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Original Research

Clinical and Laboratory Parameters for Differential Diagnosis of Necrotizing Faciitis and Cellulitis

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ABSTRACT

ObjectiveS: Necrotizing fasciitis (NF) requires surgical intervention and has high morbidity and mortality. Furthermore, it can be confusing with some skin diseases such as cellulitis. We investigated the roles of clinical and laboratory parameters at the time of admission to the hospital in the differential diagnosis of NF and cellulitis patients.

Methods: Patients with cellulitis and NF located between the nipple level and the knee between January 2018 and January 2021 were included in our retrospective study. The fever, history, complete blood count results, blood biochemistry, C-reactive protein and procalcitonin values of the patients at the time of admission to the emergency department, length of hospital stay, mortality rates, and laboratory risk indicator for necrotizing fasciitis (LRINEC) scores were recorded and evaluated whether there was a difference in both patient groups.

Results: A total of 55 patients, including 26 patients in the NF group and 29 patients in the cellulite group, were included in the study. It was observed that patients with NF applied to the hospital statistically earlier, had higher leukocyte, platelet and neutrophil levels, had longer hospital stays and had higher mortality numbers.

Conclusion: In high leukocyte, platelet, and neutrophil levels in the case of cellulitis patients, the clinician should follow the patient's clinic course closely and keep NF in mind.

Keywords: Cellulitis, fournier gangrene, leukocyte, necrotizing faciitis

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Necrotizing soft-tissue infection is an infectious disease that involves the skin and subcutaneous tissues, causes necrosis in a large area, and progresses rapidly.[1] The term necrotizing fasciitis (NF) is used synonymously with necrotizing soft-tissue infection. NF incidence, time, geographical area, population age, etc. varies according to many factors.[2] The incidence of NF varies between 0.3 and 15.5/100,000.[3] Mortality rates are very high and despite developing treatment methods, it has decreased from 25% to 30% to 20% in the last 30 years.[2] The development of shock, the advanced age of the patients, and the presence of comorbid diseases such as diabetes are indicators of poor prognosis in patients with NF.[1]

Fournier's gangrene (FG), which is a common form of NF, is a serious and life-threatening emergency that requires early diagnosis and treatment. It was defined by Fournier in 1883 as an unexplained fulminant gangrene of the male genitalia, and it was stated that it is a rapidly progressive scrotal

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infection seen in young healthy men without an identifiable etiology.[4] Subsequent studies have revealed that FG has a similar clinical course to NF and is considered to be a polymicrobial subset of NF. Furthermore, studies indicate that FG can be observed in all age ranges and genders.[5] Trauma to the scrotum or perianal region, urinary tract infection, and perianal region infections are blamed as etiological factors in the vast majority of Fournier's gangrene patients. It is thought that microorganisms reaching the subcutaneous tissues proceed by dissection along the fascial planes. Perianal and colorectal etiologies cause the majority of cases.[5]

Cellulitis is an inflammatory skin disease of infectious origin involving the dermis and subcutaneous tissues. Its severity can range from mild to life-threatening and is observed relatively frequently.[6] Although it can be seen in any part of the body, it is most commonly observed in the lower extremities.[7] The diagnosis of cellulitis is usually based on the morphological features of the lesion and the presence of symptoms such as erythema, edema, warmth, and pain. Fever and systemic findings are observed in complicated cellulitis cases.[8,9]

Fournier's gangrene is often confused with scrotal cellulitis, strangulated hernia, or scrotal abscess. Crepitation may occur before gangrene develops, but is present in only 19%–64% of patients at the time of diagnosis.[5]

Symptoms such as fever, redness, edema, and pain observed in patients with NF are similar to the symptoms of cellulitis. Although imaging methods are helpful, specific findings may not be visualized in early stage NF. It has been reported that the laboratory risk indicator for necrotizing fasciitis score (LRINEC), a scoring system using laboratory parameters in the diagnosis of NF, offers high positive and negative predictive values.[10]

In this study, we aimed to evaluate whether there is a difference in inflammatory parameters between patients with NF and cellulitis patients.

