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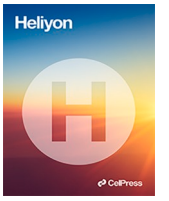

Case report

Clostridium ramosum alone caused Fournier's gangrene in an older Chinese patient with abnormal interleukin levels: A rare case report

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ABSTRACT

Clostridium ramosum is an uncommon Clostridium but is one of the essential anaerobic bacteria that makes up the intestinal microbiota. A highly variable body temperature, the white blood cell count, or an elusory prognosis can reflect *Clostridium ramosum* infection, especially in patients with Fournier's gangrene. Fournier's gangrene is a rare soft-tissue infection with necrosis that occurs mainly in the perianal and genital regions, males being more susceptible. Here, we report a 70-year-old Chinese man with Fournier's gangrene and high levels interleukins who suffered from *Clostridium ramosum* infection, identified and verified by matrix-assisted laser desorption ionization/time-of-flight mass spectrometry (MALDI-TOF MS) and 16S rRNA sequencing. Fournier's gangrene severity index (FGSI) of the patient was measured once the patient was admitted to hospital. His FGSI was 6, indicating no abnormal condition. He had abnormally high interleukin (IL)-6, IL-8, and IL-10 levels, associated with severe inflammatory conditions. Despite the patient's resuscitation and standardized treatment with antimicrobial drugs, the symptoms did not improve. The patient's condition deteriorated, and he died on hospitalization day 5. Abnormally elevated IL-6, IL-8, and IL-10 levels were a novel finding in a case of *Clostridium ramosum* infection, leading to Fournier's gangrene. In the present case, a perianal abscess was the predisposing condition for Fournier's gangrene. Close attention should be paid to the isolation and identification of pathogenic *Clostridium ramosum* during the bacteriological examination of patients with perianal abscesses. IL-6, IL-8, and IL-10 may be critical biomarkers that supplement the FGSI for diagnosing *Clostridium ramosum* infection leading to Fournier's gangrene in immunosuppressed persons.

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1. Introduction

Clostridium ramosum, also known as *Erysipelactoclostridium*, has seldom been demonstrated to be harmful to humans. Nevertheless, after first being documented as distinct from appendicitis in 1898, instances of this condition have sporadically been observed in children with otitis media, immunocompromised patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and intraperitoneal infection [1–3]. *Clostridium ramosum* is a Gram-variable, spore-forming obligate anaerobe [4]. *Clostridium ramosum* can be isolated from clinical samples, but it is seldom identified as the only underlying cause of Fournier's gangrene [5,6]. Fournier's gangrene is more common in elderly men than in elderly women, and it is linked with poorer outcomes for those with impaired immunity. Patients suffering from Fournier's gangrene must be given antibiotics as soon as possible. Patients with type 2 diabetes, postponed entrance to healthcare facilities, and sepsis are prone to dying of Fournier's gangrene, the mortality rate being as high as 40 % [6–8]. *Escherichia* coli and *Bacteroides* are the two bacteria that most frequently cause Fournier's gangrene. Fifteen percent of Fournier's gangrene patients have been reported to harbour Clostridium species [9,10]. So far, only two cases of gangrene caused by *Clostridium ramosum* have been described [11,12]. In a 2024 case report, Fournier's gangrene developed in a patient with *Streptococcus anginosus* infection; only the white blood cell (WBC) count was described, which adds little value in the cases of sole *Clostridium ramosum* infection [13]. Here, we report a rare fatal instance of Fournier's gangrene triggered by *Clostridium ramosum* alone in an individual with aberrant IL concentrations.

2. Case presentation

A 70-year-old Chinese man complained of perianal pain that had gotten worse during the previous four days, as well as overall weariness and a diminished sense of taste. He suffered perianal pain four days before his current hospitalization.

