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Necrotizing soft tissue infection of the upper extremities in patients with diabetes mellitus in a tertiary care center-a retrospective study

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ABSTRACT

Background: Necrotizing soft tissue infection (NSTI) of the upper extremities is a rare, but potentially life-threatening infection in patients with type 2 diabetes mellitus (T2DM). We analyzed the clinical characteristics and the outcome of NSTI of upper extremities in these patients.
Methods: This was a retrospective study analyzing the clinical characteristics and the outcomes of 33 T2DM patients with NSTI of upper extremities, who were treated in the department of hand surgery between January 2011 and December 2017.
Results: Predisposing factors for NSTI were recognized in 16 (48.5%) patients. Eleven (33.3)% patients had septic shock while ten (30.3%) had acute renal insufficiency at the time of presentation, of which six required dialysis. The mean glycosylated hemoglobin was 9.6(±2.6)% and the random plasma glucose at admission was 271(±96) mg/dl. Monomicrobial infection was seen in 16(49%) patients and polymicrobial infection in 9(27%) patients. Gram-positive causation was found in 25(66%) patients. Twelve (36.4%) patients required amputation, six (18.2%) of which were major. Death occurred in more than one-fifth (21.2%) of the patients during treatment.
Conclusion: Necrotizing soft tissue infection of the upper extremities in T2DM is associated with increased risk of severe infection, amputation and mortality.

1. .Introduction

Necrotizing soft tissue infection (NSTI) is a rapidly progressive form of pyogenic infection which is characterized by necrosis of the subcutaneous tissues and superficial fascia. It is associated with serosanguinous exudates and lack of bleeding from the underlying muscle [1,2]. NSTI is mainly categorized into two groups, type-I and type-II. Type-I is caused by a polymicrobial infection, whereas type-II is caused by group-A streptococcus [3,4]. T2DM is an important predisposing factors for NSTI, which constitutes about 40–45% of cases described in literature [5].

NSTI of upper extremities in patients with T2DM is a rare entity [6,7]. It is also recognized as 'tropical diabetes hand syndrome' or 'diabetes hand sepsis syndrome' since this type of infection has been mainly reported in tropical countries [8,9]. The most common presenting symptoms of NSTI include edema, erythema, severe pain, tenderness, skin bullae and necrosis [10,11]. It can sometimes be fulminant, which may lead to severe sepsis, multi-organ dysfunction and gangrene [12,13].

NSTI of upper extremities is a surgical emergency. The diagnosis is almost always made clinically. Sometimes, it can be difficult to differentiate NSTI from cellulitis and deep palmar abscesses. In such cases, a frozen section or biopsy obtained during surgical exploration may help in establishing the diagnosis [14,15]. Early clinical recognition, prompt surgical debridement and intensive medical care are essential components in the management of NSTI. Delay in treatment is associated with a very high mortality rate, varying from 12.1 to 41.6% along with a rate of amputation ranging between 4.1 to 27.8% [16–18]. This condition continues to pose a problem in Asian as well as African countries [18–20]. This infection is more common and more severe in patients with T2DM, leading to increased amputations, mortality and poor clinical outcomes [21,22].

This study aims to determine the clinical presentation, the microbiological profile and the outcome of treatment in patients with NSTI of upper extremities in patients with T2DM.

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2. .Methods

This is a retrospective study which included 33 patients of T2DM with NSTI of the upper extremities, treated in the department of hand surgery between January 2011 and December 2017. The diagnosis of NSTI was mainly clinical and further diagnosis was confirmed at the time of surgery from the presence of the typical findings: serosanguinous fluid on incision of the deep fascia, which was non-viable, friable and yellowish with no haemorrhage of the underlying muscle [21,22]. If there was any doubt regarding the diagnosis, a frozen biopsy was taken at the time of debridement for confirmation [23,24]. A wound swab was also obtained for aerobic microbiological cultures in all patients and antibiotic susceptibility was assayed in culture-positive samples.

Patient information was obtained from the centralized hospital electronic database. The following data was captured using a proforma: age, gender, co-morbidities, site of involvement of NSTI, clinical signs, predisposing factors, history of previous surgical intervention, delay in presentation (due to a delay in referral or a travel-related delay) from the onset of symptoms, the biochemical investigations, types of surgical procedures, duration of hospitalization, complications and clinical outcomes. Glycaemic profile - random plasma glucose at admission and glycated hemoglobin (HbA1c) - was included in the study. Venous plasma glucose, serum creatinine and albumin were measured by using reagents supplied by Roche (Manheim, Germany) on the Roche Modular P 800 system. HbA1c was measured by an ion-exchange chromatography (HPLC) on the BioRAD VARIANT II Hemoglobin Testing System (Hercules, CA, USA) (CV-3.1%). Patients with no previous history of diabetes were labelled as having diabetes based on HbA1c $\geq$ 6.5% and a persistence of hyperglyceamia during follow-up [25].

