Annals of Hematology (2020) 99:1741–1747
https://doi.org/10.1007/s00277-020-04061-y

ORIGINAL ARTICLE

Necrotizing fasciitis in haematological patients: a different scenario

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Received: 10 February 2020 / Accepted: 27 April 2020 / Published online: 12 May 2020

Abstract

To describe and compare the characteristics of necrotizing fasciitis (NF) in patients with and without haematological malignancy. All adult patients diagnosed with NF and treated at our hospital were included (January 2010–March 2019). Diagnosis was based on intraoperative findings or consistent clinical/radiological characteristics, and patients were classified as group A (with haematological malignancy) or group B (without haematological malignancy). Student's *t* (quantitative), Fisher's exact (qualitative), and Kaplan-Meyer tests were used for the statistical analysis. The study included 29 patients: 8 in group A and 21 in group B. All haematological patients had severe neutropenia (0.2 [0.02–0.5] $\times 10^9$ cells/L; $p < 0.001$) and positive blood cultures (100% vs. 61.9%; $p = 0.04$) at diagnosis. Gram-negative bacilli NF was more common in group A (87.5% vs. 9.5%; $p = 0.001$), predominantly due to *Escherichia coli* (50% vs. 9.5%; $p = 0.056$). Surgical treatment was less common in haematological patients (5 [62.5%] vs. 21 [100%]; $p = 0.015$). Overall, 9 (31%) patients died: 4 (50%) in group A and 5 (23.8%) in group B ($p = 0.17$). The univariate analysis showed that mortality tended to be higher (OR 3.2; 95%CI 0.57–17.7; $p = 0.17$) and to occur earlier (2.2 ± 2.6 vs. 14.2 ± 19.9 days; $p = 0.13$) in haematological patients. The LRINEC index ≥ 6 did not predict mortality in either group. In our study, NF in patients with haematological malignancies was mainly due to Gram-negative bacilli, associated to high and early mortality rates. In our experience, the LRINEC scale was not useful for predicting mortality.

Keywords Necrotizing fasciitis · Gram-negative bacilli · Neutropenia · Haematological malignancy · Bacteraemia

Introduction

Necrotizing fasciitis (NF) is a skin and soft tissue infection defined by necrosis of the fascial planes, with a fulminating course and high mortality [1–4]. Some comorbidities, such as diabetes mellitus, liver cirrhosis or haematological diseases, raise the risk of developing this infection [2, 5, 6].

NF is classified as type 1 (polymicrobial), type 2 (monomicrobial caused by group A β-haemolytic streptococci or *S. aureus*), type 3 (monomicrobial caused by Gram-negative bacilli [GNB] including marine-related organisms) and type 4 (fungal infection) [1, 7, 8].

GNB incidence in NF has been gradually increasing in recent years, especially among immunosuppressed (IS) patients and in areas where the local population is involved in fishing [5, 8], and is associated with high mortality. It has been suggested that NF in IS patients might have an atypical presentation, leading to a delayed diagnosis. Because prompt diagnosis and surgical treatment are essential to achieving a better prognosis [9, 10], this delay may be associated with impaired outcomes [2]. However, there is a paucity of published

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data describing NF characteristics in this context, making management of these severe infections a challenge among IS patients.

Consequently, it is crucial to better understand the characteristics of NF among IS hosts, in order to start early and appropriate treatment to improve outcomes.

The aim of our study was to evaluate and compare the clinical and microbiological characteristics of NF in patients with and without haematological malignancy (HM) and to analyse the risk factors associated with mortality.

Materials and methods

Study design and population

The study was designed as a retrospective cohort including all adult patients (age ≥ 18 years) diagnosed with NF and recorded in the Haematology, Orthopaedics and Infectious Diseases Department records of Hospital Universitari Vall d'Hebron between 1 January 2010 and 31 March 2019. This facility is a 1000-bed tertiary hospital in Barcelona (Spain) with one of the leading Haematology Departments in Spain. Patients were classified as group A (patients with HM) or group B (patients without HM), and the groups were compared in terms of clinical/microbiological characteristics and impact on outcomes. After the first visit in the Emergency Department, the same surgical and medical team treated all patients included.

