

Diabetes mellitus and necrotizing fasciitis – a deadly combination; case report

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ABSTRACT



Necrotizing fasciitis is a rapidly destructive affliction of soft tissues, with a mortality rate that may reach 73% of the cases. It is characterized by a progressive inflammation and extended necrosis of the subcutaneous tissue and the fascia. Necrotizing fasciitis was first described in 1848, and later in 1920 Meleney identified 20 patients in China in which the infection was presumably triggered by hemolytic streptococcus, linking pathological bacteria to the condition. In 1952, Wilson coined the term necrotizing fasciitis although without successfully identifying the specific pathological bacteria involved. In most cases, both risk and aggravating factors are present, the main risk factors being diabetes mellitus, liver cirrhosis, renal failure, and immunosuppressant states. Location may vary, but most frequently the disease occurs in the limbs, the trunk, and the perineum. Treatment depends on the location and the time of diagnosis and may range from large incisions with extensive debridement to organ amputations such as those of the limbs or breasts. Treatment is complex and expensive, and besides surgery, includes the administration of broad-spectrum antibiotics, anti-inflammatory drugs, intensive therapy support, and long-term hospitalizations. The prognosis is guarded. The present case entails a 56-year old female patient who presented with many risk factors favoring the occurrence of necrotizing fasciitis, namely diabetes mellitus, liver cirrhosis (decompensated with ascites and portal encephalopathy phenomena), untreated hepatitis B infection, chronic renal failure with diabetic nephrotic syndrome, and obesity.

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Introduction

Necrotizing fasciitis has been defined as a severe infection of soft tissues which includes extended necrosis of the fascia and the subcutaneous tissue, with the relative sparing of the muscles and skin [1]. As the disease progresses, the thrombosis of cutaneous perforants will cause the devascularization of the skin, leading to its necrosis. Sepsis will invariably develop, depending on the bacteriological cultures. There are 3 types of necrotizing fasciitis: type I consists of polymicrobial infections, type II consists of group A streptococcal infections alone or associated with Staphylococcal infections, and type III consists of *Vibrio* species infections. However, recent

studies have revealed that the microbial flora is constantly undergoing change and is becoming increasingly resistant to antibiotics, for example, with reported cases in which the *Staphylococcus aureus* has been resistant, including to Methicillin [2]. Moreover, given that necrotizing fasciitis most often occurs on biological soil, bacteria with increased aggressiveness may also be involved, for example *Klebsiella pneumoniae* [3]. Despite aggressive treatment, the mortality rate remains high, ranging between 52 and 72% [4,5]. In most cases, necrotizing fasciitis occurs when there is decreased immunity, being associated with diseases such as myelodysplastic syndrome, liver cirrhosis, diabetes mellitus, cancer, and chronic obstructive arteriopathy [6-8].

Case Report

A 56-year-old female patient presented to the surgical unit with painful right inguinal adenopathy. Clinically, the presence of a right inguinal adenopathy of about 4/2/2/ cm was noticed. It was mobile, well outlined, painful spontaneously and also upon palpation. The patient presented with associated decompensated type II diabetes mellitus, liver cirrhosis decompensated both parenchymatously and vascularly, with ascites occurring due to a HBV infection, alcohol consumption, and obesity. Preoperative tests also revealed moderate anemia (Hb=9.8 mg/dl) and chronic renal failure, probably due to diabetic nephropathy (creatinine 1.4), while the inter-clinical consultation on internal medicine also revealed stage II AHT.

Despite the associated pathology, and after the preliminary postponement of the surgical intervention, the patient insisted on the surgical removal of the inguinal ganglion, on the one hand, because of the local pain, and on the other hand because of the suspicion of the family doctor of a possible lymphoma at onset.

The ablation of the inguinal ganglion was performed under local anesthesia, through a minimally invasive approach, a horizontal incision at approximately 4-5 cm under the inguinal arch, about 5-6 cm long. The immediate postoperative evolution was favorable, without any complications.

On admission, the patient had been on a course of self-administered Augmentin for 3 days. Two days after the intervention, the patient requested the discharge, and 6 hours later she returned, indicating pain at the incision site. Locally, the patient presented slight edema and erythema along with mild pain. She was re-operated on and the local necrosis of the fascia was noticed. It was debrided and broad-spectrum antibiotic therapy was initiated (Meronem with Vancomycin), as well as volemic support. The cultures showed the presence of enterococcus. Despite the established medication, the necrotizing fasciitis extended, the incisions were enlarged, with massive debridement, but the blood glucose level could not be established.

