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Necrotizing Fasciitis - A Single Center Case Series

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1. Abstract

1.1. Aims: Necrotizing fasciitis is a potentially life-threatening infection with rapidly spreading necrosis of the superficial fascia and involvement of subcutaneous tissue. The aim of this study is to address the mortality, comorbidities, pre-disposing factors, difference in virulence, treatment and outcome among patients diagnosed with necrotizing fasciitis in Denmark.

1.2. Methods: This study is a retrospective cohort study enrolling patients admitted to the University Hospital, Rigshospitalet, Denmark in 2010-2012. Inclusion criteria were the ICD3 code DM725A and the diagnosis was validated by an operational description of either necrosis of the fascia, dishwater pus, lack of bleeding or a positive finger test (lack of resistance to finger dissection in normally adherent tissues).

1.3. Results: 115 patients were identified. The 30-day mortality was 7,8% and the 90-day mortality 19,1%. In 2005-2008 the numbers were 8,2% and 11, 8%. Men, 69%, were overrepresented. 13,9% had a skin disease at the place of NF, 21,7% had had surgery within 4 weeks prior to the diagnosis and 13,9% had a cancer diagnosis at the time of diagnosis.

1.4. Conclusion: The present study compared with earlier findings show unchanged 30-day mortality and a slight increase in 90-day mortality. Of interest regarding predisposing factors 13,9% had a skin disease at the place of debut of necrotizing fasciitis. It is important to validate the diagnosis, as 8,7% hereafter were excluded in this study.

2. Introduction

Necrotizing Fasciitis (NF) is a rare infection, potentially life-threatening, with rapidly spreading necrosis of the superficial fascia and involvement of the subcutaneous tissue. NF is classified into the following categories; Type 1 (polymicrobial/synergistic, mixed aerobes and anaerobes), Type 2 (often monomicrobial, usually group A B hemolytic streptococcus), Type 3 (gram negative, often marine-related, most commonly Vibrio species) and Type 4 (Fungal) [1]. Early symptoms are erythema, edema, fever and pain (typically out of proportion to objective findings). Later symptoms are bullae, dysesthesia/anesthesia, hard skin upon palpation, crepitation, discoloration and systemic manifestations. Mortality is reported from 6-76% in the literature, most commonly around 15-35% [2-13]. Concerning mortality, time to diagnosis and surgical resection is of great importance [14]. It is not known why the same pathogens cause this severe infection in some patients and not in others, and why it is also diagnosed among patients without comorbidity [15].

Treatment of necrotizing fasciitis with a possible need for HBO was in 2010 – 2012 centralized to two centers in Denmark. Treatment consists of intensive care therapy, extensive surgery until vital bleeding tissue, early broad spectrum antibiotics, HBO (daily for the first three days, hereafter optional), although, if the patient's condition is esteemed as too unstable, hyperbaric treatment awaits, and finally, optionally IVIG. In Danish guidelines IVIG is recommended (25 g x 1) during the first three days to patients with

confirmed shock and suspected/verified streptococcal infection, typically seen in patients with an extremity focus. Initial antibiotic treatment consists of meropenem (2 g x 3) and clindamycin (600 mg x 3). Surgical resection is performed immediately if allowed by clinical condition, hereafter debridement is performed at regular intervals guided by clinical and surgical state of the patient, daily if needed. Nutritional therapy, fluid and volume resuscitation starts early and patients with large skin resections are treated in a heated room by open exposition, imitating the treatment given to burn victims as they might become poikilothermic (having a body temperature strongly correlated with that of the external environment).

The aim of this article is to address the comorbidities, pre-disposing factors, microbiology, treatment and outcome among patients diagnosed with NF in Denmark. Further to compare the results with a similar earlier study [2].

3. Materials and Methods

The present study is a retrospective single-centre cohort study of patients diagnosed with NF. Patients were identified through the database at the Copenhagen University Hospital Rigshospitalet, Denmark, by the diagnostic code; DM725A; fasciitis necroticans. The inclusion period was from the 01/01/2010 until the 20/06/2012 and the search resulted in 126 patients. The diagnostic code was validated by a surgical description of necrosis of the fascia, dishwater pus (dishwater colored fluid), lack of bleeding or a positive finger test (lack of resistance to finger dissection in normally adherent tissues), this resulted in exclusion of 11 patients.

