Successful Treatment of Necrotizing Fasciitis of the Upper Extremity Caused by *Vibrio vulnificus*: Two Case Reports and Literature Review

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Case Report

Keywords: Vibrio vulnificus, Necrotizing Fasciitis, emergency debridement surgery, upper limb, bacteraemia, anti-infective drug.

Posted Date: January 29th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-154368/v1

Abstract

Background: Vibrio vulnificus infection patients are more common in China's coastal areas and military activities, but there have been very rare reports successful treatment and limb salvage patients.

Case presentation: We present two cases of patients with the successful treatment of necrotizing fasciitis caused by *V. vulnificus* and review the pathogenetic mechanism, epidemiology, clinical characteristics, and treatment of this infection.

Conclusion: When ***Vibrio vulnificus*** patients develop bacteraemia and necrotizing fasciitis symptoms,emergency surgical debridement combined with anti-infection therapy should be considered.

Background

Vibrio vulnificus grows in water with the appropriate temperature and salinity and is mainly obtained by seafood ingestion or direct contact [1]. In susceptible individuals, traumatic infections can be fatal, leading to severe wound infections and even septic shock, which may require amputation [2]. The pathogenesis of *V. vulnificus*-associated sepsis is very complex and includes iron uptake, cell damage, adhesion-related proteins and virulence regulation [3]. *V. vulnificus* infection is mainly manifested by clinical events such as primary sepsis and traumatic infection, and signs of multiple organ dysfunction syndrome (MODS) soon appear [4]. In the diagnosis and treatment of this disease, it is important to evaluate these pathogenic bacteria in combination with medical history and bacteriological culture results so that more sensitive antibiotics and timely surgical intervention can be selected to effectively improve the prognosis of patients. In this report, we share a case of the successful diagnosis and treatment of septic shock caused by *V. vulnificus* infection (which occurred at a national first-level trauma center and summarize the typical clinical manifestations and treatment methods.

Case Presentation

Case 1

A 46-year-old male with no history of chronic liver disease or cancer was admitted to our emergency department with a diagnosis of severe fever caused by an accidental stab wound that he had sustained on the dorsum of his right hand while handling seafood 2 days before. The patient's right palm became swollen and uncomfortable, and he immediately rushed to the local hospital for treatment. The first doctor empirically applied antibiotics based on the medical history. The exposure time from the first onset was 6 hours, and the patient exhibited ecchymosis and blisters around his right palm and wrist joints. The local hospital only administered antibiotics as conservative treatment and did not perform emergency surgical incision and drainage interventions. The results of high-throughput sequencing of this patient's blood drawn from the local hospital suggested that the source of infection was *V. vulnificus*. The patient was transferred from the local hospital to our hospital for treatment after 17 hours. Physical

examination revealed that his right upper limb was severely inflamed with ecchymosis and several blisters (Fig. 1a). A preoperative examination was conducted, and the patient was given a third-generation cephalosporin and quinolone as a combination anti-infective drug treatment. The right forearm incision and drainage were performed immediately in the emergency department, but a negative pressure drainage device was not used (Fig. 1b). The patient's vital signs gradually improved on the 7th day. After a series of treatments, the wound did not deteriorate further, nor did it progress to necrotizing fasciitis. After the 24th day, a right hand skin graft was performed. The patient's limb salvage was successful. He recovered and was discharged on the 26th day after the operation.

