Case Report **IJCR (2022) 6:270**

International Journal of Case Reports (ISSN:2572-8776)

Sudden death due to atypical Fournier's gangrene following Methicillin-resistant Staphylococcus aureus (MRSA) infection: a forensic case

Stefano Tambuzzi[#], Guendalina Gentile[#], Enrico Muccino, Riccardo Zoja

Dipartimento di Scienze Biomediche per la Salute - Sezione di Medicina Legale e delle Assicurazioni - Università degli Studi di Milano, via Luigi Mangiagalli, 37, 20133 Milano, Italy.
[#]co-first authors

ABSTRACT

Fournier's gangrene is a rare and progressive necrotizing infection affecting the perineal, periureteral, perianal, or genital area associated with high mortality rates. A 34-year-old obese man went to the emergency room, complaining of painful perianal and perineal swelling. He was hospitalized and the computed tomography (CT) scan revealed large bilateral anorectal abscesses, anteriorly extended to the base of the scrotum and on the right to the ischiorectal fossa. A diagnosis of Fournier's gangrene was made and broad-spectrum antibiotic therapy was started. After the abscesses drainage, microbiological examinations were performed. However, the clinical conditions furtherly worsened and the patient was moved to the medical intensive care unit. The microbiological analyses tested positive for Methicillin-resistant Staphylococcus aureus (MRSA) and the antibiotic therapy was modified accordingly. Despite the treatment, the hypotension worsened and the patient died from sepsis and multi-organ failure. Upon autopsy, we observed an external macroscopic picture devoid of the typical destructive lesions that usually characterize Fournier's gangrene. Therefore, we found ourselves faced with an atypical case which, in the absence of the clinical data, would certainly have been difficult to diagnose based on the autopsy findings only.

The presented case is deemed of interest for both clinicians and medical examiners since it is about a highly aggressive and fatal Fournier's gangrene in the absence of destructive external manifestations. Moreover, this atypical case of Fournier's gangrene was sustained by an emerging and highly aggressive microbial agent, eventually evolved into sudden death.

Keywords: Autopsy; Fournier's gangrene; S. aureus; Sudden death.

***Correspondence to Author:**
Dr Guendalina Gentile
Sezione di Medicina Legale, Università degli Studi, Via Luigi Mangiagalli, 37, 20133 Milano, Italy

How to cite this article:
Stefano Tambuzzi, Guendalina Gentile, Enrico Muccino, Riccardo Zoja.Sudden death due to atypical Fournier's gangrene following Methicillin-resistant Staphylococcus aureus (MRSA) infection: a forensic case. International Journal of Case Reports, 2022, 6:270.

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Introduction

Fournier's gangrene (FG) is a rare and progressive necrotizing fasciitis or gangrene, sometimes with a fulminant course, affecting the perineal, periureteral, perianal, or genital regions.[1] By inducing thrombosis of the small subcutaneous vessels and necrosis of the overlying skin, it can also spread to the subcutaneous tissues of the thighs and abdomen.[2] The diagnosis is clinical and although etiological factors are increasingly known, there are controversies regarding its description, classification, and treatment. It is a life-threatening condition, with a high mortality rate, between 20 and 40%, and in other studies even between 4% and 80%.[3] Its lethality is related to the rapidly progressing into endotoxic shock or disseminated intravascular coagulation (DIC)[4] and it makes FG a medical emergency, for which some predisposing factors and pathologies have been recognized, such as older age, diabetes mellitus, primary anorectal, and genitourinary infections, low socioeconomic status, recent perirectal or perineal surgery, alcoholism and hypertension.[5] Malnourished or obese individuals or those with kidney failure, chronic liver disease, malignant tumors and other conditions such as HIV-infection are also prone to FG with a more severe or fatal course.[5]

In this report, we present a case of rapidly evolving lethal FG with the patient's sudden death in the total absence of destructive external manifestations.

Case Report

A 34-year-old obese man (height 173 cm and weight 99 kg) went to the emergency room, complaining of lower abdominal and buttock pain, as well nausea for 2 days. He denied tobacco or alcohol use, and any previous injection drug use. Vital signs at presentation were temperature of 37.6°C, pulse of 87 beats/minute, blood pressure of 140/90 mmHg, and oxygen saturation (oximetry) on room air of 98%. Abdominal examination revealed tenderness to palpation in the lower quadrants without peritoneal signs. No abnormalities were noted on genitourinary examination. He had aching and painful bilateral perianal and perineal swelling, that was crackling on palpation.