Definitions

We defined haematological patients as those diagnosed with HM and/or who had undergone haematopoietic stem cell transplantation (HSCT). Neutropenia and severe neutropenia were defined as absolute neutrophil count below 500 and below 100 cells/mm^3, respectively. NF diagnosis was based on intraoperative findings: absence of resistance to blunt dissection of the fascia, presence of necrotic fascia and/or purulent exudate with appearance of dirty "dishwater" fluid and/or consistent histopathological findings [11, 12]. When surgery was not performed, the diagnosis was based on clinical characteristics (local pain, fever, erythema and swelling of the affected area) associated with consistent radiological findings (muscle fascia enhancement by CT scan or MRI). Adequate antibiotic treatment was defined as at least one antibiotic showed to be susceptible in vitro against the causative microorganism. Cure was defined as the absence of clinical signs of infection after antibiotic discontinuation. Related death was established when NF was recorded as the underlying or contributing cause of death during hospitalization.

Microbiological methods

Affected tissues were collected for microbiological and histopathological study. For cultures, the samples were homogenized and inoculated onto conventional media for aerobic and anaerobic bacterial growth. Incubation time was lengthened to 7 to 10 days if no growth was observed. Any microorganisms isolated were identified by an automated biochemical testing system or by mass spectrometry (Vitek® 2 ID Cards and Vitek MS MALDI-TOF, respectively; both from Bio- Mérieux Inc., France). Antimicrobial susceptibility was assessed by microdilution (Vitek® 2 AST, Bio-Mérieux Inc.) or diffusion in agar (Rosco Neo-Sensitabs™, Denmark; and Bio-Mérieux Inc.) according to the EUCAST (European Committee on Antimicrobial Susceptibility Testing) and CLSI (Clinical and Laboratory Standards Institute) recommendations. Multidrug-resistant (MDR) bacteria were defined as those acquiring non-susceptibility to at least one agent in three or more antimicrobial categories as defined by standard consensus [13].

Data collection and variables

Patients' demographic characteristics, baseline haematological malignancy, malignancy-related treatment, clinical presentation, additional tests and microbiological results were retrospectively recorded in an Excel database. Times from symptom presentation to diagnosis, from hospital admission to start of empirical treatment and from hospital admission to surgery were also recorded. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) scale [14] was calculated in all cases.

Statistical analysis

Categorical variables are expressed as the number and percentage, and numerical data as the median and interquartile range (IQR) or the mean ± standard deviation, as appropriate. Fisher's exact test was used for qualitative variables and Student's t test for quantitative variable analysis. The survival analysis was contrasted using the Kaplan-Meyer test. All statistical tests were two-tailed, and statistical significance was set at $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics 21.0 (IBM Corporation, Armonk, New York, USA).

Results

Clinical characteristics

During the study period, 29 cases of NF were identified: 8 in group A and 21 in group B. Table 1 summarizes the baseline characteristics of the study population. Five patients from

