

COVID-19 AND FOURNIER'S GANGRENE: IS THERE A CORRELATION BETWEEN BOTH DISEASES?

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Abstract: Background: Reports on the development of Fournier's Gangrene (FG) in patients with coronavirus disease 2019 (COVID-19) are rare. **Aim:** This study reports a series of cases of patients with both diseases and to summarize the literature on the subject. **Methods:** We retrospectively examined electronic medical records dated between March 2020 and December 2021 of all adult patients with COVID-19 admitted to the Clinics Hospital of Ribeirão Preto (HCFMRP-USP) to identify those who had a diagnosis of FG. The diagnosis of COVID-19 was made by RT-PCR. We assessed the following patient characteristics: age; sex; tobacco use; laboratory data; and comorbidities such as human immunodeficiency virus (HIV), obesity, diabetes mellitus, systemic arterial hypertension, and alcoholism. **Results:** Four patients met the inclusion criteria. All the patients were female and had at least two comorbidities, including obesity (n=4, 100%), systemic arterial hypertension (n=3, 75%), diabetes mellitus (n=2, 50%), cardiovascular disease (n=1, 25%), chronic kidney disease (n=1, 25%), and hematologic disorders (n=1, 25%). They were all admitted to the intensive care unit and underwent surgical debridement under anesthesia. All the patients received hyperbaric oxygen therapy. The mean age was 62.75 years (range 60-66 years), and the mean length of stay was 30 days (range 22-37 days). One patient died (n=1, 25%). **Conclusion:** This is the first report in the literature on a series of cases of FG in patients with COVID-19. FG associated with COVID-19 is a serious, potentially lethal condition.

Keywords: Necrotising fasciitis; Fournier's gangrene; Infection; Morbidity; Mortality; Treatment outcome; Wound healing.

CORE TIP

Fournier's gangrene (FG) is a polybacterial infection caused by anaerobic and aerobic

microorganisms that act synergistically, leading to necrotizing fasciitis that primarily affects the perianal, genital, and perineal regions. It is a rare condition that presents high morbidity and mortality if left untreated. We present herein a case series of four patients diagnosed with FG during hospitalization for COVID-19.

INTRODUCTION

Over the past two years, the coronavirus disease 2019 (COVID-19) pandemic has become a public health emergency of international concern. By the end of December 2021, over 300 million people had a confirmed diagnosis, and there were more than 5.5 million fatalities (1). Most patients with COVID-19 complained of only mild symptoms, such as fatigue, myalgia, or cough, but the disease progressed into severe complications in over 15% of patients, who required intensive treatment (2). The disease caused by SARS-CoV-2 (COVID-19) is an infectious disease characterized by systemic inflammation, which may increase baseline thrombosis risk, especially in hospitalized patients (3).

As the pandemic progressed, other clinical findings related to the disease began to emerge (mainly in critically ill patients), particularly thromboembolic events (4). Changes in laboratory parameters linked to hemostasis (such as D-dimer levels, platelet count, and clotting time) have been associated with a worse prognosis (5). Data show that more than 70% of patients who died from COVID-19 presented evidence of microembolic phenomena (4, 6). The high prevalence of thromboembolic events, acute deep vein thrombosis with or without a pulmonary embolism, myocardial infarction, stroke, and peripheral vascular changes (7).

Fournier's gangrene (FG) is a specific form of necrotizing fasciitis, localized on the external

genital organs, as well as in the perianal region, accompanied by thrombosis of the feeding arteries, leading to gangrene of the skin and subcutaneous tissue, with manifestations of severe intoxication and multiple organ failure (8). FG is a polymicrobial infection caused by anaerobic and aerobic bacteria that act synergistically, leading to necrotizing fasciitis. Its pathophysiology involves infection and obliterating endarteritis, giving rise to thrombosis of cutaneous and subcutaneous vessels and to necrosis of the skin of the affected region consequently (8). The diagnosis is mainly made on a clinical basis by identifying characteristic crepitus and tender lesions (9). There are systemic diseases associated with the development of FG, including obesity, diabetes mellitus, systemic arterial hypertension, alcoholism, and tobacco use. In addition, there are other risk factors for FG, such as rectal cancer (10) and in situations where the individual is immunocompromised, such as infection by the human immunodeficiency virus (HIV), radiation therapy and chemotherapy, steroid use, and postoperative complications (11). However, there are no reports on the association between FG and COVID-19. Therefore, we report the clinical characteristics and outcomes of a series of four patients with FG who also had COVID-19 and analyze a possible correlation between both diseases.

