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The case of septic shock that deserved a closer look

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A 66-year-old lady with history of heroin and Z-drug dependence, Hepatitis C, hypertension and recurrent deep vein thrombosis attended the emergency department for chest discomfort and vomiting with suspected coffee ground vomitus for 1 day. She also complained of chronic bilateral lower limb swelling and pain.

Her vital signs on arrival were stable with blood pressure 114/77mmHg, pulse rate 60 bpm and SpO2 95% on room air. Her Glasgow Coma Scale was full. She was found to have fever with a temperature of 38.4^{o}C. On physical examination, she appeared to be tired looking with dehydration. There was erythema and edema over bilateral lower limbs from the ankles up to the shins, which the patient claimed to be a chronic condition. There was no crepitus or excruciating tenderness over the lower limbs, and there was also no wound that suggested recent self-injections. Chest examination was unremarkable while abdominal palpation showed mild epigastric tenderness. Per rectal examination revealed brown stool. Electrocardiogram showed sinus rhythm at a rate of 127 bpm without acute ST segment changes. Point-of-care tests revealed hemoglobin 15g/dL and blood glucose level 2.4mmol/l, so intravenous dextrose solution was given. The venous blood gas analysis did not show metabolic acidosis. X-ray studies of the chest and abdomen were unremarkable.

During reassessment, she was found to be hypotensive with systolic blood pressure dropped to 70 mmHg. She was then immediately transferred to the resuscitation room for further management. Due to difficult intravascular access, central line insertion at the right internal jugular vein was performed under ultrasound guidance. She was in refractory shock despite fluid resuscitation. Noradrenaline infusion was started. Intensive Care Unit was consulted. Computed tomography of abdomen and pelvis was performed to rule out intraabdominal source of sepsis and the result was unremarkable. She was managed as septic shock and was admitted to the Intensive Care Unit (ICU) under the medical specialty.

During the stay in ICU, the patient complained of worsening pain over the lower limbs. She also had increasing inotrope demand despite antibiotics. Therefore, bilateral lower limb necrotizing fasciitis was suspected. Emergent bilateral lower limb debridement was done after consulting orthopedics surgeons. The operation was done 20 hours after the initial presentation in the emergency department.

The orthopaedic surgeons documented several findings during the operation including chronic scars and pigmentations as well as erythema of both lower limbs from dorsal feet up to anterior knees. However, there was no documented classical appearance of necrotising fasciitis including purple discolouration, blisters or bullae. Meanwhile, incisions were made over medial and lateral sides of both legs which showed a positive finger test and the presence

of “dishwater“ discharge. Second-look debridements were subsequently performed twice until bilateral lower limb wound bases were clean with relatively healthy underlying fascia. For microbiological result, the blood culture showed initially presence of *Streptococcus pyogenes* but it was negative upon repeated blood culture after antibiotic administration on the same day. The superficial wound swab also showed presence of *Streptococcus pyogenes* and *Staphylococcus aureus*. However, intraoperative tissue culture was negative. She was given intravenous linezolid and meropenem initially, and later changed to intravenous ceftriaxone according to the blood culture sensitivity profile. She was also given stress dose steroid.