Case 2

A 60-year-old female with a history of gout and rheumatic heart disease was admitted to our emergency department with a diagnosis of severe fever with bacteraemia due to a scratch on her right index finger caused by the scales of a crucian carp 12 hours earlier. On the same day, the patient's right hand became swollen and purple in hue, and the little finger of the same hand was swollen with purple and black discoloration. She immediately rushed to our hospital for treatment. The exposure time from the first onset was 12 hours. The initial diagnosis was severe septic shock and right forearm compartment syndrome. Physical examination revealed severe inflammation of the right upper limb with ecchymosis and several blisters (Fig. 2a). The swelling of the right forearm rapidly progressed to the proximal part of the limb, and the blisters expanded and ruptured within 12 hours; the patient's condition then deteriorated rapidly, and septic shock appeared. She underwent acute incision debridement immediately after admission (Fig. 2b). The drainage fluid of the wound during the operation was cultured, and the test result suggested Aeromonas veronii. The patient was transferred to the intensive care unit for treatment after the operation. Treatment measures included anti-infective therapeutics, fluid resuscitation, vasoactive drugs, daily dressing changes, and continuous renal replacement therapy (CRRT). The results of high-throughput sequencing after the first operation indicated that the infectious bacterium was *V. vulnificus*. After a series of treatments, the wound did not improve and instead progressed to necrotizing fasciitis. On the 12th day, the patient underwent wound debridement and expansion along with amputation of the right little finger, and the postoperative wound was treated with a vacuum sealing drainage (VSD)/negative pressure drainage device (Fig. 2c). The patient's condition improved after this operation, and she was transferred to the general ward to continue treatment. A right forearm skin graft was performed on the 24th day, and the patient's limb salvage was successful. She recovered and was discharged on the 41st day.

Clinical characteristics and treatment

General information regarding the 2 admitted patients with *V. vulnificus* infection is shown in Table 1. Disease characteristics are as follows: The patient first manifested with an acute onset, swelling of the affected area, severe pain, and impaired mobility, followed by ecchymosis, tension blisters and even skin necrosis in the affected area. One severely ill patient developed septic shock within 24 hours. In addition to the typical clinical manifestations of the two patients, namely, fever, low blood pressure or symptoms

of septic shock, and characteristic vesicular lesions, the female patient had a history of rheumatic disease. Laboratory examinations of the two patients revealed that the white blood cell counts; proportion of neutrophils; C-reactive protein, procalcitonin, and blood sugar levels; and other indicators were all elevated. Moreover, haemoglobin, albumin, and platelets were decreased. Incision of the skin of the affected area showed extensive necrosis of the fascial tissue, a large amount of water-like exudate from the irrigated tissue, and no obvious odour.

Table 1

General information of the two cases

Case	Age	Sex	History	Pathogen	Time of the first visit	Bacterial culture	
						Wound secretions	Blood
1	46	male	no	handling of fish	6 hours	+	+[c]
2	60	female	yes [a]		12 hours	+ [b]	

a: Female with a history of rheumatic immune disease.

b: The results from the culture of wound secretions suggested Aeromonas veronii.

c: The results of blood-based NGS indicated *Vibrio vulnificus*.

Results of aetiological examination

V. vulnificus was cultured in the tissue fluid and blood from the first affected area of the female patient. The male patient was referred with next-generation sequencing (NGS) [5] results reported at the local hospital as indicating *V. vulnificus*. After the two patients were transferred to our hospital for multiple debridement procedures and combined antibiotic treatment, the final culture result was negative. The results of the drug sensitivity test showed that *V. vulnificus* was sensitive to most antibiotics, among which third-generation cephalosporins and quinolones had the lowest minimum inhibitory concentration (MIC) value and the strongest in vitro sensitivity.

Treatment (Table 2)

The patients were actively rehydrated to correct shock. According to the NGS results combined with treatment guidelines, the administered antibiotics comprised cefotaxime combined with quinolone therapy [6]. The two patients underwent emergency debridement immediately after diagnosis; in addition, debridement operations were repeated many times, and wound sealing and negative pressure drainage were performed.

Table 2

Two cases of the treatment of patients infected with *Vibrio vulnificus*					
Case	Antibiotics	Operation time	Surgical approach	CRRT (ICU)	Hospital Day(HD)
1: male	Piperacillin sodium Tazobactam sodium + Levofloxacin	3-times	Left upper limb debridement + vacuum negative pressure closed suction	no	28 days
2: female	Vancomycin + Meropenem + Moxifloxacin	5-times	Right upper limb debridement + vacuum negative pressure closed suction	yes	41 days
All patients underwent more than 2 operations, and they were treated with a combination of surgery and antibiotics.					