Given the low immunity determined by decompensated liver cirrhosis, the HBV infection, and decompensated diabetes mellitus, the general condition of the patient progressively worsened, with the decrease in plasma levels of hemoglobin and albumin, with hydro-electrolytic imbalances, metabolic acidosis etc., which could not be compensated despite all the efforts. The patient died 3 weeks after the onset of the necrotizing fasciitis.

Discussions

Early diagnosis of necrotizing fasciitis is difficult because the first manifestations consist of edema, erythema, and possible mild paresthesia. Laboratory test results are unchanged from those in the first stage of the disease [9]; as a result, the condition is often diagnosed late when the first complications have already occurred. Since there are no specific signs or symptoms for diagnosis, we considered that the first step in the diagnosis of necrotizing fasciitis is its suspicion at the smallest signs of local inflammation, in immunosuppressed patients and with favoring factors.

Once suspected or diagnosed, the protocol treatment for necrotizing fasciitis includes:

1. Assessment of the biological field, co-morbidities, and aggravating and prognostic factors;
2. Large and extensive incisions, with the debridement of all necrotizing tissues;
3. Broad-spectrum antibiotic therapy;
4. Intensive therapy with inotropic support medication which supports blood pressure at values higher than 65 mm Hg;
5. Reconstructive surgery.

The assessment of the biological field is done first through a thorough case history and the study of the patient's medical history in order to identify associated diseases, and second, through detailed laboratory tests: a complete blood count, ionogram, C-reactive protein, blood glucose levels, stress hyperglycemia ratio (IQR), HbA1c, glycemic variation (the difference between the level of hyperglycemia and that of hypoglycemia), urea, sodium, albumin, creatinine, liver transaminases, GGT, ALP, bilirubin. Additionally, glycosylated hemoglobin, AgHBs, HCV, HIV, uric acid, etc. can also be ordered [8-10].

The value of blood glucose levels and glycemic variations is currently a debated topic. Many critical illnesses cause stress-induced hyperglycemia by producing excessive catecholamine, glycogen, and inflammatory cytokines, thus leading to the increase of glucogenesis and insulin resistance [11]. Yet hyperglycemia may also be a distinctive sign of severity in patients with associated diseases [12]. Egi et al. have demonstrated that acute hyperglycemia can affect mortality in diabetic patients with other critical illnesses [13]. However, glycated hemoglobin (HbA1c) is not influenced by acute stress or sepsis [14].

Po-Chuan Chen et al. conducted a study on 252 patients, which focused on the role of glycemic variation as a predictive factor for necrotizing fasciitis. This study revealed that a glycemic variation ≥ 146 mg/dl with or without hyperglycemia on admission and with an APACHE II score ≥ 15 , had favored the development of

complications in patients with necrotizing fasciitis, especially bacteremia and acute renal failure. Thus, it was used as a predictive factor in the occurrence of complications and the evaluation of the prognosis in patients with necrotizing fasciitis [8].

The American Society of Anesthesia (ASA) has developed a system of evaluation for the systemic inflammatory response syndrome (SIRS) that we find useful (Table 1).

In the case of monomicrobial infections, the most frequently implicated germs are group A streptococcus, group B streptococcus, staphylococcus aureus, aeromonas hydrophilia, vibrio vulnificus, Escherichia coli, klebsiella pneumoniae, and pseudomonas aeruginosa, while in the case of plurimicrobial infections, there may be various

combinations of these germs [15]. Approximately 60-80% of the infections related to necrotizing fasciitis are monomicrobial [16, 17]. Finegoldia magna may also be implicated when determining microbial infections in the case of necrotizing fasciitis in the diabetic patient [18]. Finegoldia magna is a Gram-positive anaerobic coccus of the Clostridiales family, which together with other Gram-positive anaerobic cocci (GPAC), had been known until 1999 to be part of Peptostreptococcus magnus, being a pathogenic germ that normally colonizes the skin and the mucous membranes, but which can cause severe infections in case of low immunity, as in the case of a diabetic patient [19,20]. The Klebsiella Pneumoniae infections are associated with an increased risk of death [15] (Table 1).

Table 1. The evaluation system of the Systemic Inflammatory Response Syndrome (SIRS) [15].