Complete blood count revealed white blood cell count of 12680 U/L [RR 4.00 – 10.00 $x10^9$ U/L], hemoglobin of 13.3 g/dL [RR 14-18 g/dL], and a normal platelet count. Renal and hepatic function panels were all within normal limits except for a glucose of 140 mg/dL, and PCR of 12.31 mg/dL [RR <0.5-1 mg/dL]. The patient had no serological evidence of HIV, hepatitis B, or hepatitis C infection. The patient was hospitalized and he underwent abdominal computed tomography (CT), which revealed large bilateral anorectal abscesses, extending anteriorly to the base of the scrotum and on the right to the ischiorectal fossa, with evidence of gas under pressure. Based on clinical and radiological findings, a diagnosis of Fournier's gangrene was made. Clinicians started antibiotic therapy with Ceftriaxone and Metronidazole. Immediately, the drainage of the abscesses was performed and the microbiological examination of the purulent material started, finally placing packing with gauze. Over the night a worsening of vital parameters occurred, with the development of paroxysmal nocturnal dyspnea and increasing of the temperature to 39°C. The pulse was 127 beats/minute, the blood pressure 110/65 mmHg, and respiratory rate 45/minute. The genitourinary examination was still normal. The patient's blood cell count had slightly decreased to 11345 U/L and hemoglobin to 12.6 g/dL. The renal panel revealed a glucose of 237 mg/dL and a creatinine of 2.5 mg/dL. The patient was directly admitted to the medical intensive care unit and placed on mechanical ventilation. Antibiotic therapy was implemented with the introduction of Imipenem and Fluconazole. A specialist urological consultation confirmed the diagnosis of FG and indicated extensive debridement of the perianal abscess cavities. After 48 hours from the collection of the purulent drained samples, the microbiological cultures were positive for methicillin-resistant

Staphylococcus aureus (MRSA) susceptible to rifampicin and vancomycin. Antibiotic therapy was modified accordingly, but the hypotension rapidly worsened and, despite the administration of vasopressors and intravenous fluids, the patient died from sepsis and multi-organ failure.

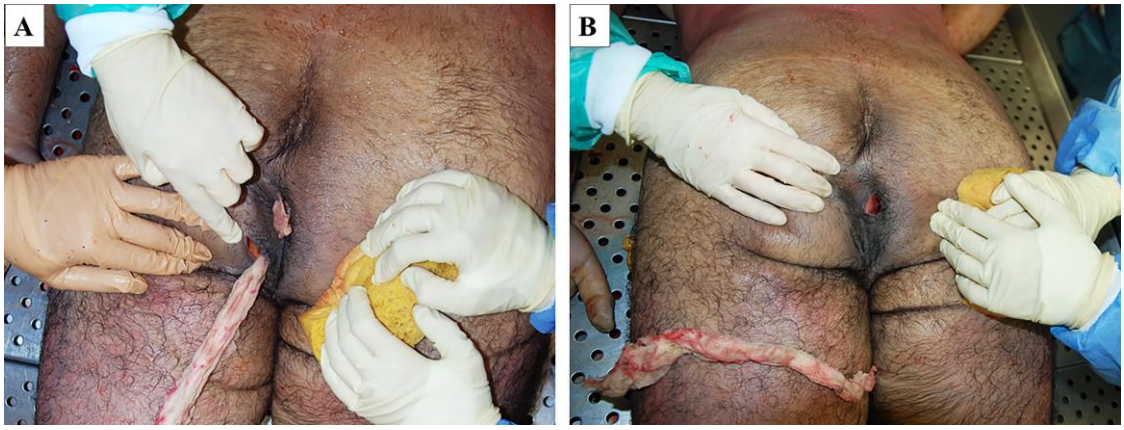

Fig. 1. In A, evidence of the perianal intracorporeal cavity which was packed with gauze; in B, evidence of the perianal intracorporeal cavity after the gauze removal.