Table 1 Baseline characteristics of patients with necrotizing fasciitis

	Total $n = 29$ (100%)	Group A Haematological $n = 8$ (27.6%)	Group B Non-haematological $n = 21$ (72.4%)	p Value
Sex (M)	16 (55.2)	2 (25)	14 (66.6)	0.092
Age at diagnosis (years, IQR)	57.3 (40.2–68.7)	59.2 (47.5–67.5)	48.6 (39.4–69.5)	0.4
Diabetes mellitus	3 (10.3)	1 (12.5)	2 (9.5)	1
Chronic kidney failure	3 (10.3)	1 (12.5)	2 (9.5)	1
Cirrhosis	2 (6.9)	0	2 (9.5)	
HSCT	5 (17.2)	5 (62.5)		
- Allo-HSCT	2 (6.9)	2 (25)	-	-
- Auto-HSCT	3 (10.3)	3 (37.5)		
Site of infection				0.288
- Lower limb	19 (65.5)	7 (87.5)	12 (57.1)	
- Upper limb	8 (27.6)	1 (12.5)	7 (33.3)	
- Abdominal	2 (6.9)	0	2 (9.5)	
Clinical symptoms at diagnosis				
- Fever	11 (37.9)	4 (50)	7 (33.3)	0.433
- Pain	25 (86.2)	7 (87.5)	18 (85.7)	1
- Warmth	11 (37.9)	5 (62.5)	6 (28.6)	0.197
- Swelling	17 (58.6)	6 (75)	11 (52.4)	0.408
Septic shock	26 (89.7)	6 (75)	20 (95.2)	0.176
Bacteraemia	21 (72.4)	8 (100)	13 (61.9)	0.04*
Time from presentation to diagnosis[a]	24 (24–84)	24 (24–66)	48 (23–96)	0.370
Time from admission to proper antibiotic[a]	23 (23–24)	23 (23–23)	23 (23–24)	0.440
Time from diagnosis to surgery[a]				1
< 24 h	19 (65.5)	4 (50)	15 (71.4)	
> 24 h	6 (20.7)	1 (12.5)	5 (23.8)	
Unknown	1 (3.4)		1 (4.8)	
Surgery	26 (89.7)	5 (62.5)	21 (100)	0.015*
Number of debridements (26/29)	1.5 (1–4)	2 (1–5.5)	1 (1–4)	0.640
Consistent CT scan findings	26 (89.7)	8 (100)	18 (86)	0.540
Aetiology				
Monomicrobial	23 (79.3)	8 (100)	15 (71.4)	0.12
- Gram-positive	14 (48.3)	1 (12.5)	13 (61.9)	0.001*
○ *S. pyogenes*	10 (34.5)	1 (12.5)	9 (42.9)	0.029*
○ *S. aureus*	1 (3.4)	0	1 (4.7)	0.460
○ Other[b]	3 (10.3)	0	3 (14.2)	0.180
- Gram-negative	9 (31)	7 (87.5)	2 (9.5)	0.001*
○ *E. coli*	6 (20.7)	4 (50)	2 (9.5)	0.056
○ *P. aeruginosa*	2 (6.9)	2 (25)	0	0.037*
○ *S. maltophilia*	1 (3.4)	1 (12.5)	0	0.160
Polymicrobial	5 (17.2)	0	5 (23.8)	0.120
Unknown	1 (3.4)	0	1 (4.76)	
Blood analyses				
- Haemoglobin (g/dL)	9.80 (8.30–13.20)	8.15 (6.63–8.48)	11.9 (8.8–13.9)	< 0.001*
- WBC ($\times 10^9$ cells/mm^3)	10.4 ± 1.5	1.4 ± 0.5	13.8 ± 1.5	< 0.001*
- ANC ($\times 10^9$ cells/mm^3)	7.8 (0.65–14.6)	0.2 (0.025–0.5)	10.7 (6.9–16.25)	< 0.001*
- Length of neutropaenia (days)[c]	18 (2.75–82.5)	18 (2.75–82.5)	-	-
- Platelets ($\times 10^9$ cells/mm^3)	172 ± 28.5	45 ± 17.4	220 ± 33	0.004*
- Creatinine (g/dL)	1.61 ± 0.17	1.6 ± 0.4	1.62 ± 0.2	0.88
- CRP (g/dL)	33 (12–38)	26 (9–38)	35 (14–39)	0.403

Table 1 (continued)

	Total $n = 29$ (100%)	Group A Haematological $n = 8$ (27.6%)	Group B Non-haematological $n = 21$ (72.4%)	p Value
LRINEC				
- ≥ 6	8 (27.6)	3 (37.5)	9 (42.9)	0.46
- < 6	21 (72.4)	5 (62.5)	12 (57.1)	
Patient death	9 (31)	4 (50)	5 (23.8)	0.17
- Death due to NF	9 (100)	4 (100)	5 (100)	