Clinical outcome

Both patients improved during the treatment process and finally succeeded in protecting their limbs. They were cured and discharged without major amputation.

Discussion

1. Pathogenetic mechanism

V. vulnificus is a mesophilic, halophilic, gram-negative bacterium that lives in the ocean. It belongs to the same genus as V. cholerae and V. parahaemolyticus [7]. In 1970, ROLAND first reported gangrene and endotoxic shock of the calf caused by *V. vulnificus* infection [8]. In 1979, FARMER named the organism *Vibrio vulnificus*[9]. The pathogenic mechanism of *V. vulnificus* is of great significance to the prevention and treatment of infection by this bacterium [10]. At present, research on pathogenic mechanisms mainly focuses on host defence, cytotoxicity, bacterial motility, adhesion-related proteins, virulence regulation, and biofilm formation.

1.1 Host defences include capsular polysaccharides, acid neutralization and iron overload in the body. Capsular polysaccharide (CPS) is produced by *V. vulnificus* and secreted to the outside of the cell, covering the external immunogenic structure of the bacteria, not only shielding it against the opsonin function of the complement system and the phagocytosis of macrophages but also helping the bacteria escape inherent immune surveillance, which can also determine the morphology of bacterial colonies and regulate the formation of biofilms [11]. Acid neutralization means that *V. vulnificus* can resist gastric acid by increasing the expression of lysine decarboxylase and the expression of manganese superoxide dismutase in a low pH environment in the stomach to achieve acid neutralization [12]. *V. vulnificus* obtains

iron in the blood through various iron uptake systems and then grows and proliferates. Serum iron levels can indirectly reflect the infection of the body with *V. vulnificus*.

1.2 Cytotoxicity involves lipopolysaccharide (LPS), cytolysin and repeats-in-toxin A1 (RtxA1). LPS may play a role in cytotoxicity by affecting the activity of nitric oxide synthase (NOS) in the body; LPS can also play an adhesive role to promote the formation of biofilms, causing the infected body to develop endotoxin shock and sepsis [13]. Cytolysin is an exotoxin encoded by the vvhA gene and is secreted outside of the cell. It exerts cytotoxicity that causes cell apoptosis and can destroy red blood cells to release iron into the blood [14]. RtxA1 is capable of mediating cell death and tissue necrosis after contact with bacterial cells, thereby increasing the expression of the RtxA1 gene and inducing cytotoxicity and the destruction of intestinal epithelial cells and intestinal microvilli [15].

1.3 Bacterial motility involves flagella and fimbriae. *V. vulnificus* has one flagellum, which is encoded by 6 flagellum genes (flaA, flaB, flaC, flaD, flaE, flaF), of which flaB, flaD and flaC play a major role [16]. Flagella are related to the motility, adhesion, cytotoxicity, biofilm formation and invasion of bacteria [17]. *V. vulnificus* fimbriae were first discovered by GANDER under an electron microscope in 1989 [18]. The fimbriae are related to bacterial invasion, adhesion and pathogenicity.

1.4 Extracellular proteases and adhesion-related proteins: Outer membrane protein U (OmpU) can bind to fibronectin, the main component of the mammalian extracellular matrix and is related to the adhesion function of bacteria [19]. Membrane-bound lipoprotein A (IlpA) plays a role in adhesion and immunogenicity. The extracellular protease (ECPase) of *V. vulnificus* can yield a variety of ECPases that exert cytotoxic effects, including metalloprotease (Mpase), chondroitinase (ChSase), and hyaluronidase (HAase) [20].