METHODS

TYPE OF STUDY AND POPULATION

In this study, we retrospectively examined electronic medical records dated between March 2020 and December 2021 of all adult patients with COVID-19 admitted to the Clinics Hospital of Ribeirão Preto (HCFMRP-USP) for an initial identification of those who had a diagnosis of some form of necrotizing fasciitis. Subsequently, we reviewed the records in detail to identify specifically patients with FG and

COVID-19. The diagnosis of FG was clinical, and defined by the following clinical aspects: patients who presented with erythema, pain, edema, and necrosis of the scrotum or perianal and perineal regions along with fever and chills. Other symptoms/manifestations included blisters, crepitus, cyanosis, and secretion with a strong, repulsive, fetid odor associated with sepsis. The diagnosis of COVID-19 was made by RT-PCR. All patients were admitted to the intensive care unit (ICU).

DATA COLLECTION, MEASUREMENTS, AND RESULTS

We identified the patients by searching through electronic medical records. We collected the patients' demographic and clinical data through a comprehensive review of their electronic medical records and assessed the following patient characteristics: age; sex; tobacco use; and comorbidities such as HIV, obesity, diabetes mellitus, systemic arterial hypertension, and alcoholism. All patients were classified according to the Fournier's Gangrene Severity Index (FGSI), which has been developed to stratify the risks in FG patients and to predict mortality (12). In addition, all patients were classified according to Feres anatomical classification which shows the risk of mortality with anatomical extension after the first surgical debridement (13).

ETHICS APPROVAL AND CONSENT

The need for the patients' informed consent to participate in the study was waived by the ethics committee of the Clinics Hospital of Ribeirão Preto Medical School of the University of São Paulo (HCFMRP-USP) due to the retrospective and anonymous nature of the study. It was approved by the ethics committee of the coordination center (HCFMRP-USP, CAAE: 42575321.1.0000.5440; Ethics Committee Number: 4.524.455/2021; 04.FEB.2021). All procedures were conducted

in accordance with the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

STATISTICAL ANALYSIS

We conducted a descriptive statistical analysis using frequency, percentage, mean, and range to describe all the variables.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

Four patients met the inclusion criteria and were examined. Clinical characteristics of patients at FG diagnosis, the FGSI, Feres classification, and the response to treatment are described in Table 1.

Case 1: A 20-year-old female patient with obesity and idiopathic thrombocytopenic purpura (ITP) presented with a mild respiratory

condition of COVID-19 which required oxygen therapy but no mechanical ventilation. On the fifteenth day of hospitalization after the diagnosis of COVID-19, the patient developed severe thrombocytopenia due to ITP. Moreover, a necrotizing cellulitis to the abdomen and a large vulvar with a black spot in the center was observed on the left side, and the patient's condition progressed to high fever, sepsis, clinical worsening, and the progression of necrotizing cellulitis to the abdomen and left flank with crepitus. Given the diagnosis of FG, the patient was referred for emergency surgical debridement. Surgical exploration found secretion with a strong, repulsive, fetid odor. There was improvement in the bleeding area with surgical treatment associated with hyperbaric oxygen therapy (HBOT) (Figure 1). However, the patient died due to sepsis one week after FG diagnosis.