Qualitative data are expressed as the number (%), unless otherwise indicated. Quantitative data are expressed as the mean ± standard deviation (SD) or median and interquartile range (IQR, 25th–75th percentiles), as appropriate

ANC absolute neutrophil count, *CRP* C-reactive protein, *HSCT* haematopoietic stem cell transplantation, *LRINEC* Laboratory Risk Indicator for Necrotizing Fasciitis, *NF* necrotising fasciitis, *WBC* white blood cells

[a] Times are expressed in hours

[b] The other Gram-positive microorganisms identified were 1 *S. constellatus*, 1 *S. dysgalactiae* and 1 *C. septicum*

[c] Neutropenia is defined an absolute neutrophil count < 500 cells/mm^3

group A were HSCT recipients with no other associated comorbidities. Among non-HSCT recipients, all but one were receiving chemotherapy.

All haematological patients had severe neutropenia at diagnosis with a median duration of previous neutropenia of 18 (IQR 2.75–82.50) days. Haemoglobin and platelet counts were also lower among haematological patients.

Pain at the affected area was the most common symptom in both groups; at diagnosis most patients had no fever. Lower limbs tended to be the main site of involvement in the haematological group, and most patients developed septic shock, with no differences observed between the groups. All haematological patients had positive blood cultures at presentation. Time to diagnosis after presentation was similar in both groups.

Aetiological agents (Table 1)

NF was monomicrobial in 23 (79.3%) cases: 8 (100%) in group A and 15 (71.4%) in group B. Monomicrobial episodes caused by GNB were more common in group A (87.5% vs. 9.5% $p = 0.001$), predominantly due to *Escherichia coli* (50% vs. 9.5%; $p = 0.056$) or *Pseudomonas aeruginosa* (25% vs. 0%; $p = 0.037$). Conversely, monomicrobial Gram-positive cocci NF was more common in group B (61.9% vs. 12.5%; $p = 0.001$), mainly due to *Streptococcus pyogenes* (42.9% vs. 12.5%; $p = 0.029$). Overall, we detected only 3 cases caused by MDR microorganisms: the first due to *Stenotrophomonas maltophilia* (group A), the second due to extensively drug-resistant *P. aeruginosa* (group A) and the third due to extended-spectrum beta-lactamase-producing *E. coli* (group B).

Treatment and outcomes

Broad-spectrum antibiotic treatment was started within 24 h of diagnosis in all cases and later adjusted according to microbiological results. Empirical treatment consisting of an antipseudomonal β-lactam antibiotic was started in all haematological patients, associated with amikacin in 5 (62.5%) cases. Antitoxin treatment with clindamycin was used less often among haematological patients (4 [50%] vs. 18 [86%]; $p = 0.045$). Overall, intravenous immunoglobulin was only added in 2 (6.9%) cases, both in non-haematological patients. Time to initiation of antibiotics was similar in both groups (Table 1). However, surgical treatment was less common in haematological patients (5 [62.5%] vs. 21 [100%], $p = 0.015$].

Overall, 9 (31%) patients died: 4 (50%) in group A and 5 (23.8%) in group B ($p = 0.17$), all of them due to NF. The univariate analysis showed that mortality tended to be higher in patients with HM (OR 3.2; 95%CI; 0.57–17.7; $p = 0.17$) and in NF cases caused by GNB (OR 4.6; 95%CI 0.7–28.7; $p = 0.094$), particularly those caused by *E. coli* (OR 6.5; 95%CI; 0.9–49.7; $p = 0.056$). Patients who underwent surgery tended to have lower associated mortality (OR 0.184; 95%CI 0.01–2.36; $p = 0.16$), and among these, a higher number of surgical debridements were associated with better outcomes ($p = 0.002$). Haematological patients had earlier mortality than non-haematological patients (2.2 ± 2.6 vs. 14.2 ± 19.9 days; $p = 0.13$), but this finding was not statistically significant (Fig. 1). LRINEC index ≥ 6 did not predict mortality in either group A ($p = 0.46$) or group B ($p = 0.33$).

