International Journal of Health Sciences
March 2021, Vol. 9, No. 1, pp. 77-82
ISSN: 2372-5060 (Print), 2372-5079 (Online)

Published by American Research Institute for Policy Development
DOI: 10.15640/ijhs.v9n1a10
URL: https://doi.org/10.15640/ijhs.v9n1a10

Diagnostic Challenges in Cellulitis and Role of LRINEC Score

Weny Rinawati[1]& July Kumalawati[2]

Abstract

Soft-tissue infections are difficult to differentiate due to similarities at initial onset. The diagnosis of cellulitis is generally based on clinical examination, with other diagnoses for consideration. The clinical features of cellulitis can mimic abscesses, necrotizing fasciitis, and gangrene, so they are often difficult to distinguish. If the clinical findings are not accurate enough for necrotizing fasciitis, an assessment of the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score, radiologic examination, and biopsy can be performed to determine the risk or diagnosis. The LRINEC score was developed as a diagnostic tool to potentially aid practitioners in the early detection of necrotizing fasciitis. We report a case of a 55-year-old female, with a suppurative stage of cellulitis, classification class III, caused by *Pseudomonas aeruginosa*. The suppurative stage of cellulitis was difficult to distinguish with necrotizing fasciitis. The total LRINEC score for the patient was a strong predictor of necrotizing fasciitis, but the use of the LRINEC score must consider the presence of comorbidities and intervention for abnormal laboratory results because it can reduce the accuracy of the score.

Keywords: cellulitis, interleukin 6, LRINEC, necrotizing fasciitis, soft tissue infection

Running Title: Role of LRINEC score to differentiate cellulitis

1. Introduction

Cellulitis refers to diffuse, superficial, spreading skin infections, involves the deeper dermis and subcutaneous fat (Steven et al., 2014). Cellulitis most commonly affects the lower extremities (Phoenix et al., 2012). The course is usually acute, but subacute, or chronic inflammation is also possible (Atzori et al., 2013).

Three stages of cellulitis have been proposed. The serous stage is the initial inflammatory process, which may resolve on its own or after appropriate treatment. However, this frequently develops into a suppurative phase, in which pus formation might be detected by palpation, producing the sign of fluctuation. Imaging studies are useful to reveal deep gathered abscess before clinical evidence, especially when dealing with facial and neck compartments. Once the pus is formed, resolution of the condition requires drainage, spontaneously through a fistulisation phase, or surgical procedure (Atzori et al., 2013).

The classic presentation of rubor (redness), dolor (pain), tumor (swelling), calor (heat) are the hallmarks of cellulitis (Sullivan & de Barra, 2018). These infections cause rapidly spreading areas of erythema, swelling, tenderness, and warmth, sometimes accompanied by lymphangitis and inflammation of the regional lymph nodes. The skin surface may resemble an orange peel (peau d'orange) due to superficial cutaneous edema surrounding hair follicles and causing skin dimpling because the follicles remain tethered to the underlying dermis. Vesicles, bullae, and cutaneous hemorrhage in the form of petechiae or ecchymoses may develop. Systemic manifestations are usually mild, but fever, tachycardia, confusion, hypotension, and leukocytosis are sometimes present and may occur hours before the skin abnormalities appear (Steven et al., 2014).

Diagnosis is based on clinical findings with investigations lending weight to confirm or refute diagnosis (Phoenix et al., 2012). Early recognition is mandatory to avoid potentially life-threatening complications due to a variable etiology from Gram-positive to Gram-negative bacteria and deep fungal infections. Some pathogens might cause very similar clinical entities.

[1]MD, Clinical Pathology, Laboratory of Clinical Pathology and Blood Bank, National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono, Jakarta, Indonesia, Resident of Clinical Pathology Consultant Study Program, Faculty ofMedicine, University of Indonesia, Jakarta, Indonesia
[2]MD, DMM, Clinical Pathology (Consultant), Department of Clinical Pathology, Faculty of Medicine University of Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Many mimics are also to be excluded, conditioning the treatment and patient's prognosis. History, physical examination, and laboratory data can help characterize the severity of the disease, and the probability of complications development, mainly necrotizing fasciitis (Atzori et al., 2013).

