

# Necrotizing Fasciitis in Hematological Patients: *Enterobacteriaceae* Predominance and Limited Utility of Laboratory Risk Indicator for Necrotizing Fasciitis Score

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**Immune suppression is a recognized risk factor for necrotizing fasciitis. In patients with hematological malignancies, a profoundly immunocompromised group, the predominant causative organisms are Gram negative. Clinical presentation and outcomes in these patients are similar to the immunocompetent. The Laboratory Risk Indicator for Necrotizing Fasciitis score is not reliable for risk stratification of the disease.**

**Keywords.** Gram negative; hematological malignancy; immunocompromised host; necrotizing fasciitis.

Necrotizing fasciitis (NF) is a rapidly progressive disease with a high mortality rate of up to 50% [1]. The only definitive diagnosis is the identification of a necrotizing compartment during surgery. This diagnostic dilemma has led to the use of the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score to risk stratify suspected individuals [2]. A score of 6 or greater

had a positive predictive value of 92% and a negative predictive value of 96% for likelihood of NF [2].

Immune suppression such as diabetes mellitus, obesity, and malignancy are recognized risk factors for NF [3]. However, inability to mount an appropriate inflammatory response in the immunosuppressed host may lead to altered clinical manifestations, adding further challenges to the diagnosis and management of NF.

The experience in managing NF in such patients remains limited, and the LRINEC score, derived largely from immunocompetent subjects, has never been validated in patients with profoundly altered immunity, best exemplified by patients with hematological malignancies. There is a paucity of published literature describing management of such cases. In this study, we describe the first case series of NF in patients with hematological malignancies.

## METHODS

Our institution (National University Hospital System, National University Cancer Institute of Singapore, Singapore) is a 1000-bed tertiary academic and regional referral medical center. We performed a retrospective review of patients diagnosed with a hematological malignancy and NF between January 2006 and December 2013. The case definition of NF was operative finding of unhealthy necrotic fascia, lack of resistance of fascia to blunt dissection, and/or presence of “dish-water pus” [4]. For patients who did not undergo surgery, the case definition was those with a radiological finding of deep intermuscular fascia enhancement and a clinical picture of systemic inflammatory response syndrome [5]. The patients’ demographics, comorbidities, clinical presentation, investigations, time from presentation of symptoms to appropriate antimicrobial therapy, and time from presentation of symptoms to surgery were charted. The primary outcome was NF-associated in-hospital mortality.

## RESULTS

Of the 8534 patients with hematological malignancies seen at our hospital during the study period, 9 were diagnosed with NF, giving an incidence of approximately 0.013 cases per 100 person years. The patients’ clinical characteristics are as detailed in Table 1. Almost all patients were aged 40 and above. Only 1 patient had concomitant diabetes mellitus. Three patients had acute myeloid leukemia (AML). Other malignancies included acute lymphoblastic leukemia (ALL), myeloma, myeloproliferative disease, and lymphoma. Two patients with no prior hospital

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**Table 1. Clinical Characteristics of Patients With Necrotizing Fasciitis**

