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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Necrotizing soft tissue infections of perianal and perineal region – Still a lethal infection

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SUMMARY

Introduction/Objective Necrotizing soft tissue infection is a life-threatening condition, characterized by widely spread necrosis of the skin, subcutaneous adipose tissue, fascia, and muscle.
This study aimed to determine the risk factors associated with lethality due to necrotizing soft tissue infection of perianal and perineal region, for all patients surgically treated at a tertiary referral hospital.

Methods A retrospective review of 38 patients with necrotizing soft tissue infection of the perianal and perineal region, in the period between January 2007 and December 2014, was performed. We reviewed sex and age of the patients, the presence of known risk factors (diabetes mellitus, obesity, alcoholism), localization of necrotizing soft tissue infection, duration of symptoms, length of hospitalization, the number of necessary operations done, the performance of the stoma, and the outcome. We used logistic regression to identify the predictors of lethal outcome in a univariate analysis with estimated odds ratios and 95% confidence intervals.

Results There was a significantly higher fatality rate in the group of patients over 60 years of age ($p < 0.05$), with more than 10 days from the onset of symptoms to the treatment ($p < 0.05$), with a perianal localization ($p < 0.05$), and stoma creation ($p < 0.05$). The overall fatality rate was 18.4%.

Conclusion Patients' age, time passed between the onset of the symptoms and the initiation of the treatment, perianal localization, and stoma creation were related to higher lethality risk.

Keywords: necrotizing soft tissue infection; necrotizing fasciitis; Fournier's gangrene; perianal region; perineal region

INTRODUCTION

Necrotizing soft tissue infection (NSTI) is a life-threatening condition, characterized by a widely spread necrosis of the skin, fascia, muscle and subcutaneous adipose tissue [1, 2]. In literature, it is also often called necrotizing fasciitis, or Fournier's gangrene, which is essentially only one of the forms of necrotizing soft tissue infection. A recent study that established the incidence of soft-tissue infection, using insurance databases from various states in the United States of America, determined the prevalence of NSTI to be four cases per 100,000 people per year [2]. The occurrence of NSTI is characterized by a fulminant inflammatory response, which causes obliterating endarteritis of cutaneous and sub-cutaneous blood vessels, with subsequent tissue necrosis. The high mortality rate of up to 51.5% (Table 1) is explained by the dominant influence of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which cause the systemic inflammatory response (SIRS), as well as increased level of reactive oxygen and oxygen radicals with the consequent development of multiorgan insufficiency [3–13]. Recently, attention has been paid to the so-called extracellular high mobility group box 1 (HMGB1) protein, highly conserved nuclear protein, which may form immunostimulatory complexes with IL-1β. They are present in a greater amount at the site of infection, and their level correlates to the severity of infections [14]. Up to 50% of infections occur in the perianal and perineal region with a high percentage of disseminated infections, which was explained by late diagnosis. Clinical presentation is characterized by various degrees of local and systemic inflammation.

The aim of this paper is to present the results of a retrospective study in the treatment of NSTI in the perianal and perineal region, and the impact of risk factors on the case fatality rate.

METHODS

We analyzed the treatment results in 38 patients with NSTI at a tertiary referral hospital, for the period between January 2007 and December

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Table 1. Data from literature and our study (Medline/PubMed's article) about the lethality and treatment of NSTI

References (author, ref. No., year)	Number of patients	Fatality rate (%)
Yilmazlar et al. [3], 2007	67	49
Angoules et al. [4], 2007	451	22
Basoglu et al. [5], 2007	45	8.8
Mills et al. [6], 2010	688	12
Lee et al. [7], 2011	46	15.2
Martinschek et al. [9], 2012	55	16.4
Kalaivani et al. [10], 2013	60	25
Yu et al. [11], 2013	83	33.7
Goh et al. [12], 2013	1463	21.5
Our study	38	18.4