Data on co-morbidities, predisposing factors, treatment, localization, outcome and microbiology were obtained from hospital files. Microbiological findings included biopsies taken within 48 hours of admission to the hospital.

4. Results

During the inclusion period a number of 115 patients were identified. Men, 69%, were overrepresented, 13,9% had a skin disease at the place of NF, 24,3% had diabetes mellitus (DM), 21,7% had had an operation within 4 weeks prior to NF diagnosis and 13,9% had cancer at the time of diagnosis (Table 1).

We found a 30-day mortality of 7,8% and a 90-day mortality of 19,1% (Table 3). Number of revisions had a mean of 5.4. 82,6% received HBO, most often 2 or more HBO-treatments (64,3%). Most cases had a known point of entry, 55,7 %. In patients with monomicrobial growth in a sample taken within 48 hours from admission, hemolytic streptococcus was overrepresented (56,1%), and this organism was also found in 25% of polymicrobial cases. 64,3% of the patients developed septic shock. 27,8 % Multiple Organ Dysfunction Syndrome (MODS), 11,3 % Disseminated Intravascular Coagulation (DIC) and 17,4 % Acute Tubulointerstitial Nephritis (ATIN) (Table 2).

Data regarding demographics, comorbidity, treatment, etiology and outcome among the patients who died within 30 days of the diagnosis is shown in table 3.

Table 1: Demographic data & comorbidity

Sex, n (%)	
Female	36 (31)
Male	79 (69)
Age, median, (range)	60 (5 – 86)
Weight, n (%)	
BMI < 18,5	0 (0)
BMI 18,5 - 25	65 (56.5)
BMI > 25	50 (43.5)
Smoking, n (%)	
Yes	54 (47)
No	32 (27.8)
Earlier	17 (14.8)
Alcohol abuse, n (%)*	
Yes	33 (28.7)
No	75 (65.2)
Earlier	7 (6.1)
Hypertension, n (%)	44 (38.3)
Hypercholesterolemia, n (%)	9 (7.8)
Diabetes Mellitus (DM), n (%)	28 (24.3)
*Skin disease at the place of NF**, n (%)*	16 (13.9)
Cancer, n (%)	
At the time of NF diagnosis	16 (13.9)
Earlier	5 (4.3)
HIV, n (%)	2 (1.7)
I.v. drug abuse, n (%)	3 (2.6)
Liver cirrhosis, n (%)	6 (5.2)
Hepatitis, n (%)	
Alcoholic hepatitis	2 (1.7)
Hepatitis C	4 (3.5)
Chronic Obstructive Pulmonary Disease (COPD), n (%)	18 (15.7)
*Operation within 4 weeks, n (%)****	25 (21.7)
Crepitation/air development, n (%)	45 (39.1)

*In Denmark defined as 84 g of alcohol/week for women and 168 g/week for men

**Represented diagnoses where; chronical itching skin disease, chronical/bad healing wounds, tendency to fistulas/abscesses/erysipelas/cysts or polyps, seborrheic dermatitis)

***The patient had had surgery, including dental surgery/extraction within 4 weeks prior to NF diagnosis

Table 2: Treatment, Etiology and Outcome

Number of revisions	
Mean	5.4
Median (Range)	4 (0-28)
Number of Hyperbaric Oxygen Treatment (HBO) treatments, n (%)	
0	20 (17,4)
1	21 (18,3)
2	36 (31,3)
3	16 (13,9)
4	12 (10,4)
5	6 (5,2)
6	3 (2,6)
7	1 (0,9)
Known point of entry, n (%)	64 (55,7)
Abscess, n (%)	25 (21,7)
Microbiology (sample taken within 48 hours from admission)	
Polymicrobial, n (%)	48 (41,7)
-Haemolytic streptococcus	12 (25)
Monomicrobial, n (%)	41 (35,7)
-haemolytic streptococcus	23 (56,1)
- Clostridium septicum	1 (2,4)
- E.coli	4 (9,8)
- Staphylococcus aureus	3 (7,3)
- Staphylococcus epidermidis	1 (2,4)
- Streptococcus anginosus	2 (4,9)
- Streptococcus constellatus	2 (4,9)
- Streptococcus	4 (9,8)
- Gram positive coccus	1 (2,4)
Unknown etiology, n (%)	26 (22,6)
Stage of sepsis, n (%)	
No sepsis	19 (16,5)
Sepsis	14 (12,2)
Severe sepsis	8 (7)
Septic shock	74 (64,3)
Amputated, n (%)	26 (22,6)
Multiple Organ Dysfunction Syndrome (MODS), n (%)	32 (27,8)
Disseminated Intravascular Coagulation (DIC), n (%)	13 (11,3)
Acute Tubulo Interstitial Nephritis (ATIN), n (%)	20 (17,4)
Toxic Shock Syndrome (TSS), n (%)	1 (0,9)