Age, Gender	Primary Diagnosis	Ongoing Treatment for Hematology Malignancy	Site	Symptoms	Time of Presentation to Diagnosis	Time of Presentation to Surgery	Time of Presentation of Symptoms to Appropriate Antibiotics	Blood and Tissue Cultures	LRINEC Score	ANC ×10 <sup>9</sup> /L	CRP mg/L	WBC ×10 <sup>9</sup> /L	Hb g/dL	Cr μmol/L	Mortality
43, F	Large B-cell lymphoma, postautologous stem cell transplant 2005, with relapse ALL	GMALL consolidation 1	Perianal	Fever, perianal pain, haematoma	3 d	4 d	<24 h	Negative	N/A	0.01	N/A	0.03	9.9	77	Survived
55, M	Relapsed IgG Myeloma	Revlimid, thalidomide, dex	Thigh	Fever, pain and swelling, blisters	<24 h	<24 h	<24 h	<i>Salmonella typhimurium</i> (blood and tissue)	2	1.42	39	1.68	10.5	76	Survived
75, F	Multiple Myeloma	Thalidomide, dex	Leg	Fever, pain, swelling, warmth, hypotensive	2 d	2 d	<24 h	<i>Salmonella enteritidis</i> (blood and tissue)	8	5.09	193	6.5	10.8	53	Survived
79, F	AML	Hydroxycarbamide	Hand	Fever, swelling, gangrenous	<24 h	<24 h	<24 h	<i>Vibrio vulnificus</i> (blood and tissue)	4	14	8	26.06	9.1	100	Survived
19, M	Hodgkin's Lymphoma	BEACOPP	Leg	Fever, swelling, pain	3 d	8 d	<24 h	<i>Aeromonas hydrophila</i> (tissue)	4	0.08	68	0.23	6.2	59	Survived
40, F	Newly diagnosed AML	I+A	Thigh	Fever, tender swelling after 6 d of hospitalization	<24 h	Nil	<24 h	ESBL <i>Klebsiella pneumonia</i> (blood) on day 10 of admission	2	0.12	100	0.6	7.1	43	Survived
67, M	Newly diagnosed ALL in another country	HyperCVAD	Hand	Fever, swelling, crepitus, discoloration after 7 d of admission	<24 h	24 h	<24 h	ESBL <i>Escherichia coli</i> (blood and tissue) on day 7 of admission	3	0.18	9	1.23	6.3	99	Died
68, F	Newly diagnosed AML	None	Thigh	Fever, pain and swelling	<24 h	Nil	<24 h	Negative	13	83	367	233	10.3	151	Died
87, M	Newly diagnosed MPD	None	Forearm	Pain and swelling, blisters; no fever on admission	<24 h	<24 h	<24 h	<i>Enterobacter cloacae</i> (tissue) on day 10 of admission	4	28.01	6	31.65	14.8	73	Survived

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; Cr, creatinine; CRP, C-reactive protein; dex, dexamethasone; ESBL, extended spectrum β-lactamase; F, female; GMALL, German Multicenter Acute Lymphoblastic Leukaemia; Hb, hemoglobin; HyperCVAD, hyperfractionated chemotherapy with Course A consisting of cyclophosphamide, vincristine and doxorubicin and Course B consisting of methotrexate and cytarabine; I+A, idarubicin + cytarabine; Ig, immunoglobulin; LRINEC, Laboratory Risk Indicator for Necrotizing Fasciitis; M, male; MPD, myeloproliferative disease; N/A, not applicable; WBC, white blood cells.

admission presented with NF and were diagnosed with hematological malignancy, whereas 2 patients developed NF during the first week of induction chemotherapy for AML and ALL.

Eight of the 9 patients were febrile on presentation and all presented with pain and swelling. The limbs were the most common site of involvement. Five patients (55.6%) required inotropic support and intensive care unit management. The LRINEC score was <6 for 6 patients (66.7%) and >6 for only 2 patients (22.2%).

The pathogens isolated were all Gram-negative organisms, primarily *Enterobacteriaceae*. Two patients had NF caused by extended spectrum  $\beta$ -lactamase (ESBL)-producing *Enterobacteriaceae* after 6 and 7 days of admission. All patients received appropriate empiric antimicrobial therapy within 24 hours of presentation of symptoms.

Although the clinical diagnosis was prompt for most patients (<24 hours), there was a 2- to 3-day delay for 3 patients, of which 1 was only diagnosed after magnetic resonance imaging was done on second day of admission. Surgical intervention was not universal; 2 patients did not undergo surgery. One was a newly diagnosed AML who developed NF and septic shock on the 6th day of induction chemotherapy, and this patient survived with medical therapy only. The second patient presented to the hospital with a primary diagnosis of NF and AML on admission. She received broad-spectrum antibiotics but died within 6 days. Six of the remaining 7 patients who had surgery survived (85.7%). Two patients required amputation of the infected site. The overall survival rate was 77.8%. The 2 deaths were attributable to NF.

## DISCUSSION

The key management of NF lies in a high index of suspicion, early diagnosis, appropriate antimicrobial therapy, and early surgery [3]. The hard clinical signs include crepitus, necrosis, bullae, and gas on radiologic imaging [4]. In a case series by Wong et al [6], NF patients presented with a triad of exquisite pain, swelling, and fever.