During his admission, the patient appeared fragile but attentive and had a normal temperature (36.3 °C). His blood pressure was in line with earlier measurements (93/66 mmHg), and his heart rate was 72 beats/minute. He complained of continuous perianal pain. Digital anal examination revealed a lump of about 6 × 4 cm. Pressure pain was obvious, the border was not clear, and no necrotic skin fading was detected. Laboratory results showed a WBC count of 4.54×10^9/L (normal value: 4.00×10^9/L ~ 10.00×10^9/L) with 71.8 % neutrophilia (normal value: 40 %–75 %), a lymphocyte count of 1.57×10^9/L (normal value: 1.1×10^9/L ~ 3.2×10^9/L), a haematocrit value of 0.435 (normal value: 0.4 ~ 0.5), an elevated C-reactive protein (CRP) of 247.09 mg/L (normal value: 0 ~ 10×10^9/L), a procalcitonin level of 20.19 ng/mL (normal value: 0 ~ 0.5 ng/mL), a standard bicarbonate radical concentration of 6.3 mmol/L (normal value: 21 ~ 27 mmol/L) and a serum potassium concentration of 5.63 mmol/L (normal value: 3.5 ~ 5.5 mmol/L). The patient's international normalized ratio was 1.74 (normal value: 0.8 ~ 1.3), D-dimer was 7.44 mg/L (normal value: 0 ~ 0.55 mg/L), antithrombin-III (AT-III) was 41.24 % (normal value: 75 % ~ 125 %), blood platelet count at admission was 53×10^9/L (normal value: 125 ~ 350×10^9/L), and activated partial thromboplastin time (APTT) was 79.5 s (normal value: 20 ~ 35 s), which met the criteria for a disseminated intravascular coagulation score. He had a low serum ALB concentration of 21.2 g/L (normal value: 35 ~ 50 g/L), an elevated urea concentration of 25.71 mmol/L (normal value: 3.2 ~ 7.1 mmol/L), an abnormal creatinine concentration of 500.2 μmol/L (normal value: 58–110 μmol/L) and a lactate concentration of −18.38 mmol/L (normal value: 0.4 ~ 2.2 mmol/L). T-lymphocyte subset and cytokine analyses were performed on the first day, and the results were returned on the second day (Tables 1 and 2). Except for abnormally elevated IL-1β, IL-6, IL-8, and IL-10, the other variables were normal, as shown in Table 2.

Intravenous treatment with imipenem and cilastatin sodium (1.0 g q8h) was implemented empirically for three days after blood culture samples were obtained. Gram-variable rods were observed in the Petri dish (Fig. 1). Then, the blood culture isolate was finally identified by MALDI-TOF-MS (Fig. 2), and 16S ribosomal DNA sequencing was done. The patient was diagnosed with Fournier's gangrene based on symptoms and laboratory parameters. The minimum inhibitory concentrations (MICs) of various antibiotics were determined by the E-test for Clostridium ramosum (Table 3) [14]. The strain was susceptible to piperacillin and linezolid. Then, the antibiotic was immediately changed to a combination of piperacillin-tazobactam (3.375 g q8h) and linezolid (0.6 g q12h) for synergistic antimicrobial effects. Disseminated intravascular coagulation and pancytopenia occurred despite the ongoing administration of vulnerable antibiotics and the provision of critical care; unfortunately, the patient died on hospitalization day five. His laboratory test results were notable for the white blood cell count of 2.28×10^9/L (78.6 % neutrophils).

3. Discussion

Fournier's gangrene is an extremely rare but fatal illness that affects delicate tissues of the perianal and perineal areas [15]. Many

Table 1
Result of lymphocyte subsets analysis.

Item	Result	Reference	Unit	State
Fraction of CD3+T	28	50–84	%	↓
Fraction ofcd3+CD4+T	16	27–51	%	↓
Fraction ofcd3+CD8+T	10	15–44	%	↓
Fraction ofcd3+CD4+T	1.68	0.71–2.78	%	
Fraction ofcd3+T	80	955–2860	number/ul	↓
Fraction ofcd3+CD4+T	47	550–1440	number/ul	↓

Table 2
Result of cytokines test analysis.