Early surgical debridement was performed in all patients with an initial diagnosis of NSTI. All patients were initially started on piperacillin and tazobactam, an intravenous board spectrum antibiotic. Patients with methicillin resistant staphylococcus aureus (MRSA) infection were treated with combination of linezolid and rifampicin for a period of three weeks. Good glycaemic control and standard wound care protocol were followed in all patients during the period of hospitalization. Secondary reconstructive surgery was performed either with split-thickness skin grafting (STSG) or by tissue transfers (flap cover) when the wound was ready for grafting. Amputation was considered in the setting of osteitis or difficulty in saving the limb due to an ascending NSTI. Below-elbow and trans-humeral amputations were defined as major amputations, while digital amputations were defined as minor amputations.

This study was approved by Institutional Review Committee, IRB: 11397, dated: 27/06/2018.

3. .Statistical analysis

Analysis was performed using SPSS software package (version 23, IBM Corp. in Armonk, NY). Data was expressed in mean ($\pm$SD). Spearman correlation test was used to determine the relationship between continuous variables. Fisher's exact test and Chi-square test were used to determine the association between categorical variables. A p-value of $\leq$0.05 was considered significant.

4. .Results

A total of 33 patients with T2DM and NSTI of upper extremities - treated in our institution between the year 2011 and 2017 - were included in this study. Three patients (9%) had newly detected T2DM. The mean duration of DM was 70 $\pm$ 58 months (range 0–240 months). The mean age was 51 $\pm$ 12 years. Twenty-five (76%) were male and the remaining 8(24%) were female. Details of the demographic profiles and biochemical investigations are shown in Table-1. The mean random plasma glucose was 271 ($\pm$96) mg/dl ,while the mean HbA1c was 9.6 ($\pm$2.6%). There were no obvious predisposing factors identified in half of the patients. The assessment of predisposing factors was primarily based on the patient's history. A prior history of antecedent trauma was identified in 16 (48.5%) patients. An iatrogenic injury was identified in 3(9%); one patient each had intravenous contrast extravasation, intravenous fistula for hemodialysis and venous thrombophlebitis. A prior history of surgical intervention elsewhere was noted in 10(30.3%) patients. Clinical findings at the time of presentation included soft tissue swelling in 83%, erythema in 76%, severe pain in 70% and skin bullae/necrosis in 65% of the patients. (Clinical photographs of necrotizing soft tissue infections are shown in Fig. 1A, 1B and 2). Involvement of the arm and forearm were seen in 20(60.6%) patients. De-

Table 1
Demographic profile of patients with necrotizing soft tissue infections.

Particulars	(N = 33)
	Mean (SD)
Age (in years)	51 (12)
Male	25 (76%)
Female	8 (24%)
Duration of diabetes in months * **[Median(min-max)]**	70 (58) 60 (0–240)*
Delay in presentation (days)	10(7)
Duration of hospitalization (days)	15.5 (8)
Co-morbidities	**N(%)**
Presence of predisposing factor	16 (48.5)
Presence of septic shock	11 (33.3)
Acute kidney injury	10 (30.3%)
Hypertension	13 (39.4)
Chronic kidney disease	6 (18.2)
Coronary artery disease	5 (15.2)
Biochemistry parameters	**Mean (SD)**
HbA1c (%)	9.6 (2.6)
Random plasma glucose (mg/dl)	271(96)
Haemoglobin (gm/dl)	10.7 (2.5)
Total Count (1000/per cu.mm)	16.26 (9.7)
Creatinine (mg/dl)	1.66 (1.3)
Sodium (mEq/L)	131.7 (5.6)
Albumin (gm/dL)	2.6 (0.7)
Microbiology parameters	**Mean (%)**
Polymicrobial infection	9 (27)
Monomicrobial infection	16 (49)
MRSA infection	6 (24)

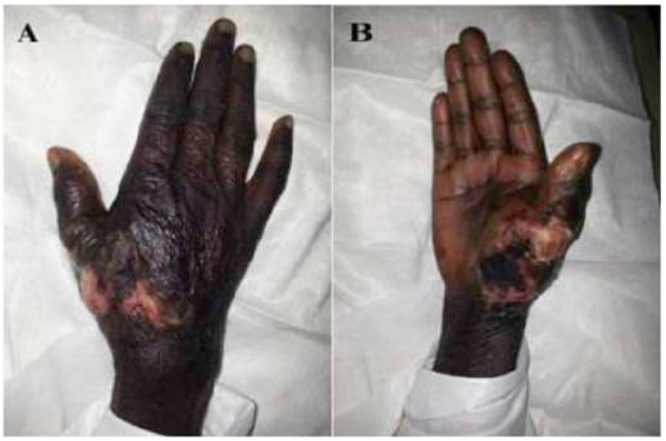

Fig. 1. A and 1 B: Flexor pollicis longus (FPL) tenosynovitis evolving into necrotizing soft tissue infection in a 63-year-old male admitted with poorly controlled type 2 diabetes mellitus.