Variable	Definition
Diabetes mellitus	The diagnosis is based on one of the four abnormalities identified by the American Diabetes Association, 2010: glycated hemoglobin (A1C) $\geq 6.5\%$, fasting plasma glucose (FPG) ≥ 126 mg/dl, random plasma glucose ≥ 200 mg/dl with symptoms, or two-hour plasma glucose ≥ 200 mg/dl during an oral glucose tolerance test (OGTT)
Functional Status	Patient requiring no, partially, or totally dependent assistance from another person for regular daily activities before surgery
Hypertension	Patient with elevated blood pressure requiring medication
Chronic renal failure	Patient with increasing creatinine levels >3 mg/dl or a decreased glomerular filtration rate of less than 60 ml/min/1.73 m ² for 3 or more months
Liver cirrhosis	Diagnosis based on clinical, laboratory, and echographic findings
SIRS	Includes the presence of two or more of the following: temperature >38 °C or <36 °C, heart rate >90 bpm, respiratory rate >20 breaths/min or PaCO ₂ <32 mm/Hg, WBC $>12,000$ /mm ³ or $<4,000$ /mm ³ , or >10 % immature (band) forms, anion gap acidosis
Septic shock	Includes sepsis and documented organ and/or circulatory dysfunction
Limb loss	Amputation of the lower or upper limb above the ankle or the wrist, respectively.
ASA score	1 = normal healthy patient 2 = patient with mild systemic disease 3 = patient with severe systemic disease 4 = patient with severe systemic disease that is a constant threat to life 5 = moribund patient who is not expected to survive without the operation

The most frequent location of necrotizing fasciitis is by far the lower limb, followed by the upper limb, the trunk, and the neck, in order of the incidence [15, 21-24]. The development of peripheral diabetic micro- and macroangiopathy in the lower limb of the diabetic patient is the main factor that favors the location of necrotizing fasciitis, especially in the lower limb of the diabetic patient. The treatment of choice for necrotizing fasciitis in the pelvic limb consists of large incisions and necrectomy, the amputation of the thigh being the last resort in saving the patient's life [25]. The development of necrotizing fasciitis in the genital and perineal regions is known as Fournier's gangrene, with an incidence of 0.4-1/100,000, with a slight increase in incidence in recent years. As in most cases of necrotizing fasciitis, the inoculation gate of germs is small [26]. However, it may also occur in less common anatomical regions, such as the breast, in which case the mortality is 72% (5), the youngest patient reported with such a location of the disease was only 23 years old, non-diabetic, and the only pathogenic association being obesity [27].

Most cases of necrotizing fasciitis of the breast have been reported during lactation, with only 6 cases currently reported unrelated to lactation [27]. In the case of necrotizing fasciitis of the breast, mortality can be reduced by up to 10% if an early diagnosis is made and the rapid establishment of the surgical treatment is possible, through massive debridement, antibiotic therapy, and anti-inflammatory treatment, along with support of volemic and hydro-electrolytic balance [28]. The cervical location of necrotizing fasciitis is also extremely rare, but not excluded, such cases being reported, sometimes even with and odontogenic starting point, the main determinism being pulp necrosis with the bacterial invasion of the periapical tissue, leading to the formation of purulent collections [29]. The periorbital area where the fascia is poorly represented is also not excluded from such pathology, cases of periorbital necrotizing fasciitis having reported local trauma, either accidental or iatrogenic (surgical), the prognosis being better in such cases. However, there is the possibility of complications such as optic neuropathy, retinal vein occlusion, keratopathy, cavernous sinus thrombosis, meningitis, vision loss and death [30-32].

The treatment for necrotizing fasciitis is complex and multimodal, consisting of broad-spectrum antibiotic therapy, anti-inflammatory drugs, hemodynamic support,

hemodynamic rebalancing, surgical treatment of cleanliness, and reconstruction. The antibiotic treatment is generally done with broad-spectrum antibiotics from the penicillin and cephalosporin classes, and, of course, is dictated by the microbial flora involved and its resistance and sensitivity to antibiotics [33]. In cases of microbial flora resistant to the usual antibiotics, Vancomycin is most often administered. The knowledge of the microbial flora generally involved in the occurrence of necrotizing fasciitis and its sensitivity can usually help establish an efficient antibiotic treatment from the outset and thus save the patient's life.