Item	Result	Reference	Unit	State
TNF-α	1.63	0–4.6	pg/ml	normal
IFN-α	0.01	0–8.5	pg/ml	normal
IFN-γ	1.34	0–7.42	pg/ml	normal
IL-2	0.65	0–5.71	pg/ml	normal
IL-4	0.29	0–3	pg/ml	normal
IL-5	0.01	0–3.1	pg/ml	normal
IL-6	14120.79	0–5.3	pg/ml	↑
IL-8	15776.2	0–20.6	pg/ml	↑
IL-1β	91.39	0–12.4	pg/ml	↑
IL-17A	0.01	0–20.6	pg/ml	normal
IL-10	4687.03	0–4.91	pg/ml	↑
IL-12P70	0.01	0–3.4	pg/ml	normal

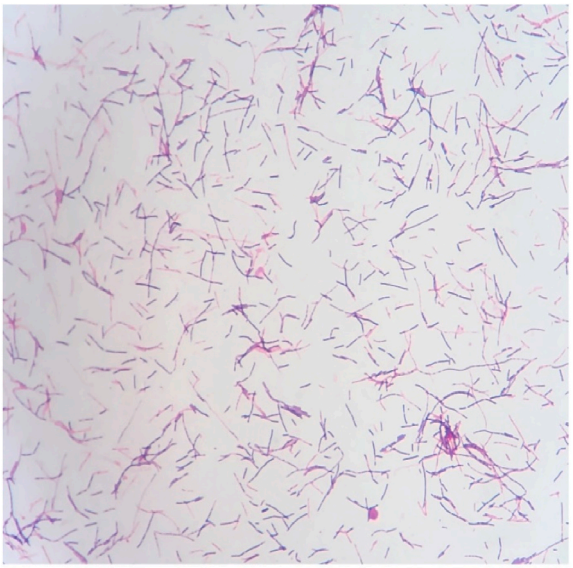

Fig. 1. The staining of *Clostridium ramosum* in blood agar was gram-variable.

studies have shown that its overall incidence is much lower in women than in male patients [16,17]. Patients with Fournier's gangrene have a high mortality rate of more than 25 % [18]. The FGSI was created to aid in the rapid identification and prediction of the prognosis of Fournier's gangrene patients. Some recent studies suggested that Uludag Fournier's gangrene severity index (UFGSI) was more potent than the FGSI [19,20], but other evidence shows that it is not [21]. The simplified FGSI (SFGSI) was subsequently published to evaluate the predictors of mortality in patients with Fournier's gangrene [22,23]. The scoring system is also recommended and applicable for early surgical intervention to maximize the survival of high-risk Fournier's gangrene patients [24]. Azmi YA et al. proposed that among the many available scoring systems, FGSI, UFGSI, SFGSI, NUMUNE Fournier score (NFS), Laboratory Risk Indicator for Necrotizing Fasciitis, age-adjusted Charlson comorbidity index, sequential organ failure assessment (SOFA), quick SOFA, and surgery APGAR score (SAS), the FGSI is the most reliable scoring system for predicting in-hospital mortality in patients with Fournier's gangrene [25].

Our patient had an FGSI score of 6 and a UFGSI score of 7 at admission; four days later, the FGSI and UFGSI increased to 10 and 11, respectively. Variations in electrolytes and the fall in his WBC count caused this change. It is generally assumed that the prognosis is poor when the score is greater than 9 [21].

Several risk factors were identified as susceptibility to Fournier's gangrene due to perianal abscess, age and immunosuppression as a result of T-lymphocyte subsets, as shown in Table 1. Only the presence of pain for four days hinted at less pronounced progression, which may have led this patient, along with his family and friends, to disregard the illness. The extended course of his Fournier's gangrene may have hampered a definitive diagnosis in this case. The sickness of the patient was more severe according to his internal (e.g., blood) variables than according to his external symptoms. This finding is in agreement with the disease process being underrecognized as a risk factor for mortality [8].