1.5 Toxicity regulation includes quorum sensing (QS), total virulence regulators and haemolysin U. Bacteria can synthesize and release a kind of autoinducer (AI) that regulates many of their biological behaviours, thus causing group-sensing effects. In *V. vulnificus*, the synthesis of CPS and fimbriae is regulated by the QS system [21]. The global virulence regulator cAMP-cAMP receptor protein (CRP) can bind to DNA and affect gene expression, including cytolysin, metalloproteinase and iron uptake systems, which are all regulated by the CRP system. Another virulence regulator, AphB, has a wide range of functions, including acid neutralization, motility, adhesion and pathogenicity [22]. Haemolysin U (HlyU) is the main regulator of *V. vulnificus* toxicity and can regulate the expression of the rtxA1, vvhA and vvpE genes.

1.6 Biofilm formation. The biomembrane composed of CPS, exopolysaccharides (EPS) and LPS can counter the effects of drugs and the host immune system [23].

2. Epidemiology

V. vulnificus exists as a free-living bacterium inhabiting estuarine or marine environments. Traditionally, three biotypes have been recognized: biotype 1, which accounts for almost all human infections; biotype 2, which consists primarily of eel pathogens; and biotype 3, an apparent hybrid of biotypes 1 and 2 that has been described in tilapia-associated wound infections associated with aquaculture in Israel [24]. Wound infections most often occur in the setting of handling seafood and generally result from exposure of a wound to salt or brackish water containing the organism [25]. Individuals with the following conditions are at increased risk for serious infection with *V. vulnificus*[26]: Alcoholic cirrhosis, Underlying liver disease including cirrhosis and chronic hepatitis, Alcohol abuse without documented liver disease, Hereditary haemochromatosis, Chronic diseases such as diabetes mellitus, rheumatoid arthritis, thalassemia major, chronic renal failure, and lymphoma. Interestingly, men, and particularly older men, appear to be at much greater risk for serious infection than women [27]. Our motherland has a vast population and a large group of patients with liver cirrhosis. The eastern coast of China has a coastline of 32,000 kilometres and a sea area of nearly 3 million square kilometres. The development of fishery operations and military activities in coastal areas makes this region a high-risk area for *V. vulnificus* infection.

3. Clinical characteristics

The trend of *V. vulnificus* infection increases with climate warming, ocean activities, and the presence of high-risk factors such as alcohol, liver disease, systemic disease, and diabetes [28]. Traumatic bacterial infection is mainly manifested in the following clinical subtypes: traumatic infection, primary sepsis, gastroenteritis and typical clinical features. Injuries with mild symptoms may result from infection with *V. vulnificus*, which may cause cellulitis with mild clinical symptoms [29]. However, in high-risk individuals (such as the female patient reported in this article) who have a history of rheumatic disease, the infection may spread quickly, causing severe myositis and necrotizing fasciitis (Fig. 1). This pathogen enters the gastrointestinal tract through contact with open wounds, thereby entering the blood system and then causing sepsis. The main disease manifestations include acute fever, chills, shock, and skin and muscle damage. People with gastrointestinal infections exhibit symptoms of acute gastroenteritis, including diarrhoea, nausea, vomiting, abdominal pain, and difficulty breathing [30]. Typical skin and muscle damage includes local or flaky erythema and ecchymosis, bloody vesicles with exudation, necrosis and cellulitis, necrotizing fasciitis, and muscle inflammation [31]. In the case of body infection caused by contact with seawater, skin and muscle damage rapidly progresses to necrosis and leads to severe sepsis, which may lead to life-threatening conditions [32]. Patients usually have underlying liver disease, alcoholism, hereditary pigmentation diseases, or the chronic diseases mentioned above, which can cause primary sepsis. Approximately one-third of patients with primary sepsis will have shock or low blood pressure within 12 hours after going to the hospital.

Three-quarters of patients exhibit unique blister lesions (Fig. 2). The infection causes complications such as reduced blood circulation, diffuse intravascular coagulation, and disorders of the digestive tract. Primary *V. vulnificus* sepsis is an extremely serious disease with a high mortality rate.