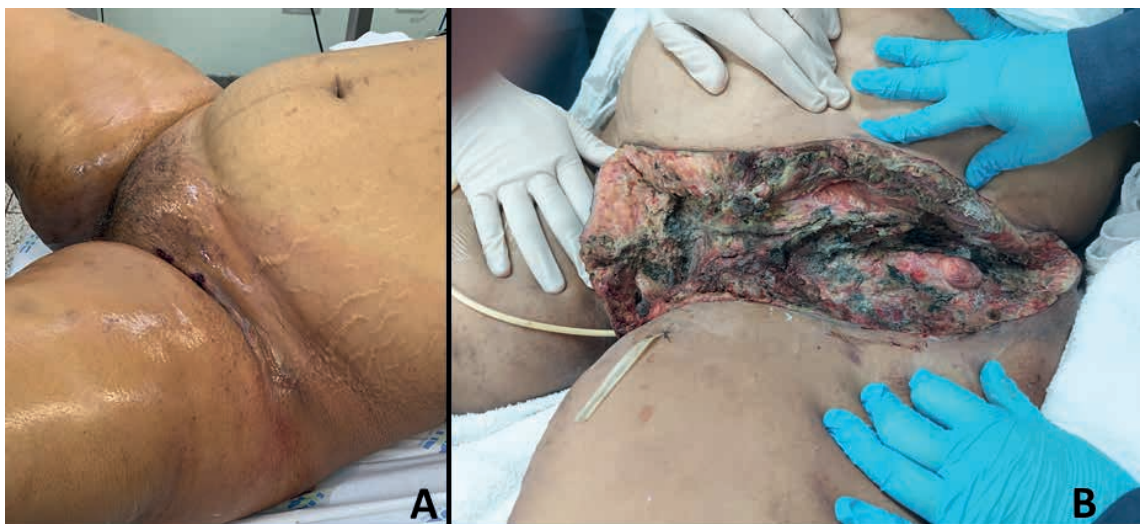


Figure 1: A. Necrotizing cellulitis to the abdomen and left flank with crepitus. B. Surgical debridement.

Case 2 - A 66-year-old female patient with diabetes mellitus and systemic arterial hypertension developed severe acute respiratory distress syndrome from COVID-19 and required mechanical ventilation in the prone position. On the ninth day of symptoms, the patient's infectious condition worsened, and there was necrotizing cellulitis in the pubic area and right vulvar region.

With the diagnosis of FG, she was referred for emergency surgical debridement, and surgical exploration found secretion with fetid odor. The patient was treated with ten sessions of HBOT in the postoperative period. There was improvement in the local infectious and systemic condition. The patient was discharged four weeks after the surgical approach.

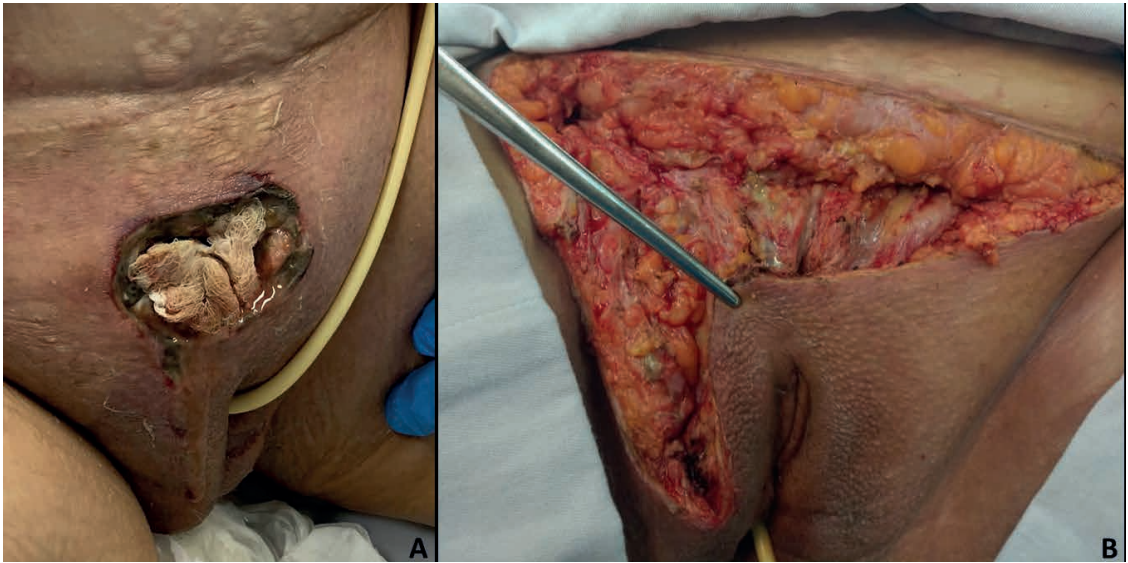


Figure 2: A. Necrotizing cellulitis in the pubic area and right vulvar region (surgical drainage). B. Clinical aspect after surgical debridement.

Case 3: A 63-year-old female patient with obesity, diabetes mellitus, systemic arterial hypertension, and coronary artery disease had a history of ischemic stroke, two episodes of acute myocardial infarction, and pulmonary thromboembolism. Five days after the onset of symptoms, the patient required ICU admission due to respiratory symptoms. On the fifteenth day after the diagnosis of COVID-19, she

presented with pain, hyperemia, and crepitus in the right vulvar region and fever and delirium. Due to the diagnosis of FG, the patient underwent extensive debridement and secretion with fetid odor was found. Ten HBOT sessions in the postoperative period, presenting good progress and resolution of the infectious condition. She was discharged three weeks after surgery.