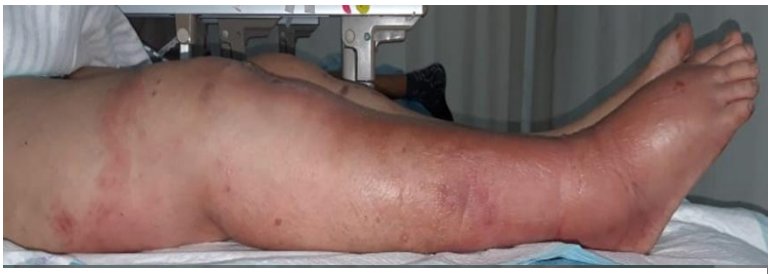
Laboratory findings usually support the infective origin, demonstrating a slight leukocytosis with neutrophilia (Atzori et al., 2013). An elevated level of C-reactive protein (CRP) is a better indicator of bacterial infection than an elevated white cell count but a normal level of CRP cannot rule out an infection (Phoenix et al., 2012). Exudates cultures by needle aspiration or swab are not routinely performed in logical, cost-effective management. Identification of pathogen and testing sensitivity to antibiotics is mandatory to adjust the treatment in those patients who fail to respond to treatment within 48 hours, and the further delay of performing culture at that moment might negatively affect the prognosis. Blood culture is of limited use because it is positive in a minority of cases and the isolates are usually the same as in the skin lesions (Atzori et al., 2013).

A radiologic examination is advisable to exclude subjacent osteomyelitis, and/or gas presence when the leg is involved (Atzori et al., 2013). Imaging techniques are useful if there is a suspicion of an underlying abscess associated with cellulitis, necrotizing fasciitis, or when the diagnosis of cellulitis is uncertain (Phoenix et al., 2012).

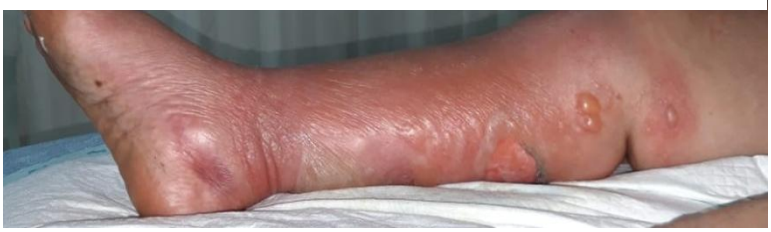
2. Case report

A 55-year-old female has been hospitalized with complaints of swelling and redness in her right leg five days before being admitted to the hospital. The swelling and redness were started from the bottom of the leg and then spreading up, accompanied by pain. The patient got fever four days before, and in the last 2 days, there have been blisters on the right leg which were breaks easily.

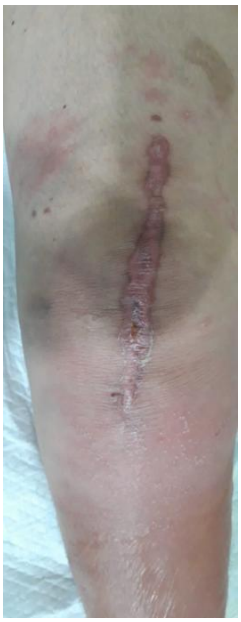
On physical examination, the following conditions were found: moderately ill, with Glasgow Coma Scale (GCS) score was E4M6V5, blood pressure 151/90 mmHg, a heart rate of 132 beats per minute, a respiratory rate of 18 breaths per minute, and no episode of fever(36.5^{0}C). A bodyweight of 68 kg and a height of 160 cm. In the distal of the right lower leg, there were erythematous plaques (Figure 1a), nummular plaques, vesicles, bullae, and pustules, with squama in several places, tenderness, warmth, and pitting edema (Figure 1b). In the right genu region was found a linear atrophic eutrophic scar, with a yellow crust over it (Figure 1c). Bilateral inguinal lymph nodes were enlarged, multiple, 0.5 cm, spongy, mobile, but not tender.