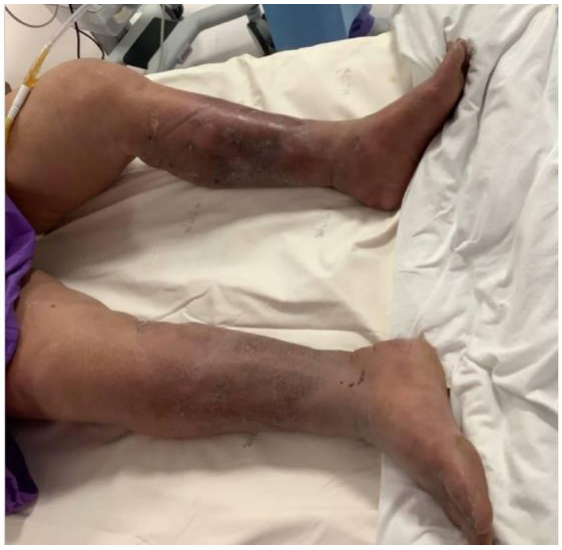

Fig.1 Clinical photo of patient’s lower limbs

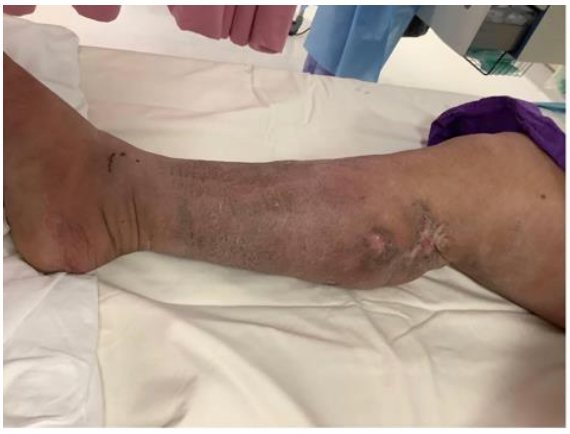

Fig.2 Clinical photo of patient’s right leg

The patient’ s condition improved gradually and was transferred back from ICU to general orthopedics ward for further rehabilitation.

Importance of Source Control in Sepsis Management

Sepsis is a life-threatening organ dysfunction caused by an unregulated response of a host to infection. Infection initiates cytokine release, leading to a global inflammatory cascade.[1] Under the recent hypothesis that bacterial load is the primary driver of septic organ dysfunction, the rapid clearance of pathogens is the central determinant of outcome in septic shock. Early appropriate antimicrobial therapy and source control are key to sepsis management. The 2021 Surviving Sepsis Campaign guidelines recommend identifying anatomical source of infection that may require source control and implementing this as soon as logistically and medically possible. The goal of source control is to eliminate the source of infection, control ongoing contamination, and restore premorbid anatomy and function. It includes draining of infected collections, debriding infected soft tissues, removing infected devices or foreign bodies and correcting anatomic derangement causing microbial contamination.[2]

Necrotizing fasciitis

Necrotizing soft tissue infections (NSTI) encompass rapidly progressing and destructive forms of fasciitis, myositis and cellulitis. They are characterized clinically by fulminant tissue destruction, systemic toxicity and high mortality.

Necrotizing fasciitis (NF), being one form of NSTI, is the infection of deep soft tissues that results in progressive destruction of muscle fascia and overlying subcutaneous fat. Infection typically spread along muscle fascia due to relatively poor blood supply. As the fascial layer

	Type I **Polymicrobial**	**Type II** **Monomicrobial**
Organisms	Often Gram positive, Gram negative and anaerobes	Monomicrobial with *group A Streptococci* or less often *Staphylococcus aureus* Other possible organism: *Vibrio vulnificus* and *Aeromonas hydrophila*
Gas Formation	Often gas in tissues May have a foul odor	No
Anatomical Locations	Following surgery or injury (post operative wounds, diabetic ulceration) Head/ neck, abdomen or anogenital area (e.g. Fournier's gangrene)	Often involves the extremities, following minor trauma that breaks the skin May occur at sites of non-penetrating trauma (including minor muscle sprain), if inflamed tissue is seeded following transient streptococcal bacteremia
Epidemiology	Typically affects patients with comorbidities (e.g. diabetes, alcoholism, obesity, renal failure)	May affect anyone (often young and healthy people) Can occur as superinfection on top of compromised skin (e.g. varicella infection)
Associated findings	Septic Shock	Septic shock Toxic shock syndrome (e.g. vomiting, diarrhea, encephalopathy, diffuse erythroderma)

Table 1. Types of necrotizing fasciitis[3]

is deep, it may not be visibly obvious. In necrotizing fasciitis, the visible findings on skin are the tip of the iceberg. Given its ability to spread rapidly and destroy overlying skin, it is a both life and limb threatening emergency.

Clinical Presentation

The degree of suspicion should be high since the clinical presentation is variable and prompt intervention is critical. Necrotizing fasciitis usually presents acutely over hours. Rarely it may present sub-acutely over days.

Early findings on skin examination are less specific. Pain is generally the most useful one. Pain is often excruciating and out of proportion to the external appearance. It may also extend beyond superficial erythema (unlike cellulitis). However, it can be painless in patient with diabetic neuropathy or in necrotizing fasciitis following trauma, surgery, or childbirth in whom the pain may be misattributed to the surgery or trauma. Other early skin findings include erythema and edema. We should make sure we fully expose patients for examination, especially those septic patients without obvious foci.