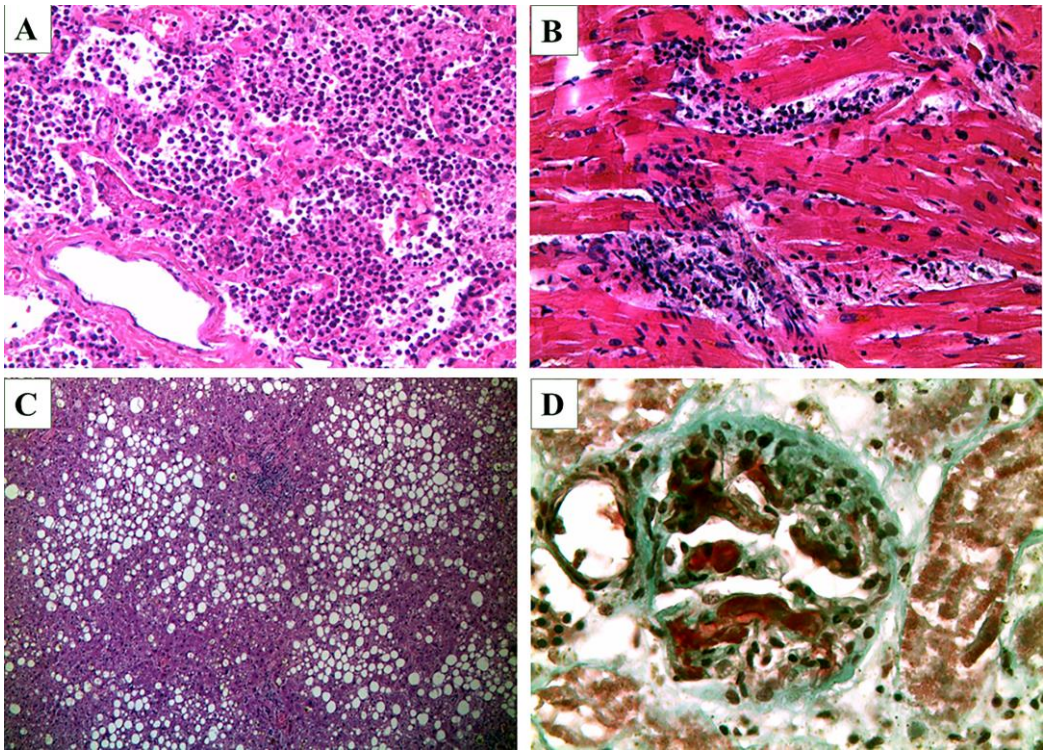

Fig. 2. In A, foci of infiltration of the pulmonary parenchyma by aggregates of neutrophilic granulocytes associated with filamentous fibrin deposits, morphologically consistent with foci of bronchopneumonia (H&E, 200X); in B, foci of infiltration of the myocardium by neutrophilic granulocytes, associated with abscesses and focal necrosis of the fibers, consistent with a bacterial myocarditis (H&E, 200X); in C, diffuse liver macrovesicular steatosis (H&E, 50X); in D, plurifocal fibrinoid necrosis of the renal glomerular loops (TM, 100X).

Gross examination

At the external examination, the genital area appeared free from lesions, and the buttocks showed two surgical incisions (3 cm in length each) near the anal orifice. Both of them were packed with gauze (Figures 1 A and 1B). After

removing the packing, large empty intracorporeal cavities were observed in both the buttocks: the one in the left gluteus was 11 cm deep, and the other in the right gluteus was 7 cm deep. The abscess cavities did not communicate with the peritoneal cavity and the scrotal sac. These cavities appeared free from blood and purulent effusions. All the viscera appeared of markedly diminished consistency, except for the lungs, which showed multiple petechiae and increased consistency of the lower lobes.

Histological examination

Standard post-fixative histological examination with hematoxylin and eosin (H&E) and Goldner's Masson trichrome staining (TM) showed a multiorgan impairment with several foci of bronchopneumonia (Figure 2A), multifocal bacterial myocarditis with myocardial abscesses, and focal areas of necrosis (Figure 2B), widespread macrovesicular steatosis involving at least 60% of the hepatic parenchyma (Figure 2C) and bilateral multifocal fibrinoid necrosis of the renal glomerular loops (Figure 2D). Tissue fragments sampled by the cavities wall showed non-specific multiple foci of inflammatory infiltrates and tissue necrosis. Therefore, histological findings confirmed the involvement of several viscera and showed clear signs of sepsis.