a



b



c

Figure 1. (a) There were erythematous plaques in the distal of the right lower leg. (b) There were nummular plaques, vesicles, bullae, and pustules, with squama in several places, tenderness, warmth, and pitting edema in the distal of the right lower leg. (c) In the right genu region was found a linear atrophic eutrophic scar, with a yellow crust over it

Thehematology parameter revealed normocytic normochromic anemia and leukocytosis with neutrophilia. Hemoglobin 11.4 g/dL (range 12 – 14), hematocrit 32.1% (range 37 – 43), MCV 82.0 fL (82 – 92), MCH 27.0 pg (27 – 31), MCHC 33.2 g/dL (31 - 36). Leukocyte 21.3 x 10^6/mm^3 (range 5 – 10x 10^6), differential counts showed 1% eosinophils, 81%, neutrophils, 14% lymphocytes, and 6% monocytes. Other laboratory parameters were elevated concentration of serum glucose 600 g/dL (normal<100), glycoHb (HbA1c) 6.7% (normal <5.7), urea

124.1 mg/dL (range 16.6 – 48.5), creatinine 2.371 mg/dL (range 0.51 – 0.95), and CRP 225.9 mg/L (normal ≤5). Whereas electrolyte parameters were within normal limit: sodium 135 mEq/L (range 136 – 146), potassium 3.4 mEq/L (range 3.5 – 5.0), and chloride 105 mEq/L (range 98 - 106).

Right genu radiologic imaging showed prosthesis total knee arthroplasty in the epimetaphysis of the right femur and the epimetaphysis of the right tibia, screws in the medial condyles of the right tibia, with good prosthesis position, no loosening periprosthesis, and soft tissue swelling in the distal femur to the proximal cruris. Previously, the patient underwent a right knee total knee replacement three months ago due to the patient's knee deformity. The patient was routinely got wound treatment at the hospital because the wound was not healedand the surgical scars were still festering. The patient has been on hypertension medication and has no history of other drugs allergy.

Pus from the pustules was incubated on blood agar and yielded positive growth after 24 hours of aerobic incubation at 37^0 C. The isolate showed Gram-negative rod, and then was examined by Vitex® 2 Compact (bioMérieux), and these rods were identified as *Pseudomonas aeruginosa* and susceptible to gentamicin, ceftazidime, ciprofloxacin, piperacillin/tazobactam, cefepime, meropenem, imipenem, levofloxacin, and moxifloxacin (Table 1). As the culture and resistance test result come out, the patient has been treated with meropenem 2 g twice daily.

Table 1. Culture and resistance test result

Specimen	Pus
Isolate	***Pseudomonas aeruginosa***
Susceptibility	
Chloramphenicol ……..…….……	R
Cotrimoxazole …….....	R
Gentamicin …….	S
Kanamycin ……..…….....…..	R
Tetracycline ……..…….....….....	R
Amikacin ……...…….	S
Aztreonam ……..	I
Sulbactam/Ampicillin ……...……...……	R
Cephalotin ……..	R
Cefotaxime …….	R
Amoxicillin Clavulanic Acid …….	R
Ceftriaxone ……	R
Ceftazidime ……	S
Ciprofloxacin ……..……...…..…..	S
Piperacillin/Tazobactam ……	S
Neomycin ……...……...……..	I
Cefepime …….....	S
Meropenem ……...…….….....	S
Imipenem …….....	S
Levofloxacin ……..….….....	S
Moxifloxacin ……..	S

I: intermediate; R: resistant, S: sensitive

On the day-9, the patient got magnetic resonance imaging (MRI) examination, and showed a lesion with rim enhancement reaches the anterior subcutisof cruris, proximal of musculus gastrocnemius (medial and lateral caput), with soft tissue swelling and fat deposition around it, suggestive of an abscess, with bone marrow edema in the proximal tibia and fibula.

3. Discussion

Necrotizing fasciitis, a life-threatening rare infection of the soft tissues, is a medical and surgical emergency. It is characterized by subtle, rapid onset of spreading inflammation and necrosis starting from the fascia, muscles, and subcutaneous fat, with subsequent necrosis of the overlying skin. Once suspected, immediate and extensive radical debridement of necrotic tissues is mandatory. Appropriate antibiotics and intensive general support avoid massive systemic diffusion of the infective process and are the key to successful treatment.