Surgical treatment can vary from the simple debridement to the disarticulation of the limb from the coxo-femoral joint [34]. Based on recent studies regarding predictive factors for pelvic limb amputation, the occurrence of necrotizing fasciitis in this limb in diabetic patients has an amputation rate that reaches 95%, compared with an amputation rate of 14.2% in all diseases for diabetic patients, having by far the highest amputation rate of the lower limb [35]. Compared to non-diabetic patients, the plurimicrobial infection rate and the amputation rate due to necrotizing fasciitis is significantly higher in patients with necrotizing fasciitis and diabetes [36].

As a therapeutic alternative, negative pressure vacuum can be used. It may also be used as a first therapeutic alternative in the necrosis of the breast [27, 37]. Neumaier suggests that negative pressure wound therapy (NPWT) may be superior to negative pressure systems, especially for aggressive infectious wounds which release many endotoxins and necrotic defects, as the negative pressure system facilitates removal of interstitial fluids [38]. NPWT systems work by introducing positive pressure in the wound bed. This creates an area of local hypoxic tissue which is surrounded by an area of hyperemia in the perilesional tissue [39]. Moreover, following the application of NPWT, debridement is accelerated in a manner similar to autolyzed debridement, and physical debridement is favored by the granulation tissue growth as well as by the local growth factors, thus facilitating healing [40]. Gabriel et al. reported that NPWT combined with topical irrigation after debridement is superior to standard NPWT treatment for infection control; this combination treatment may decrease the healing time, the length of the hospital stays, and the duration of the therapy [41]. Along similar lines, Matiassek et al. reported a case study that

combined NPWT with application of octenidine in the wound, arguing that it would facilitate more rapid healing of the wound [42].

The most concerning complications of necrotizing fasciitis are: (1) acute renal lesions (defined as increases in serum creatinine level > 0.5 mg / dL compared to prior to or upon admission); (2) acute respiratory failure that requires orotracheal intubation and mechanic ventilation support; (3) bacteremia (defined as positive blood culture); (4) septic shock (defined by the clinical criteria of sepsis and the need for vasopressor therapy necessary to maintain an average blood pressure of 65 mm Hg and lactate > 2 mmol / L in the absence of hypovolemia); and (5) death. Wound healing may also be influenced by the type of the bacteria involved, and systemic antibiotic therapy may involve disturbances of the adjacent cutaneous microbioma or distal ones in the presence of comorbidities [15,43-51].

Table 2. LRINEC Score [52].

Biologic Parameter	Value	Score
Reactive C Protein	Under 15 mg/dl	0
	Over 15 mg/dl	4
Leukocyte	Under 15,000 / μ l	0
	15,000-25,000 / μ l	1
	Over 25,000 / μ l	2
Hemoglobin	Over 13.5 mg/dl	0
	11-13.5 mg/dl	1
	Under 11 mg/dl	2
Serum Sodium	Over 135 mEq/l	0
	Under 135 mEq/l	2
Creatinine	Under 1.6 mg/dl	0
	Over 1.6 mg/dl	2
Glucose	Under 180 mg/dl	0
	Over 180 mg/dl	1

For evaluation of the severity of necrotizing fasciitis, as well as for the prognosis, we consider prediction scores to be helpful. The most widely used is the LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score (Table 1). This score classifies patients into three groups:

- low risk (LRINEC score ≤ 5 points, $<50\%$ risk of necrotizing fasciitis);
- moderate risk (LRINEC score 6-7 points, 50%-75% risk of necrotizing fasciitis);
- high risk (LRINEC score ≥ 8 points, $> 75\%$ risk of necrotizing fasciitis).

Studies on the LRINEC score have shown that a score ≥ 6 as a reduction of necrotizing fasciitis gave a positive predictive value (PPV) of 92% and a negative predictive value (NPV) of 96%. Approximately 90% of patients with necrotizing fasciitis had LRINEC scores ≥ 6 points, while only 3.1% up to 8.4% of the control-group patients had LRINEC scores ≥ 6 points. 10% of the patients with necrotizing fasciitis had a LRINEC score < 6 [52, 53] (Table 2).

Wagner's score can also be useful as predictive factors in evaluating lesions of the diabetic foot [54-56].

For the evaluation of the general state of the patient, of the severity of the disease and the general prognosis, the APACHE II score can provide good results [57] (Table 3 and 4).

Table 3. Wagner's Classification for diabetic ulcer patients [53].