2014. The initial diagnosis was carried out based on the clinical examination of a patient, especially the manifestation of the local forms of inflammation (intensive severe pain, redness of the affected area, locally increased temperature, bullae and crepitation) and the so-called "finger test." This involves infiltrating the suspect area with local anesthetic and making a two-centimeter incision down to the deep fascia. If the index finger dissects the subcutaneous tissue of the deep fascia easily along the tissue plane, the test is positive. Other positive macroscopic findings are grey necrotic tissue and thin, watery, foul-smelling fluid, described as dishwater pus [12]. As part of the diagnostic procedures, computerized tomography of the small pelvis was performed in 89.5% of the patients. The treatment of NSTI includes drainage, wide incisions of the affected region, debridement, tissue decompression, the use of broad-spectrum antibiotics, and laparotomy with stoma procedure on some of the patients. We started with antimicrobial therapy early to include coverage for gram-positive, gram-negative, and anaerobic organisms. We used monotherapy regiment in 39.5% of the cases with imipenem intravenously (IV) 1 g every eight hours, and triple-drug therapy regiment in 60.5% of the patients with penicillin G one to two million units IV every six hours, metronidazole 500 mg every eight hours, and aminoglycoside 500 mg IV every 8–12 hours.

We analyzed the following patient characteristics: sex, age, the presence of known risk factors (diabetes mellitus, obesity, alcoholism), localization of the NSTI (perineal/genitourinary), duration of symptoms, length of hospitalization, number of procedures, and outcome. We used logistic regression to identify the predictors of lethal outcome in a univariate analysis with estimated odds ratios and 95% confidence intervals. All the statistical tests were two-sided, and $p < 0.05$ was considered to be statistically significant. For data analyses we used the Statistical Package for the Social Sciences (SPSS) 12.0 for Windows.

RESULTS

The distribution of patients was as follows: out of 38 patients, 23 (60.5%) were males and 15 (39.5%) were females, with an average age of 47.26 years and a standard deviation of 12.03. The average number of cases per year was 2.92. The most common risk factors in our group of patients were diabetes mellitus, present in 44.7% of cases; obesity, in 42% patients in the cohort, and alcoholism, associated with 26.3% of patients. In relation to the localization of NSTI, the largest number of patients was registered with an infection in the perianal region (86.8%), the genitourinary region (73.7%), and the extra perianal region (10.5%). Concerning the time period between the onset of the symptoms and the start of the treatment, in 57.9% of the patients, the total period was five days, in 31.6% of the patients it was 6–10 days, while 10.5% of the patients received the treatment 11–15 days after exhibiting the symptoms. With regard to local signs of skin inflammation, 76% of the cohort were presented with redness, swelling, impaired function, and severe pain, while locally increased temperature was detected in 60.5% of the patients, induration in 42%, and crepitation in 39.5% of the affected individuals. Amongst patients with severe NSTI (extremely difficult wound care owing to soilage from stool, the anal sphincter muscle affection, patients with fecal incontinence, etc.) of the perianal and perineal regions, stoma operations were performed on 12 patients (31.6%), with mortality of 41.7%, while lethality was 7.7% in the group without stoma operations (Tables 2, 3, and 4).

In relation to the age of the patients, it was noted that, statistically, there was a significantly higher lethality rate in the group of people aged over 60 years ($p = 0.022$), with more than 10 days from the onset of symptoms to treatment ($p = 0.025$), with perianal localization ($p = 0.024$) and stoma procedure ($p = 0.022$). The overall lethality rate in our series was 18.3%, or the total of seven patients, out of which there were five male (13.1%) and two female (5.2 %) patients.