However, early diagnosis is missed or delayed in 85% to 100% of cases in large published series: because of the lack of specific clinical features in the initial stage of the disease, it is often underestimated or confused with cellulitis or abscess (Lancerotto et al., 2012).

Cellulitis involves the epidermis and dermis, whereas necrotizing fasciitis involves the fascia and tissue necrosis. The clinical findings of cellulitis may resemble abscesses, necrotizing fasciitis, gangrene, and are often difficult to distinguish. Nevertheless, abscess formation and fistulization are one of the most common stages in the evolution of cellulitis, especially if it is not treated adequately so that it progresses to the suppurative stage. The evolution of cellulitis due to the expansion of infection can lead to necrosis of the subcutaneous fat and fascia, thus complicating cellulitis with clinical features such as necrotizing fasciitis. Cellulitis caused by anaerobic bacteria can form gas gangrene. Because of differences in management, the diagnosis must be made considering that necrotizing fasciitis is an emergency and requires immediate action in the form of debridement.

If the clinical findings are not accurate enough for necrotizing fasciitis, an assessment of the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score, radiologic examination, and biopsy can be performed to determine the risk or diagnosis. A biopsy is invasive so it is rarely done. The LRINEC score was developed as a diagnostic tool to potentially aid practitioners in the early detection of necrotizing fasciitis (Neeki et al., 2017). Risk category according to LRINEC is score $\leq$5, low risk, score 6 – 7 moderate risk, and score $\geq$8 high risk of necrotizing fasciitis (Table 2) (Lancerotto et al., 2012).

Table 2. LRINEC scoring system (Lancerotto et al., 2012)

	Score		Score
C-reactive protein, mg/L		Sodium, mmol/L	
<150	0	$\geq$135	0
$\geq$150	4	<135	2
Leukocyte, x 10^6/mm^3		Creatinine, mg/dL	
<15	0	$\leq$1.6	0
15 – 25	1	>1.6	2
>25	2		
Hemoglobin, g/dL		Glucose, mg/dL	
>13.5	0	$\leq$180	0
11 – 13.5	1	>180	1
<11	2		

From the laboratory results, the total LRINEC score for the patient was 9 (CRP 225.9 mg/L, score 4; leukocytes 21.3x 10^6/mm^3, score 1; hemoglobin 11.4 g/dL, score 1; sodium 135 mEq/L, score 0; creatinine 2,371 mg/dL, score 2; and glucose 335.6 mg/dL, score 1), strong predictor of necrotizing fasciitis.

However, the patient has comorbid and diabetes mellitus with high blood glucose levels, so the score may not be accurate. The study of Neeki et al. (2017) suggests that the LRINEC score may not be an accurate tool for necrotizing fasciitis risk stratification and differentiation between cellulitis and necrotizing fasciitis. This finding is consistent with Burner et al. (2016), who reported a better discrimination ability of the LRINEC score for necrotizing fasciitis cases among the diabetic population. Nevertheless, the LRINEC decision instrument misclassification rate among diabetes patients versus non-diabetes patients was 8% and 13.5% among diabetic and non-diabetic patients among the cellulitis group, respectively.

The MRI result showed a lesion that reaches the subcutis, soft tissue swelling, and fat stranding around it, suggestive cellulitis. The patient has a suppurative stage of cellulitis as indicated by the possibility of an abscess based on the presence of soft tissue swelling and fat stranding on MRI. Thus, a more accurate diagnosis for this patient is suppurative cellulitis with a strong predictor of necrotizing fasciitis.

The predisposing factors of cellulitis, in this case, were surgical wounds, obesity with a body mass index of 26.6 kg/m^2 (obesity I based on BMI >25 kg/m^2 for Asians according to WHO), and diabetes mellitus (glycoHb 6.7%). Obesity induces adipocyte hypertrophy and hyperplasia, eventually impairing the metabolic functions of the adipocytes. Obese adipose tissues secrete angiogenic inhibitors and fibrotic mediators. The extracellular matrix remodeling may further impede the process of angiogenesis by creating a stiffer environment and preventing the migration of cells and vessels. The relative hypoxia in obese individuals likely contributes to higher rates of wound infections in obese patients because of even lower oxygen tension from decreased perfusion and impaired immune system functioning. Additionally, hypoxic wounds impair the synthesis of mature collagen, leading to weaker tissue and deficiencies in the overall healing process (Pierpont et al., 2014).