Few studies have reported laboratory parameters as predictive biomarkers for the outcomes of patients with Fournier's gangrene. Ucaner et al. reported that WBC count, haemoglobin level, neutrophil count, lymphocyte count, platelet count, and CRP level were not

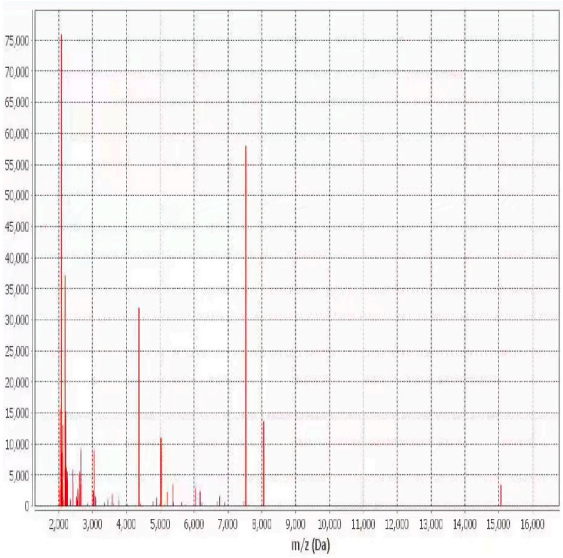

Fig. 2. MOLD-TOF Mass spectra of *Clostridium ramosum* strain investigated in the study.

Table 3
Antimicrobial susceptibility profile of *Clostridium ramosum* strain.

Antibiotics	MIC (mg/L)	Interpretation of susceptibility
Benzylpenicillin	4	R
Piperacillin/tazobactam	1.12	S
Ceftriaxone	32	R
Imipenem	4	R
Clindamycin	8	R
Erythromycin	≥512	NA
Tetracycline	≥256	NA
Levofloxacin	64	R
Moxifloxacin	64	R
Vancomycin	4	R
Linezolid	0.5	S
Metronidazole	ND	–

NA not applicable, *ND* not done, *S* susceptible, *R* resistant.

significantly correlated with patients' clinical outcomes [26].

A cytokine storm is a severe inflammatory syndrome characterized by increased levels of circulating cytokines and activation of immune cells. An uncontrolled inflammatory reaction causes a significant discharge of cytokines, triggering continuous activation of immune cells and excessive inflammation, potentially leading to a critical condition. Our patient with Fournier's gangrene had abnormal ILs, which can be seen as a cytokine storm, which has been linked to negative impacts such as organ damage and dysfunction.

High levels of cytokines, considerably above the norm, were detected and documented for the first time in patients with Fournier's gangrene. These cytokines cause cytokine storms, which have a considerable effect on the patient's illness. Cytokine storms may result in an unregulated immune reaction. The immune system, which was originally meant to fight anaerobic pathogens, unexpectedly plays a role in causing clotting issues and kidney problems.

Cytokines, small proteins that act as messengers between immune cells, are central to coordinating the immune response. In the case of *Clostridium ramosum* causing Fournier's gangrene, the immune system often triggers an amplified cytokine reaction known as the cytokine storm. This pattern includes the release of inflammatory cytokines, like IL-1, resulting in excessive inflammation. Moreover, the levels of anti-inflammatory cytokines like IL-10 are increased to balance inflammatory conditions. The delicate equilibrium between inflammatory signals that promote and those that suppress inflammation is disturbed in patients with Fournier's gangrene.

Elevated levels of IL-8, a chemokine, have been observed in patients and play a role in the progression of organ damage and dysfunction. An altered immune response, along with a cytokine/chemokine storm, has significant consequences for our patient's organ function and outlook.

Besides IL-8, abnormally elevated IL-6 and IL-10 could play vital roles in the case of Fournier's gangrene with abnormal immune responses and inflammation [27,28].

IL-10 is a well-known cytokine with potent anti-inflammatory effects. By playing a crucial role in regulating the immune system, IL-

10 controls the immune response by stopping the production of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α. IL-10 assists in regulating the immune system by controlling excessive activation, thereby preventing an overly aggressive inflammatory reaction. IL-10 can be a complex process affected by different factors. The interaction between pro-inflammatory cytokines and the immune response makes the regulatory mechanisms of immune modulation more complex, highlighting the subtle nature of immune regulation [29].

Our patient exhibited unusual levels of IL-10. IL-10 is crucial in the transient growth of mast cells to combat pathogens, leading to the release of high levels of histamine that can enhance the permeability of blood vessels, potentially assisting in breaching intestinal mucosal barriers [30]. *Clostridium ramosum*, an essential part of the usual gut bacteria, might have entered the tissues in the perianal region through the gut lining.