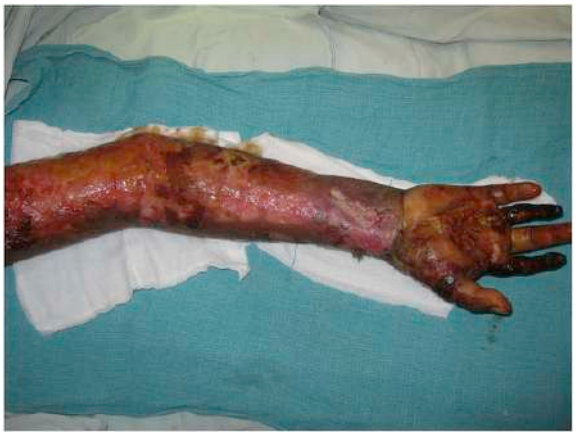

Fig. 2. Necrotizing soft tissue infection in a 55- year-old male with poorly controlled type 2 diabetes mellitus.

tails of the anatomical distribution of necrotizing soft tissue infections are shown in Table 2.

Acute complications such as septic shock were detected in 11 (33.3%) patients. Ten (30.3%) patients had acute renal insufficiency at the time of admission, of which six required dialysis. A total of 12 (36%) patients required ICU admission. The mean delay in presentation to our center from the onset of symptoms was 10 (±7) days.

Extensive surgical debridement was performed in all the patients. The majority (76.1%) of patients underwent surgical debridement within 4–6 hours of hospitalization. A tissue biopsy was taken in 7(21.2%) patients during the time of surgical debridement, while two had frozen biopsies taken. Twelve (36%) out of 33 patients needed a minor or major amputation. Five patients (15%) had undergone major amputations, of which 4 patients had below-elbow amputations and one patient had a trans-humeral amputation. Reconstructive procedures were performed in 13(39.4%) patients. Ten patients had STSG grafts. A posterior interosseous arterial flap, a fillet flap and a delto-pectoral flap were used in one patient each .

Monomicrobial infection was found to be more common, which constituted about 16 (49%) patients , a polymicrobial infection was present in 9(27%), while no growth was seen in 8(24%) patients. A total of 38 different bacterial strains, of nine different species were isolated. Gram-positive isolates were found to be more common 25(65.8%). MRSA was isolated in 7(21.2%) patients with both mono- and polymicrobial infections. Details of the microbiological profile are shown in the Table 3.

Table 2
Anatomical distribution of necrotizing soft tissues infections.

Particulars	Diabetes	
	Number (33)	Percentage (%)
Fore-arm	20	60.6%
Arm	9	27.3%
Hand –Dorsal	15	45.4%
Hand –Volar	12	36.4%
Thumb and I web space	8	24.2%
Index and II web space	6	18.2%
Middle and III web space	2	6%
Ring and IV web space	2	6%
Little finger	3	9%
Mid Palmar	3	9%
Thenar	3	9%
Extensor Tendons	0	0

Table 3
Microbial isolates in patients with necrotizing soft tissue infections.

Particulars	Monomicrobial	Polymicrobial
	(N-16) N (%)	(N-22) N (%)
Staphylococcus aureus MSSA	3(18.7)	1(4.5)
MRSA	3(18.7)	4(18.2)
Coagulase-negative staph aureus	1(6.2)	1(4.5)
Streptococcus Viridans-alpha-hemolytic	0	0
Gr-A and B beta-hemolytic Streptococcus *	5(31.2)	2(9)
Other streptococcus (C + F + G)	0	3(13.6)
Enteroccous	0	2(9)
Enterobacter and E-coli	0	1(4.5)
Klebsiella	1(6.2)	3(13.6)
Pseudomonas	1(6.2)	0
Non-fermenting GNB	2(12.5)	2(9)
Proteus mirabilis	1(6.2)	2(9)
Citrobacter diversus	0	1(4.5)

*In patients with type 2 diabetes having monomicrobial infection, 4 had a group-A beta-hemolytic streptococcus infection while 1 had a group-B beta-hemolytic streptococcus infection; MSSA- Methicillin Sensitive Staphyococcus aureus , MRSA- Methicillin-resistant Staphylococcus aureus, GNB- Gram-negative Bacilli.

The mean duration of hospitalization was 15.5 (±8) days. A total of seven (21.2%) deaths were recorderd. The presence of septic shock at the time of presentation, surgical intervention in another hospital, the presence of predisposing factors, and the type of infection (monomicrobial or polymicrobial and MRSA positivity) were not found to be significantly associated with the duration of hospitalization. There was no significant association between death and the presence of predisposing factors, surgery in another hospital, and MRSA infection.