Table 3: Demographics, comorbidity, etiology, treatment and outcome among patients who died within 30 days

Patients who died within 30 days	1	2	3	4	5	6	7*	8	9
Sex	M	M	M	M	M	M	M	F	F
Age	53	53	83	50	84	73	5	63	61
Cancer				x			x	x	
Skin disease at the place of NF		x			x				
Operated within 4 weeks prior to diagnosis				x			x		
Localization	Multiple	Multiple	Fourniers	Fourniers	Lower extremity	Lower extremity	Urogenital	Urogenital	Urogenital
Number of revisions	3	5	1	1	1	5	0	11	3
Number of HBO treatments	0	0	1	2	1	1	0	6	0
Known point of entry				x	x	x		x	x
Septic shock	x	x	x	x	x	x	x	x	
Amputation			x		x	x		x	
MODS	x					x		x	
DIC		x				x		x	
ATIN									
TSS									
Microbiology	S. aureus	Poly	Poly	Unknown	Unknown	G+ coccus	S. epidermidis	Poly	Poly

*Patient suffered from leukemia and died before surgery was possible

The 30 day mortality from NF was 9/115 = 7,8 %.

The 90 day mortality was 9+13/115 = 19,1%.

5. Discussion

The 30-day mortality in 2005-2006 was 8,2% [2]. This article shows a 30-day mortality approximately the same, 7,8%. Although the 30-day mortality has not changed a lot, the 90-day mortality has. In 2005-2006 it was 11,8%, and this article shows a mortality of 19,1%. The difference could among other causes reflect a difference in localization of the infection or different microbiology, with a shift towards more resistant bacteria [16, 17] or a difference in patient care after discharge.

We found an overrepresentation of the male sex in the material (69%) just as in the article by Skovsen et al. (67%) [2]. The localizations were the extremities (42,2%), urogenital (31,8%), abdominal (14,1%), and head/neck/thoracic region (11,8%) in the article by Skovsen et al [2]. We found a difference in locations with more patients (20,9%) with the localization head/neck/thoracic region, and fewer with the other localizations; extremities (30,4%), urogenital (22.7%) and abdominal (6.1%). Although we also had a group called “many regions” (20%), including at least one other localization than the extremities, this might have contributed to the difference in mortality. It might be more difficult to perform surgery in the head/neck/thorax area than at the extremities and the surgery might be more hazardous for the patient. It might also be more difficult to remove enough tissue, to be extensive enough and the surgeon might be more careful, wanting to spare as much tissue as possible with regards to cosmetic and social disabilities. This could result in less extensive surgery with incomplete radicality. Furthermore, amputation is not an option in the head/neck/thoracic region, which is a possibility with extremities and the male genital area, to stop infections that are out of control.

In the article by Skovsen et al. 65,9 % of patients had septic shock, 24,7% ATIN and 12,9% DIC [2]. We found septic shock in 64,3%, 17,4% suffered from ATIN and 11,3% from DIC. Possibly we have become better at treating septic shock, but with more resistant bacteria, this effect might not be seen. Similarly to Skovsen et al. we found that 21,7 % had had an operation in short time before they got their NF diagnosis, compared to 18,9%, indicating this as a predisposing condition and there might be more to this than just being an entry point for bacteria.