4. Treatment

The pathogenic diagnosis of the two patients reported in this article relied on the results of NGS. With its high-output and high-resolution characteristics, NGS not only provides us with rich genetic information but also greatly shortens the cost and time of sequencing and provides more accurate clinical guidance for the diagnosis of clinical diseases. The US Centers for Disease Control (CDC) recommended three generations of cephalosporins combined with tetracyclines as the recommended treatment for *V. vulnificus* infection. Patients with mild to moderate infections are usually treated with antibacterial drugs for 5–7 days. If patients with mild infections have no serious underlying diseases, mild wound infections usually respond well to topical treatment and intravenous infusion of antibacterial drugs (such as cephalosporins combined with tetracyclines or cephalosporins combined with quinolones). The length of treatment depends on the severity of the initial infection and the clinical response. Treatment of high-risk patients with severe infection: Patients who are presumed to be diagnosed with *V. vulnificus* sepsis should start antibacterial drugs and incision debridement as soon as possible, and when necessary, amputation plays a significant role in improving the prognosis of patients with *V. vulnificus* infection [33]. For patients with severe haemodynamic instability, a low platelet count and severe coagulopathy, emergency incision and drainage should be the first choice [34]. During the operation, the skin of the infected limb should be incised, the subcutaneous tissue should be bluntly separated, and the fascia should be exposed until the muscle membrane is formed under local anaesthesia or intravenous pain relief. The length and direction of the incision are determined according to the patient's coagulation function, skin tension, and degree of disease. After the operation, gauze soaked in iodophor and sulfamethazine solution is used for external application to facilitate dressing changes and timely assessment of the wound surface. Active treatment in the intensive care unit where possible, along with early CRRT, can help MODS patients by removing endotoxin and inflammatory mediators. Patients with acute lung injury or acute respiratory distress syndrome (ARDS) should be given non-invasive or invasive mechanical ventilation to minimize the possible consequences of low pressure and septic shock and to reduce the risk of multiple organ system failure. The affected limb should be amputated to save a patient’s life if the muscle necrosis is too severe to mend.

Conclusion

Combined with the exchange of clinical cases and experience, a clear history of exposure, a rapidly deteriorating general state and local typical bloody bullous lesions are important evidence for the diagnosis of sepsis caused by *V. vulnificus* infection. Most patients develop hypotension or shock, rapid development of symptoms and MODS within 24–48 hours, and the mortality rate exceeds 50 percent [35]. Although the culture of pathogenic bacteria is delayed, it is difficult to recognize the infection of *V. vulnificus* in time. When conditions permit, the NGS test can obtain the result of pathogenic bacteria faster and more accurately. Experienced surgeons should assess whether emergency surgery is needed to treat and control the infection as soon as possible because early surgical intervention can improve the prognosis of patients with *V. vulnificus*. We recommend the combination of anti-infection therapy and

surgical debridement as soon as possible, and surgical debridement should be performed as soon as possible after the diagnosis is confirmed. Early surgical debridement of our two patients improved their treatment outcome. Standard surgical debridement, incision and drainage can quickly alleviate the patient's pain, reduce the loss of various coagulation factors in the early stage of infection, reduce the patient's bleeding risk, and improve the patient's disease tolerance. Wound sealing and negative pressure drainage technology can help limit infection, drain exudates, and reduce oedema [36]. Whether the patient limb is amputated is based on the assessment of the patient's wound because early amputation may help completely remove the source of infection, block the chain of bacterial transmission, and enable the patient to enter the "improvement period" as soon as possible, which may benefit him/her. In view of the dangerous condition of *V. vulnificus* infection and the high mortality rate of certain populations, sufficient attention should be paid.

Abbreviations

NGS: next-generation sequencing ; CT: Computed tomography; HD: Hospital day; CRRT: continuous renal replacement therapy.