Late findings of skin examination are more specific. They include subcutaneous emphysema, purple discoloration or a bruised appearance. Blistering or bullae may also occur, and may become hemorrhagic, yielding characteristic violaceous bullae, which is an extremely worrisome finding. Eventually this evolves into frank necrosis with skin sloughing. Pain will finally transit to numbness.

Rapid progression of necrotizing fasciitis typically results in systemic toxicities like fever, vomiting or diarrhea, frank septic shock and delirium. However, fever is present in only around 25% to 40% of patients on admission.[4] Moreover, patients with type II necrotizing fasciitis due to group A *Streptococcus* often have early manifestation of toxic shock syndrome with symptoms of nausea, vomiting,

diarrhea, fever and myalgia. The constellation of these flulike systemic features plus extremity pain should be suggestive of necrotizing fasciitis with toxic shock.

Diagnosis

Early recognition of necrotizing fasciitis is critical as it is rapidly progressive and limb and life threatening.

The definitive diagnosis of necrotizing fasciitis is established via surgical exploration of the soft tissue. The presence of "dishwater" fluid is a key indicator that a necrotizing infection is at play. Finger Sweep Test is another quick test that can be carried out at bedside or operating theater under local or general anesthesia. The test is positive if the finger passes through the subcutaneous tissue without resistance after an incision is made in the affected skin.[5] This is due to the poor adherence of tissue to the fascia. The test may also reveal absence of bleeding and presence of friable tissues with "dishwater" discharge. Surgical exploration should not be delayed if there is clinical suspicion while awaiting results of radiographic imaging, culture results or other diagnostic information.

In the emergency department, point-of-care ultrasound can be used as an adjunct for evaluating necrotizing fasciitis. The ultrasound findings consistent with necrotizing fasciitis include fascial and subcutaneous tissue thickening, abnormal fluid accumulation in the deep fascia layer and in advanced cases, presence of subcutaneous air. These criteria can be recalled using a proposed "STAFF" mnemonic.[6,8] Fig.3 shows an example of the imaging findings. However, while it is not recommended to exclude necrotizing fasciitis based on ultrasound examination, it has been shown to have high specificity and may help to rule in the diagnosis. The sensitivity of ultrasound varies depending on the location and the extent of necrotizing fasciitis. Current ultrasound technology is thus unable to safely rule out the diagnosis.

The best initial radiographic imaging exam is Computed Tomography Scan.[7] The possible findings include presence of gas in soft tissues, fluid collections, absence or heterogeneity of tissue enhancement with intravenous contrast, and inflammatory changes beneath the fascia. Meanwhile, plain radiography may reveal gas within the tissues which is specific for necrotizing fasciitis, but the finding is poorly sensitive as it is a late finding which is only seen in some types of necrotizing fasciitis.

While necrotizing fasciitis is not a laboratory diagnosis, deranged laboratory should raise the index of suspicion. "Laboratory Risk Indicator for Necrotizing Fasciitis" (LRINEC Score) is a diagnostic evaluation system described by Wong et al in 2004. It based on six laboratory tests and stratifies patient into low, medium or high risk of necrotizing fasciitis, as shown in Table 2 and Table 3.[9] However, the tool has demonstrated variable sensitivity and should not be used to rule out necrotizing fasciitis.

Blood culture is positive in approximately 60% with monomicrobial (type II) necrotizing fasciitis.[10] The yield of blood culture is lower among patients with polymicrobial (type I) necrotizing fasciitis. In addition, blood culture results may not reflect all organisms involved.

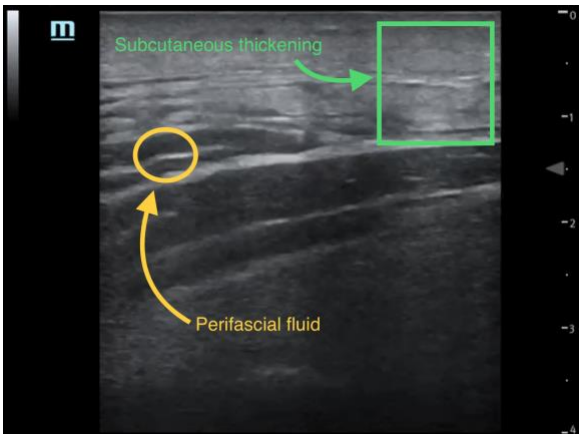

Fig.3 Ultrasound findings commonly seen in necrotizing fasciitis

Management

The management of necrotizing fasciitis consists of early aggressive surgical exploration and debridement of necrotic tissues together with broad spectrum empiric antibiotic therapy and hemodynamic support.