Eight of 9 of our hematology patients presented with the triad of typical symptoms despite being immunocompromised. Despite this, there was a delay of 2 to 3 days in diagnosis for 3 patients. Likewise, in another retrospective review comparing NF between immunocompetent and a spread of immunocompromised patients, there was no difference in physical examination findings, but, again, immunocompromised patients had a significant delay in time to diagnosis and surgery [7]. These findings underline the utmost need for a high level of clinical suspicion. A major proportion of our patients (55%) were hypotensive on presentation. In addition, most of our patients (75%) had a LRINEC score of <6 due to leukopenia, thrombocytopenia, and normal or mildly elevated CRP. This highlights that in hematology patients, the LRINEC score is not sensitive

and a low score does not exclude NF, neither does it suggest a low risk of the disease.

Necrotizing fasciitis has been classically divided into 3 main groups based on the causative organisms: (1) Type I polymicrobial, (2) Type II Group A *Streptococcus*, and (3) gas gangrene (clostridial myonecrosis) [3]. Approximately two-thirds of cases are polymicrobial, and one third is monomicrobial, with Group A *Streptococcus* being the most common cause. The infections in our series were invariably due to monomicrobial Gram-negative organisms. Our results are in concordance with a recent retrospective review reporting higher rates of malignancy in Gram-negative NF compared with Gram-positive NF [8]. Of note, our patient with *Vibrio vulnificus* NF did sustain a penetrating injury to the thumb from a shellfish. Furthermore, the case of *Salmonella typhimurium*, seen here in our series, has not been previously reported to be a cause of NF.

Patients with underlying hematological diseases are known to have multiple hospital encounters and admissions, thus conceivably they are at a higher risk of exposure to nosocomial, multi-drug-resistant organisms. However, only 2 patients had NF caused by ESBL-producing *Enterobacteriaceae* after 6 and 7 days of admission, respectively. The other 5 patients who were known to be on routine follow up in the hospital did not have drug-resistant organisms. The remaining 2 patients (highlighted at the bottom of Table 1) had no prior hospital admission because they had presented concurrently with NF and the hematological malignancy. One had no positive culture, and the second patient had *Enterobacter cloacae* in tissue culture after 10 days of hospitalization. Hence, despite the overall rate of ESBL among *Enterobacteriaceae* being 40% in our center, drug-resistant organisms were not an exceedingly common cause of NF in our patients. Nonetheless, there was a tendency to administer broad-spectrum antibiotics empirically, such as carbapenems, in this group of severely immunocompromised patients. Six patients received carbapenems empirically and the rest received either a  $\beta$ -lactam  $\beta$ -lactamase inhibitor or cephalosporin.

Although it is reported that a delay in surgical intervention leads to a higher risk of mortality [6], our patients who had delayed surgery survived. The timing of surgery has to be carefully weighed against the high operative risk in these immunocompromised patients. Necrotizing fasciitis due to monomicrobial Gram-negative organisms had been described to have a more fulminant course than Gram-positive organisms [9]. Thirty-day mortality was higher in Gram-negative compared with Gram-positive NF (42.1% vs 30.8%, respectively) [8]. It is conceivable that immunocompromised patients should have a higher mortality than the immunocompetent group [7]. However, in our case series of hematological patients with Gram negative NF, mortality was not higher, with 78% surviving the infection. This may be attributed to prompt recognition and diagnosis of NF in our center. All of our patients had received appropriate broad-spectrum antibiotics within 24 hours of

presentation and were considered for surgery where medical condition permitted. The patients were managed by a multidisciplinary team comprising hematologists, surgeons, intensivists, and infectious disease physicians in a tertiary medical center that had notable clinical experience in managing NF.

## CONCLUSIONS

This study underscores salient differences in the clinical course of NF in patients with hematological malignancies. The clinical presentation remains noticeably apparent and useful in bedside diagnosis. The LRINEC score is not a good risk stratification score, hence clinical judgment is pivotal for prompt diagnosis. Gram-negative organisms are the most common causative agents, although most are not drug-resistant even in those with prior hospitalization. The decision on the timing of surgical intervention can be challenging in the presence of comorbidities. Overall, the outcome is not worse than immunocompetent patients with appropriate antimicrobial therapy and surgical intervention in a multidisciplinary care approach.

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