Degree	The description of the injury
0	Intact Skin
I	Superficial ulcer of skin or subcutaneous tissue
II	Ulcers extend into the tendon, bone or capsule
III	Deep ulcer with osteomyelitis or abscess
IV	Partial foot gangrene
V	Whole foot gangrene

Table 4. Apache II Score [54].

Physiologic variable		Point score								
		+4	+3	+2	+1	0	+1	+2	+3	+4
1	Temperature	≥41	39-40	-	38.5-38.9	36-38.4	34-35	32-33	30-31	≤29.9
2	Mean arterial pressure (mmHg)	≥160	130-159	110-129	-	70-109	-	50-69	-	≤49
3	Heart rate	≥180	140-179	110-139	-	70-109	-	55-69	40-54	≤39
4	Respiratory rate	≥50	35-49	-	25-34	12-24	10-11	6-9	-	≤5
5	Oxygenation FiO ₂ ≥0.5 FiO ₂ ≤0.5	≥500 -	350-499 -	200-349 -	- -	<200 >70	- 61-70	- -	- 55-60	- <55
6	Arterial pH	≥7.7	7.6-7.69	-	7.5-7.59	7.33-7.49	-	7.25-7.32	7.15-7.24	<7.15
7	Serum Na (mMol/L)	≥180	160-179	155-159	150-154	130-149	-	120-129	111-119	≤110
8	Serum K (mMol/L)	≥7	6-6.9	-	5.5-5.9	3.5-5.4	3-3.4	2.5-2.9	-	≤2.5
9	Serum creatinine (mg/dl)	≥3.5	2-3.4	1.5-1.9	-	0.6-1.4	-	<0.5	-	--
10	Hct (%)	≥60	-	50-59.9	46-49.9	30-45.9	-	20-29.9	-	<20
11	WBC (in 1000)	≥40	-	20-39.9	15-19.9	3-14.9	-	1-2.9	-	<1
12	Glasgow coma score	Score -15 minus actual GCS								

The acute physiology score is the sum of the 12 individual variable points.

Add 0 points for the age < 44; 2 points for 45-54 years; 3 points for 55-64; five points for 65-74 years and six points ≥75 years.

APACHE II Score – acute physiology score + age points + Chronic health points. The maximum score is 71.

Increasing score is associated with increasing risk of hospital death.

Add chronic health status points: two points in elective postoperative patient with immuno-compromised state or a history of severe organ failure; five points for non-operative patient or emergency postoperative patient with immuno-compromised state or severe organ failure.

13 ^d	Serum HCO ₃ (venous – mMol/l)	≥52	41-51.9	-	32-40.9	22-31.9	-	18-21.9	15-17.9	<15
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Interpretation of APACHE II Scores:

0-4: ~4% death rate; 5-9: ~8% death rate; 10-14: ~15% death rate; 15-19: ~25% death rate; 20-24: ~40% death rate; 25-29: ~55% death rate; 30-34: ~75% death rate; over 34: ~85% death rate

^a APACHE II Score – acute physiology score + age points + Chronic health points. The maximum score is 71.

Increasing score is associated with increasing risk of hospital death

^b choose the worst value in the past 24 h

^c chronic health status: organ failure or an immuno-compromised state must have preceded current admission

^d optional variable

Highlights

- ✓ Necrotizing fasciitis is a severe infection of soft tissue with extended necrosis of the fascia and subcutaneous tissue and may involve muscles and skin.
- ✓ Necrotizing fasciitis is common in patients with diabetes mellitus, with high mortality for these patients.

Conclusions

Although diabetes mellitus is a risk factor for the occurrence of necrotizing fasciitis, no major differences in mortality between those with and without diabetes mellitus occurs. Thus, we can conclude that although necrotizing fasciitis is favored by diabetes mellitus, once installed, its mortality is equally high irrespective of the patient's diabetes status. However, if it is also associated with other co-morbidities besides diabetes mellitus, such as liver cirrhosis or immune-depression, the risk of death increases greatly. The diagnosis is extremely difficult, as there are practically no specific signs or symptoms or conclusive laboratory investigations. The tentative diagnosis is the suspicion of fasciitis in a patient with low immunity, which is confirmed after incisions reveal fasciitis. Treatment is complex, with broad-spectrum antibiotic therapy, volemic and hydroelectrolytic support, the treatment of associated diseases. Surgical treatment consists of large incisions and extended fasciectomy, followed by plastic reconstruction. Still, the prognosis is poor, with a mortality rate that can even reach up to 73%.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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