Variable	Value	Score
C-Reactive protein (mg/L)	≤150	0
	>150	4
Total white blood cell count (1000 cells/μL)	<15	0
	15–25	1
	>25	2
Hemoglobin (g/dL)	>13.5	0
	11–13.5	1
	<11	2
Sodium (mmol/L)	≥135	0
	<135	2
Creatinine (mg/dL)	≤1.6	0
	>1.6	2
Glucose (mg/dL)	≤180	0
	>180	1

Table 2. The laboratory risk indicator for necrotizing fasciitis (LRINEC) score

Risk Category	LRINEC Points	Probability for Presence of NF
Low	≤5	<50%
Medium	6–7	50–75%
High	≥8	>75%

Table 3. Using the LRINEC score for risk assessment

The goal of operative management is to perform aggressive debridement of all necrotic tissue until healthy viable and bleeding tissue is reached.

In general, empirical treatment should consist of broad-spectrum antibiotics with activity against gram positive, gram negative and anaerobic organisms. Antibiotic therapy should be initiated promptly after obtaining blood culture.

Acceptable empiric antibiotics regimen should include broad spectrum beta-lactam as backbone such as piperacillin-tazobactam or meropenem, plus an agent with activity against methicillin resistant *Staphylococcus aureus* such as vancomycin or linezolid, together with an antitoxin agent such as clindamycin or linezolid.[11] For patients who have exposures that may suggest an infection with specific organisms, such as trauma in freshwater, which is worrisome of *Aeromonas*, a combination of doxycycline plus fluoroquinolone should be considered. While for patient with seawater exposure which is worrisome of *Vibrio vulnificus* infection, a combination of doxycycline with third or fourth generation cephalosporin should be considered.

Hemodynamic instability is not uncommon in patient with necrotizing infection, aggressive supportive care with fluid and vasopressors should be administered. Patients with streptococcal necrotizing fasciitis (Type II) often simultaneously have toxic shock syndrome. The co-existing condition may be suspected based on clinical clues as the following:

- Relatively young age
- Lack of gas in tissues
- Other feature of toxic shock (e.g., diffuse erythroderma, prominent gastrointestinal symptoms)

Intravenous immunoglobulin (IVIG) should be considered in patient with suspected type II necrotizing fasciitis, especially if there are signs of multiorgan failure.[12] However, the evidence regarding the use of intravenous immunoglobulin as a treatment for all cases of necrotizing fasciitis is currently inconclusive and conflicting. This likely reflects that IVIG is effective in type II necrotizing fasciitis but not in other types of necrotizing fasciitis.

Hyperbaric oxygen therapy (HBOT) has also been evaluated as an adjunctive therapy for necrotizing fasciitis. Several mechanisms of

action have been proposed such as the generation of reactive oxygen species, which is both bacteriostatic and bactericidal, particularly on anaerobic bacteria.[13] Adjunctive HBOT may decrease mortality and limit the extent of debridement in necrotizing fasciitis. However, high quality data are limited due to lack of randomized trials.

Lesson To Learn

1. Early source identification and control is one of the key managements of sepsis.
2. Full exposure for inspection in septic patients without accountable foci is crucial.
3. Diagnosis of necrotizing fasciitis requires high index of suspicion since the clinical presentation can be variable and non-specific.
4. Necrotising fasciitis should be suspected in septic patients with evidence of soft tissue infection or inflammation, particularly if no other septic focus is found, even if the clinical features are not alarming, or even in some chronic skin conditions.
5. Orthopaedic surgeons should be consulted early for surgical exploration if the necrotising fasciitis is suspected.
6. The management of necrotizing fasciitis involves prompt surgical exploration, broad spectrum antibiotic therapy and hemodynamic support.

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