a newly diagnosed diabetic patient presenting with necrotizing fasciitis. Clin. Case Rep. 2020, 8, 1044–1047.