Discussion

Fournier's gangrene (FG) is a rare necrotizing fasciitis mostly caused by bacteria, both aerobic (with the prevalence of *E. coli* in 80% of cases) and anaerobic flora. Isolated bacteria are usually involved, but also polybacterial infection may be observed. An emerging pathogen in FG cases is *Staphylococcus aureus*.[6] Bacterial portals of entry are mainly the gastrointestinal tract (49.2 %), the genitourinary system (43.3%), and skin (7.5%).[7] The pathogens act synergistically through collagenase, hyaluronidase, and other enzymes to invade and destroy the fascial planes, in which they cause a suppurative reaction with enzymatic activation, platelet aggregation, inflammatory reaction, microthrombosis of the local subcutaneous vessels, and tissue destruction.[6] FG also occurs in women and children, although it affects predominantly males, with a prevalence of about 10:1 compared to females. and the age range between 50 and 70 years old.[1] Initially, symptoms are often non-specific, worsening rapidly as the tissue destruction rate is 2-3 cm/h, approximately. Pain may even be absent, due to the destruction and compression of the surrounding skin nerves or, in the case of diabetes, due to neuropathy.[2] The aggressive nature of the FG, its challenging recognition, the lack of early diagnosis, and comorbidity are the reasons for often late or advanced clinical observations that are associated with higher mortality rates.[6] The therapeutic approach involves adequate drainage/surgical toilet, proper antibiotic treatment, and debridement, but there are still no reliable criteria to follow for a good prognosis, which often progresses very rapidly into sepsis or DIC.[4]

In the case presented, a 34-year-old obese man who died in hospital following a clinical diagnosis of sepsis due to Fournier's Gangrene came to our attention. Clinical microbiological tests showed positivity for methicillin-resistant *Staphylococcus aureus* (MRSA). Although it is more frequently associated with skin and soft tissue infections, it can also cause severe sepsis, pneumonia, and necrotizing fasciitis. Moreover, *S. aureus* colonizes perineal skin but is an uncommon cause of FG, and MRSA is rarely associated with perineal infections, with only two case reports in the literature.[6,8]

Upon autopsy, we observed an external macroscopic picture devoid of the typical destructive lesions that usually characterize FG. Indeed, the genital and perianal areas were normal, and only two small surgical incisions were observed near the anal orifice. At the internal examination, however, we found two large intracorporeal cavities not communicating with each other, consistently with what was shown by the CT. In addition, clear signs of generalized visceral sepsis were observed. Also, histological examination revealed severe

features of multi-organ failure responsible for the rapid worsening of the patient's vital parameters. Therefore, we found ourselves faced with an atypical case of FG which, in the absence of the clinical data, would certainly have been difficult to diagnose based on the autopsy findings only. Indeed, in such an eventuality, most likely the forensic diagnosis would have been oriented towards bilateral perianal abscesses as a cause of sepsis, rather than a FG syndrome. This consideration pinpoints the importance of always correlating clinical information with autopsy findings, especially in cases where the diagnostic orientation is primarily clinical, as in the case of FG. Indeed, in this case, the autopsy findings alone could have led to an erroneous conclusion, with misrecognition of the real cause of death. Furthermore, if we consider that FG is rare and that MRSA etiology is an even more unusual occurrence, valuable epidemiological information would have been lost. In detail, with regard to MRSA etiology, FG is typically a polymicrobial infection and we cannot completely exclude other pathogens as contributing to this patient's infection. However, deep-tissue cultures at the time of surgery with rapid transport of anaerobic specimens did not show other bacterial pathogens, so we believe that *S. aureus* was the predominant organism in the infected tissue. In light of this evidence, MRSA is confirmed as a possible cause of FG not to be underestimated and always taken into consideration. Therefore, clinicians should consider the addition of coverage for MRSA, when starting empiric antimicrobial therapy for Fournier's gangrene and other necrotizing soft-tissue infections.

The concordance and convergence of the clinical, autopsy, and laboratory findings made it possible to attribute the patient's death to a very severe FG whose speed of diffusion was very rapid. The peculiarity of the presented case consisted in the onset of a highly aggressive and fatal FG syndrome in the absence of destructive external manifestations. We deem this atypical form of FG of possible interest for both clinicians and medical examiners as it was also sustained by an emerging and highly aggressive microbial agent, which eventually caused the patient's death despite medical treatment.

Declarations

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Conflicts of interest/Competing interests: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval: This study was performed from data from a human cadaver. This article does not contain any studies with (living) human participants or animals performed by any of the Authors. The subject involved in this study underwent a judicial autopsy at the Institute of Legal Medicine of Milan in order to identify the cause of death. Data collecting, sampling and subsequent forensic analysis were authorized by the public prosecutor. Therefore data were acquired as part of a forensic judicial investigation and in accordance to Italian Police Mortuary Regulation.

Consent to participate: The authors declared that all the investigations were carried out accordingly to the Italian Law.

Consent for publication: All the authors agree for publication

Availability of data and material: All the data have been reported in the manuscript

Code availability (software application or custom code) Not applicable

Authors' contributions: TS and GG equally contributed to this work. They devised the project and the main conceptual idea of the article, collected data, drafted the manuscript and performed literature research. reviewed and edited the manuscript. RZ guarantor of the project and directed the study, devised the main conceptual idea of the article.

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