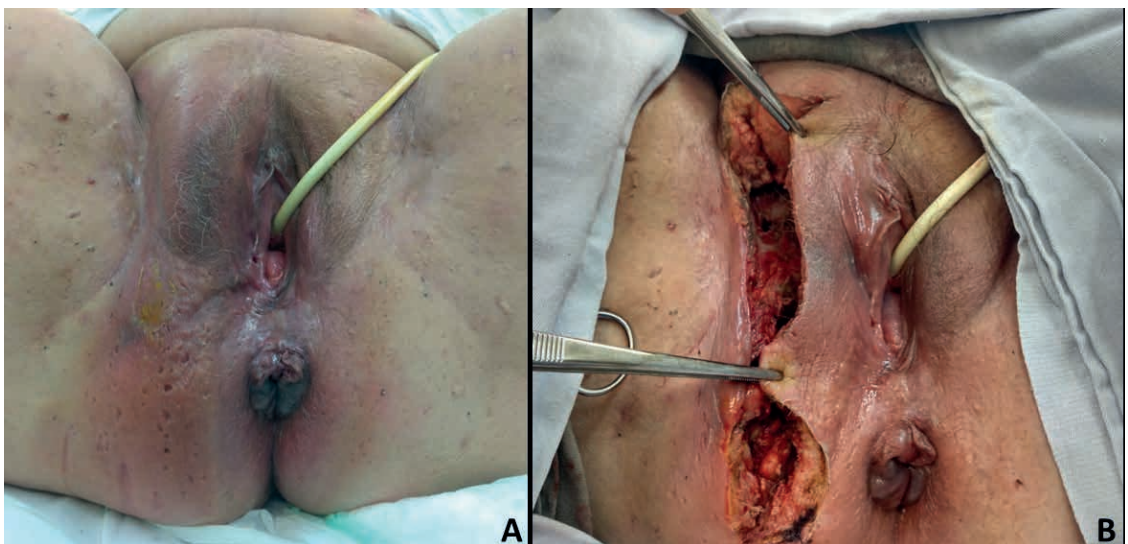


Figure 3: A. Crepitus in the right vulvar region. B. Clinical aspect after surgical debridement.

Case 4: A 62-year-old female patient with chronic kidney disease, systemic arterial hypertension, and obesity was diagnosed with COVID-19 and presented with perineal pain, hyperemia, and crepitus in the right vulvar region on the fourth day. The patient underwent surgical debridement and ten HBOT sessions and had a good response. She was hospitalized for 25 days and did not require mechanical ventilation.

DISCUSSION

The number of patients with COVID-19 has increased drastically worldwide. However, this is the first report in the literature of a series of cases of FG in patients with COVID-19. There are only publications in the literature describing one case so far (14-20).

We have known about FG longer than we have known about COVID-19, but its incidence is much less common (8). Nevertheless, both diseases are potentially fatal and related to microvascular dysfunction. Necrotizing soft-tissue infection is recognized as a severe soft-tissue infection that spreads rapidly, and it is associated with a high mortality (11).

FG is a polymicrobial soft-tissue infection of the genital and perineal region that results in necrosis of tissues, and it progresses rapidly (11). Epidemiologically, patients with diabetes mellitus, obesity, alcohol dependence, and who use illegal substances are at the highest risk. As for mortality, older adults and patients with congestive heart failure, kidney failure, and coagulopathy are at the highest risk (21). Extensive, rapid tissue injury is associated with obliterating endarteritis, associated with infection, which is evidenced by local microbiological and inflammatory factors, such as increased platelet aggregation and the degradation of anticoagulant elements in the blood itself (22).

The occurrence of thromboembolic phenomena is common in advanced stages

of COVID-19. In addition to macrovascular complications, there is sufficient evidence to support a relationship between COVID-19 and microvascular changes. Thrombi in the pulmonary microcirculation are frequent post-mortem findings in patients with COVID-19 (23). In Brazil, the occurrence of thrombosis in the microcirculation was demonstrated by monitoring sublingual vessels in 85% of living patients admitted to the ICU with a diagnosis of COVID-19 (24).