Due to their essential role in the immune response to infection, cytokines have been suggested as a possible tool for diagnosing tuberculous meningitis (TBM) [33]. Research has increasingly demonstrated that elevated levels of IL-6, 8, and 10 can also serve as biomarkers to predict the severity of sepsis or dengue infections [32,34]. Given this information, we suggest that ILs serve as biomarkers in individuals with Fournier's gangrene to indicate the severity of the disease and the likelihood of death.

The rapid identification of *Clostridium ramosum* is critical for the rational use of antibiotics and for reducing the emergence of resistant strains of *Clostridium ramosum*. The variable Gram stain, poor spore fabrication, and odd clostridial colony shape made identification of *Clostridium ramosum* in the culture of this case report more difficult (Fig. 1), which is consistent with the literature [31]. Physicians and microbiologists should maintain a high level of awareness because the Gram stain of a blood culture can be vague. MALDI-TOF MS is an essential tool that can help us quickly identify species of *Clostridium ramosu*m [35].

Usually, *Clostridium ramosum* is found in immunocompromised adults with multibacterial infections [32]. In the present case, sole *Clostridium ramosum* was isolated for the first time from the blood of a patient suffering from Fournier's gangrene. Laboratory investigations revealed an abnormal WBC and neutrophilia in typical polymicrobial Fournier's gangrene. The WBC value was almost normal in the patient who had only Clostridium ramosum [12].

The antimicrobial resistance index has also been described as an adverse prognostic factor [36]. Penicillins and vancomycin can be utilized for *Clostridium ramosum*, depending on the minimum inhibitory concentration (MIC). In previous studies, the MIC of vancomycin for Clostridium ramosum ranged from 0.25 to 2 mg/L [1], but in the current case and a recent report, it was found to be 4 mg/L. Clostridium ramosum *also* had a higher MIC of penicillin, based on the results of antimicrobial susceptibility testing. The susceptibility was good despite the low MICs of metronidazole in past studies. The current report did not test for the isolate's susceptibility to metronidazole. The current report indicated low MICs for linezolid and piperacillin-tazobactam, with a favourable susceptibility profile. In conclusion, Clostridium ramosum bacteraemia can be treated with linezolid, piperacillin-tazobactam, and metronidazole, and precise bacterial identification and susceptibility testing are crucial. In our study, the *Clostridium ramosum* strain was sensitive to piperacillin and linezolid but resistant to penicillin, ceftriaxone, and vancomycin [5]. We immediately gave the patient the antibiotics with low MICs to control the rapid infection. Even though we administered several susceptible antibiotic combinations, the patient died, maybe because the disease progressed uncontrollably against a weak host defence system. Biomarkers of the host response, including CRP, procalcitonin, IL-6, and IL-8, may provide critical data that can be used to customize treatment.

4. Conclusions

We report the first instance of Fournier's gangrene caused solely by *Clostridium ramosum* in a male patient. If Fournier's gangrene does not respond to conventional therapy, atypical organisms and cytokine storm checks are essential. The situation was more severe than it appeared outwardly, particularly with the aberrant IL-6, IL-8, and IL-10, and the disease rapidly worsened despite multimodal treatment. The high production of ILs in *Clostridium ramosum* gangrene could help identify the degree of deterioration of the infection and sensitive indicators for timely diagnosis and prognosis prediction. Comprehensive measures, such as early surgical debridement and antibiotic therapy, especially anti-anaerobic therapy, will be critical for similar patients in the future.

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Ethical declaration statement

Ethics Committee of Yancheng Third People's Hospital approved this case report (No: 2023-34) .

The patient's parents provided written informed permission for the publishing of this case report and any related photos. The Editor of this journal has access to a copy of the written permission for review.

Data availability statement

The data that support the findings of this study are publicly available.

CRediT authorship contribution statement

Hongjian Ji: Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Wei Shen:** Writing – original draft, Funding acquisition. **Xiaohua Zhou:** Validation, Project administration, Formal analysis, Funding acquisition. **Linlin Zhang:** Investigation. **Xin Zhao:** Visualization. **Qinfang Tang:** Visualization, Methodology. **Cheng Guo:** Writing – original draft.

Declaration of competing interest

The authors declare that the research was conducted without any commercial or financial relationships that could potentially create a conflict of interest.

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