Methods

Our study, which was planned as a retrospective analysis of the data, started after the approval of the Local Human Ethical Committee (Date: May 22, 2020, No: 2362). The population of our study consists of a total of 243 patients between the ages of 18 and 80 who applied to the emergency department between January 2018 and January 2021 and were diagnosed with NF, Fournier's gangrene, and cellulite. Informed consent was obtained from all hospitalized patients and the study was conducted in accordance with the Declaration of Helsinki.

The treat of the necrotising fasciitis patients had been performed by a multidisciplinary team including surgeon, infection diseases specialist, dermatologist, urologist, and wound care nurses. The criteria for inclusion in the study were cases located between the nipple level and the knee, no abscess pouch and patients who were hospitalized for cellulite group, and cases located between the nipple and knee for NF group. Exclusion criteria from the study were acquired or congenital major immunodeficiency, any malignancy, presence of inflammatory bowel disease, and pregnancy.

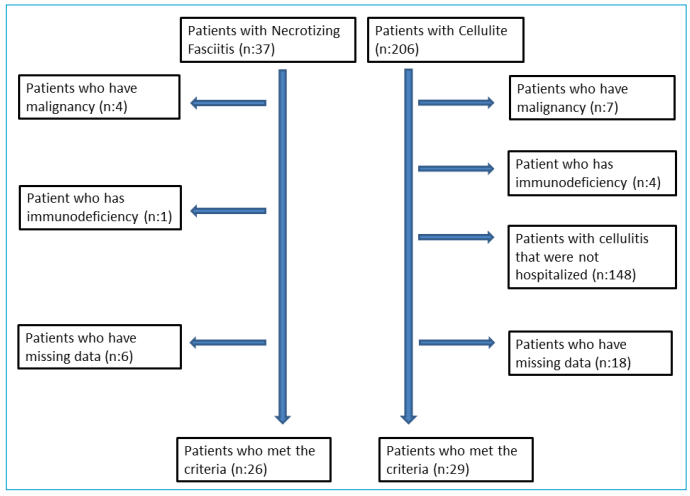

Figure 1. Flow diagram of the necrotizing fasciitis and cellulite patients that included in the study.

Considering the inclusion and exclusion criteria of the study, the hospital records of a total of 79 patients were examined, and complete blood counts, blood biochemistry values, C-reactive protein and procalcitonin values, imaging methods, length of hospital stay, and mortality rates were noted from the hospital records. When missing records excluded from the study, a total of 55 patients were included in the study (Fig. 1).

Statistical Analysis

The data were analyzed in Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) program. The sample size was calculated 21 individuals for each group according to 80% power and <0.05 level of significance. The distribution of variables was measured with the Kolmogorov–Smirnov test. The analysis between independent and normally distributed groups was performed with the Student t-test, and the analysis of the independent and non-normally distributed groups was performed with the Mann–Whitney U Test. Chi-square test and Fisher's exact test were used in the analysis of qualitative independent data. The cutoff values were calculated with the roc-curve analysis.

Results

A total of 55 patients were included in the study, with a mean age of 56.30±14.78 years and a female/male ratio of

1.03. A total of 26 patients in the NF group and 29 patients in the cellulite group were included in the study. The demographic data of the patients and their history at the time of admission to the hospital are given in Table 1. It was observed that the patients who developed cellulite applied to the hospital statistically later than NF patients.

The hemogram parameters, infection markers, and mortality data of the patients included in the study at the time of admission to the hospital are shared in Table 2. The patients with NF have significantly increased level of platelet, neutrophil, need for intensive care, and the number of days hospitalized compared to cellulite patients.

Table 1. Demographic data and self-history of patients analysis between groups

	Necrotizing Fasciitis (n=26)	Cellulite (n=29)	p
Age (years) (mean±SD)	52.65±15.84	59.59±13.19	0.083
Gender			
Female	13 (50%)	15 (51.7%)	0.898
Male	13 (50%)	14 (48.3%)	
Smoking			
Yes	11 (42.3%)	15 (51.7%)	0.485
No	15 (57.7%)	14 (48.3%)	
Chronic Disease			
Yes	23 (88.5%)	24 (82.8%)	0.708
No	3 (11.5%)	5 (17.2%)	
History of infection in the same area			
Yes	6 (23.1%)	9 (31%)	0.508
No	20 (76.9%)	20 (69%)	
Fever (>38°C)			
Yes	12 (46.2%)	8 (27.6%)	0.153
No	14 (53.8%)	21 (72.4%)	
Time to apply to the hospital (days) (median-IQR)	3.00-3.00	5.00–4.00	0.020

IQR: Interquartile range; SD: Standart derivation.