The late mortality in COVID-19 cases with prolonged stays in the ICU has a clear correlation with thromboembolic phenomena. Some biomarkers were described as predictive of the severity of COVID-19 (25). In our study, the mortality rate was 25%. Other case series show mortality rates that vary from 3.7% up to 76% (9, 11). Comorbidities play an important role in determining the survival of FG patients. Mortality can also be predicted by FG scores or anatomic classifications, such as Uludag Fournier's Gangrene Severity Index (UFGSI) (26), Feres classification (13), laboratory risk indicator for necrotizing fasciitis (LRINEC) score (27). Laboratory investigations can be used to assess the risk of developing FG using the LRINEC score. However, this score has shown a limited sensitivity when used in an emergency setting, such as our cases. Thus, we used the FGSi which has been developed to stratify the risks in FG patients and to predict mortality (12).

Studies show that in more than 80% of the cases the infection is polymicrobial, as observed in our series (9). The diagnosis is mainly made on a clinical basis by identifying characteristic crepitus and tender lesions. Therefore, imaging can be useful in atypical presentations; however, it should not delay treatment, since any delay can result in high mortality (9).

We presume that FG associated with severe cases of COVID-19 indicate a potentially

between these two diseases which can aggravate a disease that already has a high morbidity and mortality (28). The presence of FG may be a predictive of worse evolution in COVID-19, however, due to the to the small number of patients included, we could not determine any predictive parameter of the severity of FG associated with COVID-19. All patients had similar FG severity index score.

However, despite having different etiology, both diseases have some similar characteristics. Thrombosis has been shown to be a complication of COVID in critically ill patients. At the beginning, COVID-19 is primary a pulmonary disease. However, as a consequence of disease evolution, mainly in severe or critically ill patients, patients with COVID-19 are in higher risk of development of pulmonary thrombosis and in systemic organs.

On the other hand, in FG, bacteremia is considered a starting link in the mechanism of the development of necrosis of the fascia that initiates the cytokine cascade leading to the damage of the endothelium, which in turn activates by means of thromboplastin, a coagulation cascade with inhibition of fibrinolysis and the formation of disseminated microthrombosis of vessels feeding the fascia (8). Thus, our study raises the hypothesis that both diseases may have endarteritis obliterans as a common denominator and thrombosis. Future studies should be carried out and new series with a greater number of patients included should be done to demonstrate this hypothesis.

This study demonstrated the magnitude of FG when it is associated with COVID-19, with a severe, potentially lethal condition. However, limitations must be addressed. First, it was a single-center experience, with a small number of patients included in the study. Second, the data was collected retrospectively. However, due to the rarity of the association

of both diseases, it is not possible to carry out a prospective in this situation. Finally, due to the small number of patients included, we could determine any predictive parameter of the severity of FG associated with COVID-19. However, patients with any comorbidities are at high risk.

In short, this is the first report in the literature of a series of cases of FG in patients with COVID-19. FG associated with COVID-19 is a severe, potentially lethal condition, and the pathologies of both conditions are similar and correlated. Early diagnosis and management can reduce morbidity and mortality.

FUNDING

None

DECLARATIONS

Ethical approval and consent to participate
The need for informed consent to participate was waived by the ethics committee of the Hospital das Clínicas of the Ribeirão Preto Medical School, University of São Paulo (HCFMRP-USP) due to the retrospective and anonymous nature of the study. The study was approved by the ethics committee HCFMRP-USP (CAAE: 42575321.1.0000.5440; 04.FEB.2021). All procedures were conducted in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

DECLARATION OF COMPETING INTERESTS

All authors report no conflict of interest.

AUTHORSHIP STATEMENT

Parra RS and Féres O take responsibility for the integrity of the work as a whole, from inception to published article.

AUTHOR CONTRIBUTION

RSP: study design, data analysis, data interpretation, and manuscript writing and manuscript revision.

MRF: study design, data collection, data analysis, data interpretation, and manuscript writing.

LD: data collection, data analysis, data interpretation.

LFF: data collection, data analysis, data interpretation, and manuscript draft.

JJRR and OF: data analysis and interpretation, manuscript writing and manuscript revision.

All authors contributed to the analysis and interpretation of data, revision of the manuscript for important intellectual content, granted

final approval of the version to be published and agreed to be accountable for

all aspects of the work in ensuring that questions related to the accuracy or

integrity of any part of the work are appropriately investigated and resolved.

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Figure legends

Figure 1: A. Necrotizing cellulitis to the abdomen and left flank with a black spot in the center, with crepitus at clinical examination. B. Surgical debridement.

Figure 2: A. Necrotizing cellulitis in the pubic area and right vulvar region (surgical drainage). B. Clinical aspect after surgical debridement.

Figure 3: A. Hyperemia and edema in the right vulvar region, and crepitus during clinical examination. B. Clinical aspect after surgical debridement.