Table 2. The univariate analysis of sex and age as risk factors for fatal outcome

Characteristics		Survivors		Non-survivors		OR	95% CI	p
		n	%	n	%			
Sex	Male	18	78.3	5	21.7	1	/	/
	Female	13	86.7	2	13.3	0.554	0.093–3.312	n.s.
Age (years)	20–29	2	100	0	0			
	30–39	7	100	0	0			
	40–49	12	92.3	1	7.7			
	50–59	6	66.7	3	33.3			
	60–69	4	57.1	3	42.9	3.314	1.187–9.250	< 0.05*

* Statistically significant difference
n – number of patients; OR – odds ratio; CI – confidence interval; n.s. – not significant

Table 3. The time from the onset of symptoms and length of hospitalization as predictors of fatal outcome (univariate logistic model)

Variable		Survivors		Non-survivors		OR	95% CI	p
		n	%	n	%			
Time from the onset of symptoms (days)	< 5	19	86.4	3	13.6			
	5–10	11	91.7	1	8.3	0.576	0.053–6.233	n.s
	11–15	1	25.0	3	75.0	19.000	1.454–248.237	< 0.05*
Length of hospitalization (days)	< 10	5	62.5	3	37.5			
	10–15	6	100	0	0.0	0.000	0.000–0.000	n.s
	16–20	10	83.3	2	16.7	0.333	0.041–2.686	n.s
	> 20	10	83.3	2	16.7	0.333	0.041–2.686	

* Statistically significant difference

Table 4. Univariate analysis of the risk factors of death in NSTI of the perineal and perianal region

Variable		Survivors		Non-survivors		OR	95% CI	p
		n	%	n	%			
Diabetes mellitus	No	18	85.7	3	14.3	1	/	/
	Yes	13	87.5	4	23.5	1.846	0.352–9.692	n.s
Obesity	No	19	90.5	2	9.5	1	/	/
	Yes	11	68.8	5	31.3	4.318	0.714–26.127	n.s
Alcoholism	No	24	85.7	4	14.3	1	/	/
	Yes	7	70.0	3	30.0	2.571	0.462–14.324	n.s
Perianal localization	No	2	40.0	3	60.0	1	/	/
	Yes	29	87.9	4	12.1	0.092	0.012–0.730	< 0.05*
Genitourinary localization	No	8	80.0	2	20.0	1	/	/
	Yes	23	82.1	5	17.9	0.870	0.140–5.402	n.s
Extraperianal localization	No	29	85.3	5	14.7	0.172	0.020–1.522	/
	Yes	2	50.0	2	50.0	1	/	n.s
Stoma procedure	No	24	92.3	2	7.7	1	/	/
	Yes	7	58.3	5	41.7	8.571	1.357–54.150	< 0.05*
Number of operations	≤ 3	16	88.9	2	11.1	1	/	/
	≥ 4	11	68.8	5	31.3	3.636	0.595–22.234	n.s

* Statistically significant difference

DISCUSSION

Concerning the distribution of the initial infection of the anorectal and urogenital region, the data in literature emphasize more prominent cases of the perianal rather than perineal NSTIs with ratios of 50% : 25%, and 71% : 35.6%, reported by Elliott et al. [15] and Hakkarainen et al. [16], respectively. In our study, infection occurred in the perianal region in 86.8% of the cases (abscesses, phlegmons, states following an injury, etc.), which simultaneously represented a risk factor for the ultimate outcome of the treatment, with the statistically significant increase of mortality by 0.024. Initially, extraperineal localization was found in four (10.5%) patients, which was then extended to the perianal region. Out of the four patients, in 5.2%, or two patients, NSTI occurred in the lower part of the front abdominal wall, and in 2.6%, or one case each, in the gluteal region and the back side of the upper leg. In two of these patients, infection followed perforations of the rectum and sigma, while the other patients indicated previous injuries with existing hematomas of the gluteal region and the region of the front abdominal wall. The literature data on the existence of NSTI with different localizations, occurring through the perforation of the hollow organs of the abdominal cavity, have been mostly presented as rare case reports [1, 17–23]. In relation to the origin of NSTI, Martinschek et al. [9] present the data on 55 patients where the infection was initially localized on lower extremities in 63.2%, on the anterior abdominal wall in 30.9%, and on the perineum in 14.5% of the cases. Mishra et al. [24] stated that the most common places of occurrence were the extremities, i.e. in 36–55%, thorax and abdomen, i.e. 18–64%, and the perineum, up to 36% of cases. Yilmazlar et al. [3] published a retrospective study which involved 67 patients. In 50.7% of the patients, the infection was localized in the anorectal and urogenital region, in 30% on the skin of the extremities, and in 19.4% on other locations (conditions after trauma, post-operative wounds, etc.). In the same study, 64% of the patients had a disseminated form of NSTI, while only 36% of them had a localized form. They showed a high percentage of disseminated infections originated from the perianal and perineal region, which was explained by late diagnosis. Most probably, due to the inconvenient location of the initial infection, the patients hesitated to see a physician [25–28]. The NSTI spread in the anogenital region is considered to be 2–3 cm per hour, in the direction of the anterior abdominal wall, ischiorectal fossa, gluteal region and thigh, explained by the fascial anatomy of the perineal region and pelvic floor. Due to this rapid spreading of the infection, it is clear that timely diagnosis is a prerequisite for successful treatment. Infection with necrosis of male genital region is