Table 2. Analysis of blood parameters and patient prognoses between groups

	Necrotizing Fasciitis (n=26)	Cellulite (n=29)	p
Hematocrit (%) (mean±SD)	34.73±6.97	34.35±4.80	0.812
Monocyte ($\times10^3$) (median-IQR)	0.98–1.09	0.82–0.80	0.180
Platelet ($\times10^3$) (median-IQR)	302.00–268.00	244.00–117.00	0.030
Neutrophil ($\times10^3$) (mean±SD)	18.57±9.03	11.78±6.78	0.003
Lymphocyte ($\times10^3$) (mean±SD)	1.73±0.75	1.45±0.77	0.176
Neutrophil/Lymphocyte (median-IQR)	13.27–12.23	7.51–8.52	0.129
Platelet/Lymphocyte (median-IQR)	196.20–139.58	171.95–234.31	0.578
Procalcitonin (ng/mL) (median-IQR)	0.98–4.52	0.56–1.62	0.655
Need for intensive care			
Yes	10 (38.5%)	4 (13.8%)	0.036
No	16 (61.5%)	25 (86.2%)	
Number of days in hospital (days) (median-IQR)	23.50–24	8.00–7.00	0.000
Mortality			
Yes	6 (23.1%)	1 (3.4%)	0.043
No	20 (76.9%)	28 (96.6%)	

IQR: Interquartile range; SD: Standart derivation.

Table 3. Evaluation of the distribution of LRINEC score parameters between groups

	Necrotizing fasciitis (n=26)	Cellulite (n=29)	p
WBC ($\times 10^3$) (median-IQR)	19.67–14.40	13.65–8.60	0.016
C Reactive Protein (mg/dL) (median-IQR)	35.43–122.31	93.94–156.95	0.106
Hemoglobin (g/dL) (mean±SD)	11.57±2.32	11.45±1.60	0.812
Sodium (mEq/L) (mean±SD)	134.00±4.16	134.81±4.55	0.495
Glucose (mg/dL) (median-IQR)	147.00–107.00	146.00–70.00	0.810
Creatinine (mg/dL) (median-IQR)	0.91–0.44	0.86–0.54	0.569
LRINEC score (median-IQR)	5.00–3.00	5.00–5.00	0.802

LRINEC: The laboratory risk indicator for necrotizing fasciitis score; IQR: Interquartile range; SD: Standart derivation; WBC: White blood cell.

Comparison of LRINEC scoring parameters between groups is given in Table 3. When the parameters were examined one by one, a significant difference was found in favor of the NF group only in the white blood cell (WBC) counts, while no significance was observed in any other parameter or in the total LRINEC score.

When the cutoff values were investigated for the parameters that were significant, the cutoff value for WBC was found to be 21,875 with the 50% sensitivity and 89.6% specificity; for platelet was found to be 333,000 with the 46.1% sensitivity and 89.6% specificity; for neutrophil was found to be 17,420 with the 50% sensitivity and 86.2% specificity.

Considering the localization of the diseases, in patients with NF, three patients in the thigh region, one patient in the suprapubic region, one patient in the anterior abdominal wall, and 21 patients in the perianal region; In cellulitis patients, it was observed that the disease developed in the suprapubic region in three patients, in the back in two patients, and in the thigh region in 24 patients.

Mortality due to comorbid diseases and sepsis developed in 6 (23.1%) patients who underwent surgical intervention and intermittent debridement treatment in the patients who developed NF. One (3.4%) patient who developed cellulitis died due to sepsis despite antibiotherapy.