Declarations

Acknowledgements

We gratefully acknowledge the intense individual effort and support from many sources to make this study possible, as well as the contributions of plasma donors.

Authors' contributions

LN and GPC have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. GPC and ZGF conducted concept and design. LN, ZGF and HXQ performed the data collection, analysis and interpretation. LN and GPC drafted the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

This study was approved by the Medical Ethical Committee of zhejiang university medical of second hospital with the participants' written informed consent (ZEYYMECT:L20205487 L011).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

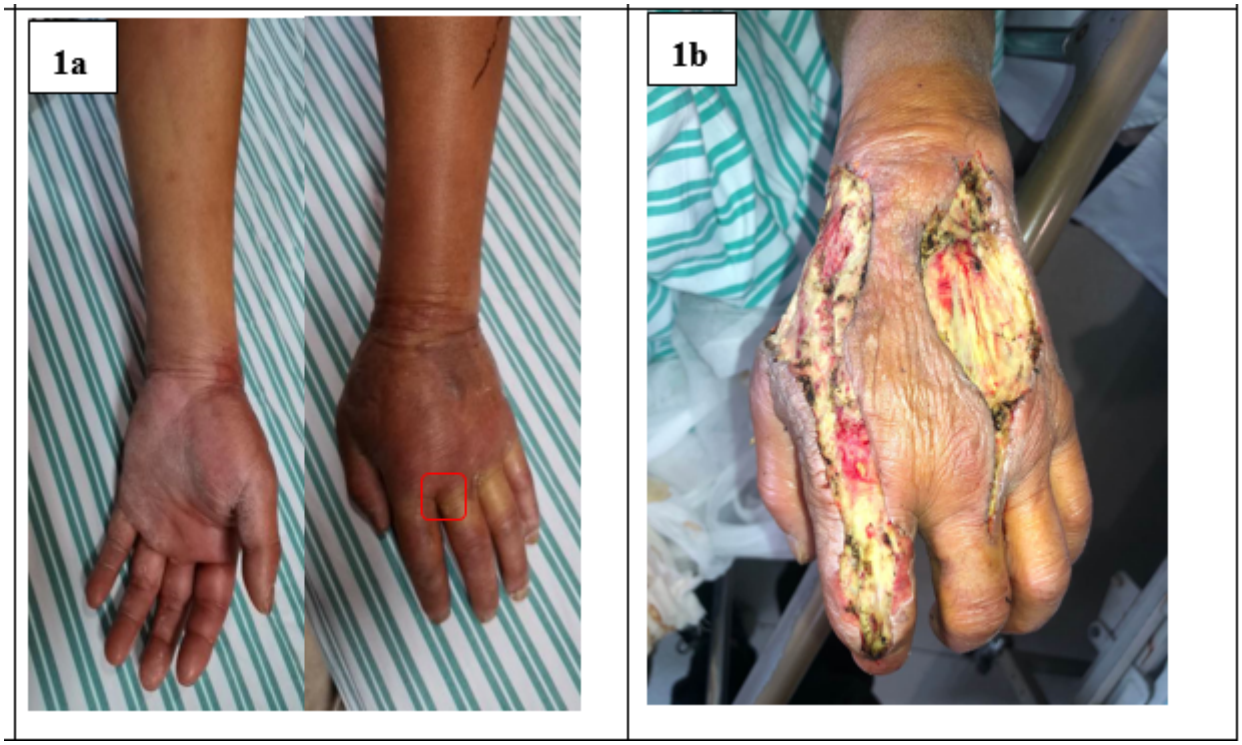

Figure 1

Surgical photographs of patient, Case 1 male: a: Preoperative, b: Postoperative. The red mark in the picture is the location of the patient's wound injury.