mostly localized at the level of the skin and subcutaneous tissue, due to excellent vascularization, and the existence of resistant tunica vaginalis. In cases of disrupted Colles' fascia, the infection spreads towards the ischiorectal fossa, gluteal region, and thigh [9, 29, 30]. With regard to the sex, NSTI of the perianal and perineal region is more frequent in men, with a greater mortality rate than in women, which was also confirmed in the results of our study. Chinchilla et al. [30] present findings that there is significantly greater mortality in people older than 80, which is similar to the results presented by Glass et al. [31]. The results of our study show that people older than 60 have a higher risk of lethal outcome. The age of the patient represents a risk factor for the final outcome of the treatment. However, in certain studies, the age risk limit is different, dependent on the number of examined patients, as well as on the comorbidity present [11, 15]. The time period from the onset of the symptoms to the treatment also represents a significant risk factor, dependent on the NSTI localization and the present comorbidity. Early diagnosis and surgical treatment is mandatory for successful outcome; otherwise, development of clinical signs of sepsis is probable. Taking into account that NSTI is often accompanied by the state of sepsis, the treatment includes the principle of the so-called "source control." In 2002, Schein et al. [32] and Marshall et al. [33] introduced the principle of "source control", which included treatment measures (drainage, debridement, and tissue decompression) with the aim of eliminating the source of infection, preventing further spreading and restitution of anatomic structures and function of the affected region. All the patients in our study underwent the principle of "source control." Boyer et al. [34] published their study results, including multivariate analysis, according to which the time from diagnosis to surgical treatment exceeding 14 h in patients with septic shock was independently associated with hospital mortality. Kalaivani et al. [10] indicated that in all patients with statistically significant higher lethality rate the average length of time from the onset of symptoms to treatment was 13.5 days, which is similar to the results in our study. It is clear that lethality is directly related to the length of period from symptom occurrence to the surgery. Length of hospital stay, according to literature and our experience, does not show a statistically significant difference in lethality, and does not represent a risk factor for the treatment outcome [10, 16, 30].