Discussion

To our knowledge, this is the first study to compare the characteristics of NF between haematological and non-haematological patients. Our results show that monomicrobial NF in patients with HM is mainly caused by GNB; these patients tended to have a more aggressive course and higher mortality despite adequate and prompt antibiotic treatment. Although

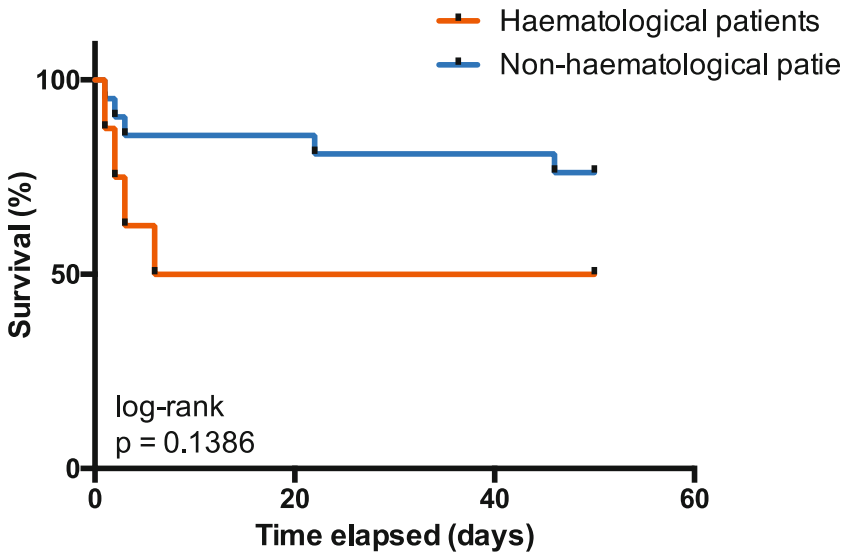

Fig. 1 Kaplan-Meyer survival analysis between group A (haematological patients, $n = 8$) and group B (non-haematological patients, $n = 21$). Log-rank test $p = 0.1386$

haematological patients underwent fewer surgeries, it is difficult to determine if this was the cause of their higher mortality or if their underlying disease made surgery more ill-advised.

Our findings are consistent with prior studies reporting an increase in monomicrobial NF cases due to GNB among patients with underlying malignancies [15] with incidences as high as 77% [16]. All our haematological patients had positive blood cultures, a higher rate compared with other series describing bacteraemia in 20% to 55% of IS individuals. This high percentage could be explained by an increased risk of abdominal GNB translocation facilitated by prolonged and severe neutropenia observed in haematological patients compared with other IS individuals. We only found one study specifically evaluating NF characteristics in haematological patients [16] which also described a predominance of GNB NF, with 55.5% positive blood cultures.

In our experience, *E. coli* was the main causative microorganism of NF in haematological patients (50%). *E. coli* has been classically associated with polymicrobial NF [17]; however, some authors have also cautioned about *E. coli* monomicrobial pyomyositis and NF in haematological patients [18, 19]. Shaked et al. [19] described 7 cases of *E. coli* NF. Overall, 85.7% of their patients had positive blood cultures, and 71.4% had an underlying HM, of which 60% (3/5) were neutropenic, consistent with our results. In a post hoc study, they reported an overall 22% incidence of monomicrobial *E. coli* NF [15], which is comparable with our figure of 21% (6/29) if we include all NF in our study. Thus, we believe that empirical treatment of NF in patients with HM should include a broad-spectrum antibiotic with good coverage against GNB.