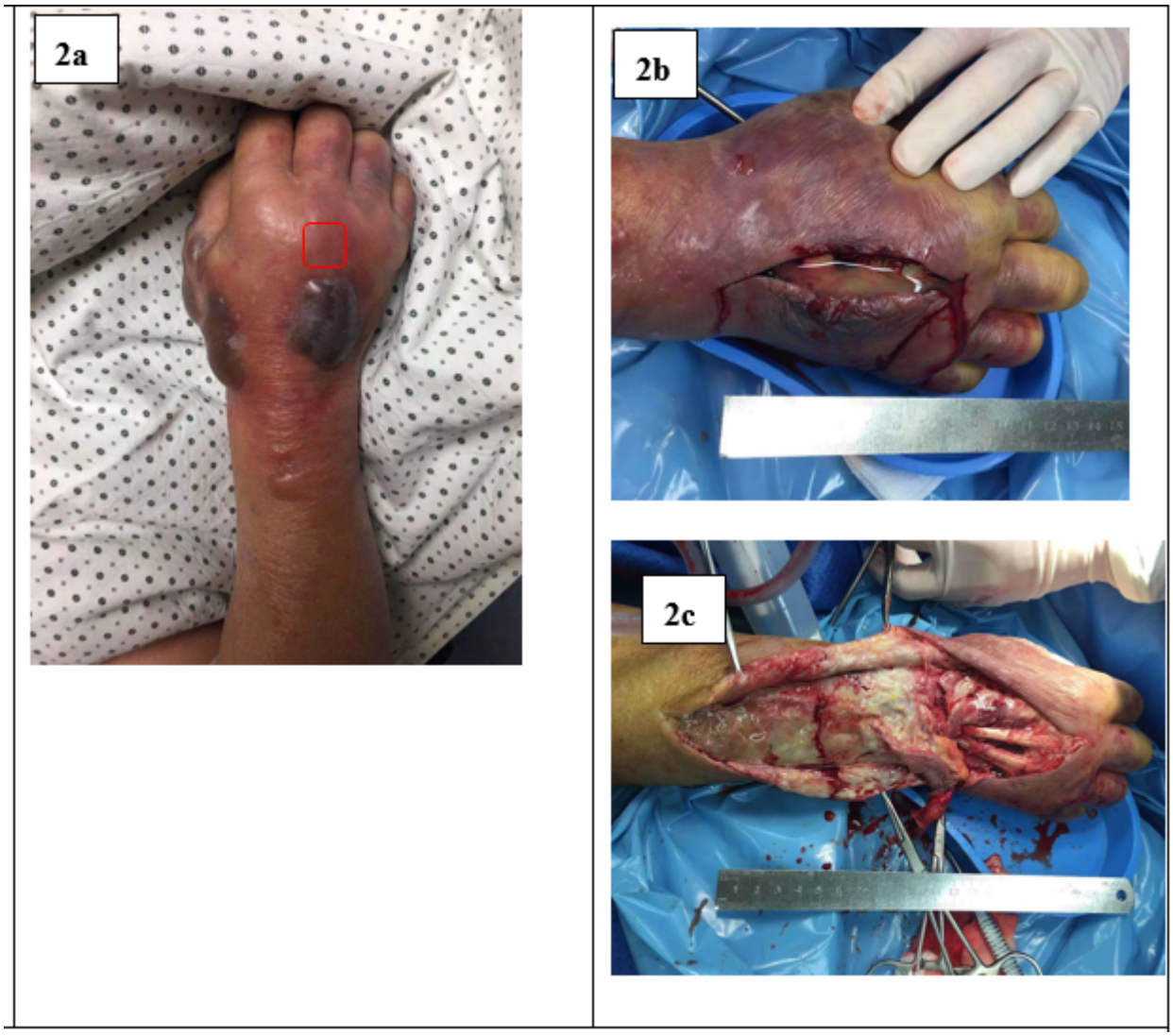

Figure 2

Surgical photographs of patient, Case 2 female: a: Preoperative, b: Picture of the patient's first emergency debridement surgery. c: Picture of the patient's second emergency debridement surgery. The red mark in the picture is the location of the patient's wound injury.