In many studies, up to 82% of patients show comorbidities: diabetes mellitus (DM), obesity, alcoholism, smoking, immunodeficiency, malnutrition, and low socio-economic status [33]. A systematic review of Angoules et al. [4] analyzed 12 studies with 451 patients, where DM was the predominant risk factor in 31%, smoking in 27%, alcoholism in 17%, cirrhosis in 8%, HIV-positivity in 6%, various stages of malignancy in 3%, and taking of corticosteroids and chronic kidney insufficiency in 3% of the cases. Other rare risk factors presented in the same study were angina pectoris in 2% of the cases, chronic liver insufficiency in 2%, chronic obstructive pulmonary disease in 1.3%, peripheral vascular disease in 1.3%, and esophageal varices in 1.1% [4]. Lethality rates have been reported to be statistically significantly higher in the presence of elevated serum creatinine and first debridement 24 hours after admission to the hospital [10]. Lee et al. [7] observed 46 patients with monomicrobial necrotizing fasciitis and found that lethality was significantly higher among patients with chronic liver disease, chronic renal failure, reduced serum albumin values, thrombocytopenia, and longer stays in the intensive care unit, as well as in the group of patients who required mechanical ventilation. We found that 73.7% of patients presented with a variety of known risk factors, the most common of which being DM, in 44.7%, followed by obesity with 42%, and alcoholism with 35.7%. It is obvious that risk factors are present in more than two thirds of patients with NSTI, and the most frequent among them is DM. This should be kept in mind during the treatment [11]. Irrespective of the presence of a high percentage of different comorbidity states, the data in literature and the results of our study do not present a statistically significant lethality increase in people who suffer from DM, obesity, and alcoholism [6, 7]. In treatment of severe forms of NSTI, it is often necessary to create a stoma. In a previously published results of a retrospective study of NSTI treatment in 67 patients, 24 of them, or 35.8%, had a temporary stoma, but without a statistically significant lethality increase [3]. Similarly, we performed a stoma surgery on 12 out of 38 patients, indicating that a stoma surgery can be expected in one third of patients with NSTI of the perianal region. In our study, however, performing a stoma surgery represented a risk factor with a significantly greater lethality rate compared to patients who did not have a stoma surgery performed, i.e. by $p = 0.022$. Data from literature on the mortality rate in the treatment of NSTI are quite different, which is probably a consequence of different numbers of patients recruited, consideration of various clinical characteristics, and statistics. Literature data and the data from our study are shown in Table 1. Clearly, as an extremely dangerous infection, NSTI should be identified and treated as early as possible.

Limitations of our study are the following: the data were retrospectively collected from patient files, and small number of patients

CONCLUSION

NSTI is a life-threatening infection, characterized by widely spread necrosis of the skin, subcutaneous adipose tissue, fascia and muscle. One of the most common localizations of the infection is the perianal and perineal region. Patients' age, time passed between the onset of symptoms and the initiation of treatment, perianal localization, and stoma creation were related with higher lethality risk.

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Некротизирајућа инфекција меких ткива перианалне и перинеалне регије – и даље смртоносна инфекција

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САЖЕТАК

Увод/Циљ Некротизирајућа инфекција меких ткива представља по живот опасно стање, које се карактерише широким захватањем коже, поткожног масног ткива фасције и мишића.

Циљ ове студије је да одреди факторе ризика за настанак леталитета због некротизирајуће инфекције меких ткива перианалне и перинеалне регије код свих пацијената третираних у здравственој институцији терцијалног нивоа.

Методе Приказана је ретроспективна серија од 38 пацијената са некротизирајућом инфекцијом меких ткива перианалне и перинеалне регије у периоду од јануара 2007. до децембра 2014. године. Анализирани су следећи подаци: пол, старост, присуство фактора ризика (дијабетес мелитус, гојазност, алкохолизам), локализација инфекције, дужина трајања симптома, дужина хоспитализације, број изведених операција, извођење стоме и исход лечења.

Резултати Уочен је значајно већи леталитет у групи пацијената старијих од 60 година живота ($p < 0,05$), код оних са више од 10 дана трајања од почетка симптома до третмана ($p < 0,05$), са перианалном локализацијом ($p < 0,05$) и код испитаника са изведеном стомом ($p < 0,05$). Укупан морталитет износио је 18,4%.

Закључак Висок ризик за настанак леталитета регистрован је у групи старијих пацијената, код оних са дужим периодом од почетка симптома до третмана, перианалном локализацијом инфекције и изведеном стомом.

Кључне речи: некротизирајућа инфекција меких ткива; некротизирајући фасциитис; Фурнијеова гангрена; перианална регија; перинеална регија