HBO and Intravenous Immunoglobulin (IVIG) are among the most discussed treatment options. HBO is a medical treatment where the patient, enclosed in a chamber, breathes 100% oxygen at a pressure > 1 atmosphere absolute. The proposed benefits are; enhanced ability for white blood cells to kill aerobic bacteria, stimulation of collagen formation, increased levels of superoxide dis-

mutase, vasoconstriction and thereby decreased edema formation and increased tissue oxygen tension with increased effect of antibiotics. A "super oxygenated zone" builds, forming a barrier which slows spreading of the infection, cause damping of the systemic inflammatory response, impair the virulence of bacterial pathogens, promote angiogenesis and healing of wounds, promote the pliability of red blood cells and terminate lipid peroxidation [6, 8]. A systematic review from 2015 (searching the Cochrane Central Register of Controlled Trials, MEDLINE, the Cumulative Index to Nursing and Allied Health Literature, EMBASE and the Database of Randomized Controlled Trials in Hyperbaric Medicine) failed to locate relevant clinical evidence to support or refute the effectiveness of Hyperbaric Oxygen Treatment (HBOT) in the management of necrotizing fasciitis. Good quality clinical trials are needed to define the role, if any, of HBOT in the treatment of individuals with necrotizing fasciitis [18]. There are few small retrospective studies that show positive results from HBO [5]. In a Danish cohort study including patients with Necrotizing Soft Tissue Infections (NSTI) an improved 30-day and 90-day survival in hospitals offering HBOT as an adjunct to the multidisciplinary treatment was reported. However, authors state that these results should be interpreted cautiously due to missing confounders, such as clinical variables and potentially different treatment modalities across hospitals. Mortality among HBOT-treated individuals was noticeably reduced compared with those who did not receive HBOT. Again authors state that the difference should be interpreted carefully due to potential selection bias based on which patients are offered HBOT as an adjunct. Presumably, some may have been in such critical hemodynamic condition were in-hospital transportation to HBOT were deemed unachievable, thereby indicating that the HBOT-treated patients represent a selected cohort [15]. IVIG was primarily used in the treatment of Toxic Shock Syndrome (TSS). The proposed mechanisms of action are that IVIG may opsonize Group A Streptococcal bacteria, promote clearance, antagonize or neutralize streptococcal super antigens and modulate immune cytokine responses [3, 8]. A randomized, blinded, placebo-controlled trial with 87 patients included concluded that in patients with NSTI treated in an intensive care unit, there were no apparent effects of adjuvant IVIG on self-reported physical functioning at 6 months[19]. An observational study reported that one 25g IVIG dose was sufficient to yield plasma-neutralizing activity against streptococcal superantigens, why this study recommend the use of IVIG [20]. Though all proposed mechanisms of action, there are also side effects from HBO (reversible myopia, barotraumatic lesions (ear, lung), CNS and pulmonary oxygen toxicity) [21] and IVIG (anaphylaxis and possibly renal impairment) [22]. We had a higher proportion of patients 17.4% that did not receive HBO, whereas Skovsen et al. reported 3.5%, this might have contributed to the difference in 90 day mortality rates. The reasons for the difference in number of patients who were not treated with HBO might have been a different judgment concerning if a patients clinical condition was stable enough, the patients could have been diagnosed at a later point in their infection, they might have had a more aggressive infection or it might have been at a different localization. There is a need for controlled studies with a large number of patients, possibly in countries where HBO is not a standard regimen as it is unethical to remove a treatment we have already introduced believing in its potential. For example, in the USA only 1% of patients received HBO at specialized centers [23]. In the study by Skovsen et al. 8% had DM and among them there was a mortality of 0%. In this study 24,3% had DM, of which 2 of the 9 patients who died within 30 day and 5 of the 22 patients who died within 90 day had diabetes. A proposed predisposing factor we looked into in this study was if the patients had a skin disease at the place of NF. Skin diseases reported were chronically itching skin disease, chronically/bad healing wounds, tendency to fistulas/abscesses/cysts/erysipelas or polyps and seborrheic dermatitis. 13,9% of the patients had a skin disease, which might indicate a connection.

Our main limitations are the single-centre and retrospective nature of our study. Although treatment is centralized and transport routes are not that far in Denmark, patients might have been too critically ill upon diagnosis for transportation.

6. Conclusions

The present study compared with earlier findings show unchanged 30-day mortality and a slight increase in 90-day mortality. Of interest regarding predisposing factors 13,9% had a skin disease at the place of debut of NF. It is important to validate the diagnosis, as 8,7% hereafter were excluded in this study. There is a need for controlled studies with a large number of patients documenting the effect and regimen of HBO, possibly in countries where this is not a standard regimen as it is unethical to remove a treatment we have already introduced believing in its potential.

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