Diabetes mellitus increases the susceptibility to infections. Decreased mobilization of polymorphonuclear leukocytes, chemotaxis, and phagocytic activity may occur during hyperglycemia. The hyperglycemic environment also blocks the antimicrobial function by inhibiting glucose-6-phosphate dehydrogenase (G6PD), increasing apoptosis of polymorphonuclear leukocytes, and reducing polymorphonuclear leukocyte transmigration through the endothelium. Regarding the mononuclear lymphocytes, the proliferative function of CD4 T-lymphocytes and their response to antigens is impaired. Mononuclear cells and monocytes of persons with diabetes mellitus secrete less interleukin (IL)-1, as well as that of interferon (IFN)-γ and tumor necrosis factor (TNF)-α. The complement system is one of the main mechanisms responsible for humoral immunity. Some studies have detected a deficiency of the C4 component in diabetes mellitus, and this reduction of C4 is probably associated with polymorphonuclear dysfunction and reduced cytokine response (Casqueiro et al., 2012).

Classification on the base of area involvement is useful, as common localized forms tend to be less severe than very diffuse forms. Eron's Clinical Classification, adopted from the CREST guidelines considers four classes of patients with different prognosis and management (Eron et al, 2003; Atzori et al., 2013). Cellulitis classification of the patient was class III because there was a history of fever 4 days before admission, increased heart rate, leukocytosis, and diabetes mellitus as comorbid.

C-reactive protein (CRP) is a marker for inflammation, and its levels increase during bacterial infection. An elevated level of CRP was caused by bacterial infection, which increases the release of proinflammatory cytokines such as interleukin-6 (IL-6) thereby increasing CRP expression (Sproston & Ashworth, 2018).

Normochromic normocytic anemia might be caused by an infection. The release of proinflammatory cytokines such as IL-6 will increase at infection. IL-6 is also involved in the regulation of serum iron levels via control of their transporters, and induces hepcidin production (Tanaka et al. 2014). Hepcidin is an acute-phase protein responsible for the regulation of intestinal iron absorption, iron recycling by macrophages, and iron metabolism (Kaur et al., 2020). Hepcidin will inhibit iron absorption in the duodenum, and will bind and inhibit ferroportin so that iron cannot be removed from macrophages and the reticuloendothelial system, thereby inhibiting erythropoiesis. Other proinflammatory cytokines such as tumor necrosis factor (TNF-α) stimulate macrophages for premature erythrophagocytosis of erythrocytes. Due to erythrophagocytosis, hypoferemia, and inhibition of erythropoiesis will cause anemia (DeLoughery, 2014). When IL-6 reaches the bone marrow, it promotes megakaryocyte maturation, thus leading to the release of platelets. These changes in red blood cell and platelet counts are used for the evaluation of inflammatory severity in routine clinical laboratory examinations (Tanaka et al. 2014).

Neutrophilia is caused by infection because the release of IL-6 in infection causes diminished endothelial surface adhesion molecules expression and chemokines production (Su et al., 2017). The ability of neutrophils to adhere to the endothelium of blood vessels will decreases, thereby increasing the release of neutrophils from the marginal pool into the circulation.

Elevated concentration of urea (124.1 mg/dL) and creatinine (2,371 mg/dL) possibly due to acute kidney injury (AKI) according to the criteria of the Acute Kidney Injury Network (an increase in serum creatinine >0.3 mg/dL in 48 hours or >1.5x baseline in 7 days). From the eGFR calculation, it was 23 ml/minute/1.73m^2, indicating a decrease in kidney function. AKI may be due to infection that increases the release of proinflammatory cytokines. IL-1, LPS, TNFα, and IL-4 are the common inducers for endothelial cells to generate IL-6. IL-6 promotes Ang II type 1 receptor (ATR1) gene expression and leads to Ang II-induced vasoconstriction and reactive oxygen species production which ultimately results in endothelial dysfunction (Su et al., 2017).