Discussion

Cellulite classically presents with signs of redness, pain, swelling, and temperature increase. The severity of cellulitis can vary from no systemic findings with localized erythema to multiorgan failure and sepsis. NF should be kept in mind in cases of rapidly progressive clinical worsening, which is initially observed as cellulitis.[11]

The timing and development of skin manifestations may distinguish cellulitis from some common diseases with a more chronic clinical course. Findings of bilateral lower extremity erythema in a patient with no fever and normal inflammatory markers should prompt the clinician to reconsider the diagnosis of cellulitis. Systemic features are common and may precede the onset of skin changes. Careful clinical examination may reveal events that disrupt skin integrity, such as ulcers, trauma, eczema, or cutaneous mycosis.[12]

Classic manifestations of NF include soft-tissue edema (75% of cases), erythema (72%), severe pain (72%), tenderness (68%), fever (60%), and skin bullae or necrosis (38%).[13] Increasingly, severe pain is the most important clinical clue for NF and its onset typically occurs long before shock or organ dysfunction occurs. However, patients receiving analgesic agents, including NSAIDs, may have no or relieved crescendo pain. In patients who have had surgery, childbirth, or trauma, pain may be attributable to normal post-operative pain, typical postpartum discomfort, or the trauma itself, respectively, rather than acute infection. Patients with altered mental status or those with diabetes-related neuropathy may also lack pain. In these cases, the absence of a strong clinical clue may delay the correct diagnosis and appropriate treatments. Therefore, all patients presenting with a sudden onset of severe pain in an extremity, with or without an obvious portal of bacterial entry or the presence of fever, should be evaluated urgently for serious soft tissue infection.[3]

It is sometimes difficult to diagnose NF in the early stages, and cellulitis is one of the diseases included in the differential diagnosis of NF. There are few studies in the literature that directly compare NF and cellulite.[14] In a case report, it was reported that a patient diagnosed as scrotal cellulitis and treated with antibiotherapy was diagnosed with scrotal NF in the late period, developed multiorgan failure, underwent multiple surgeries, and was followed in the intensive care unit for a long time.[15] In a recent case–control study, it was reported that the factors distinguishing NF from cellulitis are recent surgery, pain disproportionate to clinical symptoms, hypotension, skin necrosis, and the development of hemorrhagic bullae.[14]

Body temperature above 38°C is one of the criteria for systemic inflammatory response syndrome and can be considered as a factor indicating the severity of the disease. Fever is a clinical finding that can be observed in both NF and cellulitis patients. In our study, fever was observed in both disease groups, although the difference was not significant, but it was observed that fever was more common in NF patients.

The level of procalcitonin, which is one of the inflammatory markers, increases in NF patients.[3] It is known that the level of procalcitonin has a positive correlation with body temperature. In a study, it was reported that there was a correlation between the severity of NF and blood WBC, CRP, and procalcitonin values. Furthermore, in the same study, it was reported that WBC was the most significant criterion in terms of correlation with disease severity.[16] In a study evaluating the prognosis of another pro-inflammatory marker, CRP, in patients with NF, it is mentioned that CRP is the most valuable parameter.[17] In another study evaluating inflammatory markers in lower extremity erysipelas and deep vein thrombosis, it was reported that CRP had a better diagnostic value compared to procalcitonin, and WBC, and its concentration was relatively low in localized inflammatory conditions.[18]

The LRINEC scoring system, which is based on blood CRP, total WBC count, hemoglobin, sodium, creatinine, and glucose values in the diagnosis or exclusion of NF disease and evaluates over 13 points, has 96% positive predictive value of according to 96% negative predictive value if it has 6 points and above.[10] In our study, only the WBC value was found to be higher in NF patients and no significant difference was found between all other parameters and the total LRINEC score.

Neutrophil/lymphocyte ratio is one of the parameters used in the diagnosis of many inflammatory diseases.[19] In one study, it was shown that it is higher in cellulite patients than in healthy controls, and in another study, the neutrophil/lymphocyte ratio, which is already high in NF patients, is much higher in mortal patients.[19,20] In our study, we did not observe any differences in neutrophil/lymphocyte ratio.

The limitations of our study can be listed as the small number of patients, its retrospective nature, and the inability to calculate the body/mass index of the patients.

Conclusion

In conclusion, early diagnosis is very important due to the differences in the treatment algorithm and prognosis of NF and cellulitis patients, which can be confused with each other in the early stages. In our study, it was shown that especially high WBC, platelet, and neutrophil between these two groups play a role in the differential diagnosis of NF and can guide the clinician for early diagnosis and treatment.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Istanbul Training and Research Hospital (No: 2362, dated: 22.05.2020).

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Conflict of Interest: None declared.

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