5. .Discussion

The study analyzed the demographic profile, predisposing factors, biochemical, bacteriological profile and clinical outcomes in terms of duration of hospitalization, mortality and the rate of amputation in patients with T2DM and NSTI of upper extremities. The mean random plasma glucose at admission was 271 (±96) mg/dl and average HbA1c was 9.6 (±2.6)%. A study by Sharma et al. has shown that patients with poor glycaemic control (random blood glucose of ≥180 mg/dl and HbA1c of ≥9%) were associated with more severe forms of infection and higher amputation rates [26].

The mean age of our study patients was 51 ± 12 years (range 28–81 years). In previous studies, NSTI of upper extremities was found to be more common in adults with ages ranging between 17 and 80 years. Most of the patients in this study were male, which may be because they engage in more manually intensive labor when compared to women in our reference population and therefore had a greater chance of being exposed to trauma. Occupation has a direct association between gender and development of NSTI [27]. However, a study by McLigeyo et al. has shown that women were more prone to developing NSTI due to trivial trauma sustained during household activities [28].

No obvious predisposing factors were recognized in 51.5% of patients. Similarly, many previous studies documented no obvious predisposing factors in more than 50% of patients with NSTI. Clinical findings at the time of presentation included soft tissue swelling in 83%, erythema in 76%, severe pain in 70% and skin bullae/necrosis in 65% of the patients. These clinical features were comparable with those from previous studies [10,29].

In this study, the overall monomicrobial infections were more common than polymicrobial infections. A gram-positive bacterial isolate was found to be more common than gram-negative ones. A study from Taiwan displayed a similar pattern of increased monomicrobial

and gram-positive infections [6]. The most common gram-positive isolates were staphylococcus aureus and streptococci. In our study, MRSA constituted about more than 50% of staphylococcus related NSTI. More recently, there have been reports of increase in MRSA related NSTI in the community-based studies [30,31]. The most common gram-negative bacterial isolates were Klebsiella, Proteus mirabilis and non-fermenting GNB.

In this present study, 12 (36.4%) patients were admitted in ICU, of which 69% required ventilator support and 54% needed inotropic support. An Australian study showed that more than 93% of patients with NSTI required ICU admission, of which 79% needed mechanical ventilation and 71% received inotropic support [32]. A similar study by Tillou et al. from USA reported a 61% admission rate ICU in patients with NSTI. In our study, the majority of patients (76%) had surgical debridement within 4–6 hours after admission to hospital [33]. Previous studies showed that early surgical intervention could reduce the amputation rate and survival rate in patients with NSTI [17,34,35]. A study by Kobayashi et al. showed that a delay in surgical debridement for more than 12 hours were associated with an increased number of surgical debridement, acute renal failure and septic shock [36]. In our study, five patients (15%) required second debridement. The amputation rate was 36%, of which 15% had a major amputation. In a previous series of diabetic hand infections, the amputation ranged between 16.2 and 39%. The study by Gonzalez et al. has showed the amputation rate to be more common among patients with deeper tissue infections, polymicrobial infection and renal failure [13]. In another series, amputation was found to be very high in patients with chronic kidney disease [37]. A few recent studies have reported very low amputation rates because of early identification and early surgical intervention [38]. Zhao et al. used the LRINEC score (Laboratory Risk Indicators for Necrotizing Fasciitis) for early recognition of NSTI [16]. In our study, the CRP was not estimated in most of the patients; therefore, we were not able to use the LRINEC score to differentiate NSTI from other soft tissue infections of the hands at the time of initial presentation.

The mean duration of hospitalization was 15.5 ±8days. In a similar study by Jalil et al. the duration of hospitalization was 13 days in patients with diabetic hand infections [38]. Overall deaths in our study was seven (21.2%). A similar study from Japan reported a mortality rate of 15.5% in patients with upper extremities necrotizing soft tissue infections. However, the mortality rate was found to be higher among patients with an age more than 70 years or having sepsis, liver dysfunction or renal dysfunction [39]. In our study, no significant association was found between death and delay in presentation, previous surgical procedure and types of microbes isolated.

6. .Limitations of the study

The follow-up outcome was not studied; there was a highly variable duration of follow-up among individual patients. The status of microvascular complications was not assessed given the retrospective nature of the study. Education and economic status was also not evaluated.

7. .Conclusion

Necrotizing soft tissue infections of upper extremities are one of the rare complications in patients with diabetes mellitus. Those with poor glycaemic control, delay in presentation and prior surgical intervention at another hospital are prone for more severe forms of infections.

Declaration of competing interest

None of the authors has any conflict of interest to disclose.

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