In our case, no major pathogenic bacteria were found. The result of the aerobic pus culture yielded *Pseudomonas aeruginosa*. In cellulitis, Gram-negative bacteria are usually mixed infections with Gram-positive bacteria, with the main causative pathogens being *Staphylococcus aureus* and *Streptococcus pyogenes* (especially *S. pyogenes* α-hemolyticus Group A).

4. Conclusion

The diagnosis of cellulitis is made by excluding other skin diseases that have a clinical picture resembling cellulitis because of differences in management. The clinical findings of cellulitis may resemble an abscess, necrotizing fasciitis, and gangrene, especially cellulitis evolution. The evolution of cellulitis often occurs due to inadequate management so that it continues to the suppurative stage, or due to the expansion of the infection so that it can cause necrosis of the subcutaneous fat and fascia which then complicates cellulitis. If the clinical findings are not accurate enough to determine the risk or diagnosis for necrotizing fasciitis, an LRINEC score, radiological examination, and biopsy may be performed. The use of the LRINEC score must consider the presence of comorbidities and intervention for abnormal laboratory results because it can reduce the accuracy of the score.

5. References

Atzori L, Manunza F, Pau M. (2013). New trends in cellulitis. EMJ Dermatol, 1, 64-76.

Bechar J, Sepehripour S, Hardwicke J, Filobbos G. (2017). Laboratory risk indicator for necrotizing fasciitis (LRINEC) score for the assessment of early necrotizing fasciitis: A systematic review of the literature. Ann R Coll Surg Engl, 99, 341-346. doi: 10.1308/rcsann.2017.0053.

Casqueiro J, Casqueiro J, and Alves C. (2012). Infections in patients with diabetes mellitus: A review of pathogenesis. Indian J Endocrinol Metab, 16, Suppl1, S27–S36. doi: 10.4103/2230-8210.94253

DeLoughery TG. (2014). Microcytic anemia. N Engl J Med, 371, 1324-1331. doi: a0.1056/NEJMra1215361

Eron LJ, Lipsky BA, Low DE, Nathwani D, Tice AD, Volturo GA. (2003). Managing skin and soft tissue infections: Expert panel recommendations on key decision points. J Antimicrob Chemther, 52 (Suppl 1), i3-17.

Kaur S, Bansal Y, Kumar R, Bansal G. (2020). A panoramic review of IL-6: Structure, pathophysiological roles and inhibitors. Bioorganic & Medicinal Chemistry, 28, 115327. doi: https://doi.org/10.1016/j.bmc.2020.115327

Lancerotto L, Tocco I, Vindigni V, Bassetto F. (2012). Necrotising fasciitis: Classification, diagnosis, and management. J Trauma, 72, 560-566. doi: 10.1097/TA.0b013e318232a6b3

Phoenix GK, Das S, Joshi M. (2012). Diagnosis and management of cellulitis. BMJ, 345, e4955. doi: 10.1136/bmj.e4955

Pierpont YN, Dinh TP, Salas RE, Johnson EL, Wright TG, Robson MC et al. (2014). Obesity and surgical wound healing: A current review. Hindawi Publishing Corporation, Article ID 638936, 1-13. doi: http://dx.doi.org/10.1155/2014/638936

Sproston NR, Ashworth JJ. (2018). Role of C-reactive protein at sites of inflammation and infection. Front Immunol, 9, 754. doi: 10.3389/fimmu.2018.00754

Stevens DL, Bisno AL, Chambers HF, Dellinger P, Goldstein EJC, Gorbach SL, et al. (2014). Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis, 59, e10-52. doi: 10.1093/cid/ciu296

Su H, Lei C-T, Zhang C. (2017). Interleukin-6 signaling pathway and its role in kidney disease: An update. Front Immunol, 8, 405. doi: 10.3389/fimmu.2017.00405

Sullivan T, de Barra E. (2018). Diagnosis and management of cellulitis. Clin Med, 18 (2), 160-163. doi: 10.7861/clinmedicine.18-2-160

Tanaka T, Narazaki M, Kishimoto T. (2014). IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. doi: 10.1101/cshperspect.a016295