Although recent studies have suggested the need to use new antibiotics with activity against MDR bacteria [20], our results suggest that this approach is not universally justified, as we detected only 3 cases of NF caused by MDR bacteria. However, when treating NF in a patient diagnosed with HM, local epidemiological data and prior antibiotic exposure should always be considered. Some authors recommend the addition of clindamycin to treat NF-associated streptococcal toxic shock syndrome [21], but its role in GNB NF has not been adequately studied. Moreover, intravenous immunoglobulin was rarely used in our hospital because its benefit for survival is still unclear [22]. In view of this, we use an antipseudomonal β-lactam with a β-lactamase inhibitor or a cephalosporin, both associated with amikacin, to empirically treat NF in these patients, as this is also our empirical treatment for febrile neutropenia. In non-IS patients, we also add clindamycin, which is withdrawn once clinical stabilization is achieved. We observed that surgical treatment was less common among haematological patients, with only 62.5% (5/8) undergoing surgery, compared with all 21 non-IS patients. This is consistent with the findings of other authors, who have reported lower percentages of surgical treatment among IS vs. non-IS patients, even though the underlying causes of IS were different from ours [2]. It has been shown that early and aggressive surgical treatment, often involving subsequent debridements with extensive resections, is crucial to improving survival [9, 10]. One possible explanation for why haematological patients are less likely to undergo surgery could be a fear of high intraoperative mortality due to increased intraoperative bleeding in the context of severe pancytopenia. To aid preoperative assessment of these patients, the LRINEC scale has been suggested to be useful when diagnosing NF and deciding on the indication of surgical treatment to reduce mortality [14, 23]. However, recent studies show that this scoring system is inaccurate [24, 25], particularly in haematological patients [16]. Consistent with these data, we observed that a LRINEC score ≥ 6 did not predict mortality in either group, making it useless for therapeutic decision-making.

In our series, although all patients started adequate antibiotic treatment within the first 24 h of admission, global mortality tended to be higher and earlier among haematological patients, in particular when NF was due to *E. coli*. This is consistent with previous studies where monomicrobial GNB NF was associated with high mortality rates, varying between 17 and 70% [5, 15, 25, 26]. This worse outcome may be multifactorial. As previously discussed, haematological patients were less likely to undergo surgery, which probably has important prognostic implications. However, host-related factors (severe immunosuppression) and factors related to the causative microorganism may also be significant contributor factors for mortality. In the case of some *E coli* strains, several intrinsic virulence factors such as *cnf1* toxin gene expression have been described [19, 27]. Unfortunately, we were unable to perform a genotypic analysis of our *E. coli* strains.

Conclusions

In our study, NF in patients with HM was mainly caused by GNB bacteraemia, probably facilitated by severe neutropenia and subsequent abdominal bacterial translocation. Although our series is small, these results highlight the importance of starting an early broad-spectrum beta-lactam antibiotic treatment ensuring an adequate GNB coverage, considering local MDR epidemiology, in contrast to NF in non-haematological patients. NF in haematological patients was associated with high and early mortality rates. In our experience, the LRINEC scale was not a useful tool for predicting mortality.

Limitations

Our study has several limitations. First, this was a single-centre study; therefore, our data cannot be generalized to other settings. This design, together with the low incidence of NF, explains the small number of patients included, especially in group A. Second, we were unable to perform *E. coli* genotyping analysis. In contrast, the greatest strength of the study was its homogenous cohort of NF diagnosed and treated by the same multidisciplinary team with a high degree of expertise in this pathology. To our knowledge, this is the first study to specifically compare the characteristics and risk factors for NF mortality between haematological patients and non-haematological individuals.

Acknowledgements We thank Helen Casas and Laura Casas for English language support.

Authors' contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Adaia Albasanz-Puig, Dolors Rodriguez-Pardo and Isabel Ruiz-Camps. The first draft of the manuscript was written by Adaia Albasanz-Puig, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding information This work was supported by Plan Nacional de I+D+ i 2013-2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación cooperativa, Ministerio de Economía, Industria y Competitividad, Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0003)—co-financed by European Regional Development Fund "Investing in your future", Operational Programme Smart Growth 2014–2020.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Vall d'Hebron Research Institute Ethics Committee.

Human and animal rights and informed consent Informed consent was waived due to the retrospective cohort design. This article does not contain any studies with animals performed by any of the authors.

Consent to publish Not applicable.

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