Egyptian Journal of Surgery Vol 26, No 2, April, 2007

ORIGINAL ARTICLE

FOURNIER'S GANGRENE: CLINICAL, BIOCHEMICAL, BACTERIOLOGIC, IMMUNOLOGIC STUDY AND TREATMENT OUTCOME

By
Saleh El Awady,[1] Wael Khafagy,[1] Mohamed Abd El-Raof,[2] Elham Ragab,[3] Mohamed Fareed[1]
[1] Surgery, [2] Mansoura General Hospital, [3] Clinical Pathology, Mansoura University Hospital, Egypt

Correspondence to: Saleh El Awady, Email: zadarm@yahoo.com

Aim: *Identify Fournier's disease associations, outcome and survival factors.*
Methods: *Fournier's gangrene patients (34) were treated between 2003 to 2006. Data were collected about medical history, physical findings, metabolic tests, bacteriologic typing, immunologic screening for T cell function, serum IL-2, ICAM-I and γIFN with their management.*
Results: *The disease had age range 3 – 67 years, polymicrobial nature, and low serum albumin (3.3 ± 0.6 mg/dl). Inadequate T-cell function (18255.3 ± 1641 CPM) and high ICAM-I, IL-2, γIFN (10.5 ± 0.7, 93.3 ± 1.6, 131 ± 2 pg/ml) were detected in Fournier's disease but serum IL-2 was relevant to outcome (P = 0.0001). The survival factors were patients' age (P = 0.0001), presentation timing (P = 0.001), both disease extent (P = 0.0001),septic shock(P = 0.01),severe SIRS (P = 0.001), serum albumin(P = 0.0001) and IL-2.*
Conclusion: *Fournier's disease is consistent with deviated metabolic status and immunologic dissonance, inciting local gangrenous process, these parameters are significant for disease outcome.*

Keywords: *Necrotizing fasciitis, immunologic dissonance, SIRS.*

INTRODUCTION

Fournier's disease is a necrotizing soft tissue infection of the perineum and genitalia that rapidly progress to gangrene,[1] with rising reports due to awareness and longevity.[2]

Necrotizing fasciitis elicits variable immune response (innate & adaptive), triggering cytokines and adhesive molecules activation.[3] The relative contribution of T helper 1 (Th1) and T helper 2 (Th2) cytokines determine the outcome, from eradication till systemic inflammatory response syndrome (SIRS).[4,5]

The Fournier's disease continues to challenge surgeons regarding its aetio-pathogenesis and management,[6] also its predictive and prognostic factors are still lacking (Fournier's gangrene severity index scoring(FGSIS).[7]

Recently, severe cases suffering from toxic shock or necrotizing fasciitis had higher frequencies of IL2, IL6, and TNF-alpha producing cells in their circulation compared to non-severe cases,[8] similarly Lungstras -Bufler et al.,[9] found significantly higher gamma interferon in Fournier's gangrene patients.

In the present work, thirty four Fournier's gangrene male patients were studied as regard their clinical, metabolic, bacteriologic, immunologic associations together with their prognostic value.

PATIENTS AND METHODS

From January 2003 till October 2006, 34 Fournier's

gangrene male patients admitted to Mansoura University hospital and Mansoura General Hospital were included in a prospective study with the control group of 18 age matched, healthy male, blood donors. Patients were informed about the study and if accepted they signed a written consent.

The clinical data include age, medical history (co-morbid, predisposing illness) and consultation time. The disease extent was according classified to Mansoura Colorectal Surgery Unit (M-CRSU) policy for disease extent created by modifying burn score= as, isolated (penis – scrotum – scrotum till coccyx), limited (all perineum – a region of ischial tuberosity) and extensive (more than a region of ischial tuberosity- beyond the perineum) (Figs 1,2).

The medical, surgical, biochemical, bacteriological, immunological procedures and statistics.

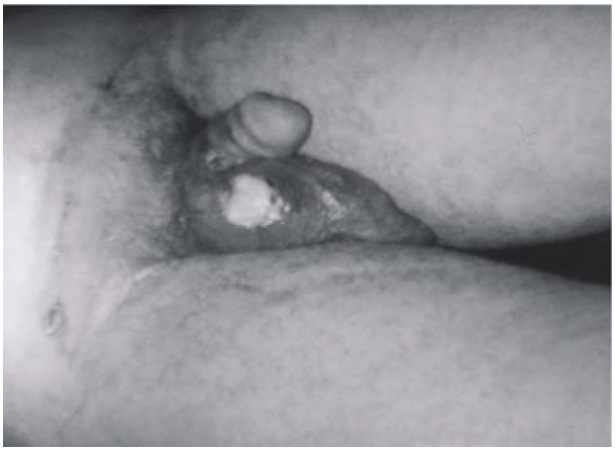

Fig 1. Isolated Fournier's gangrene (active stage).

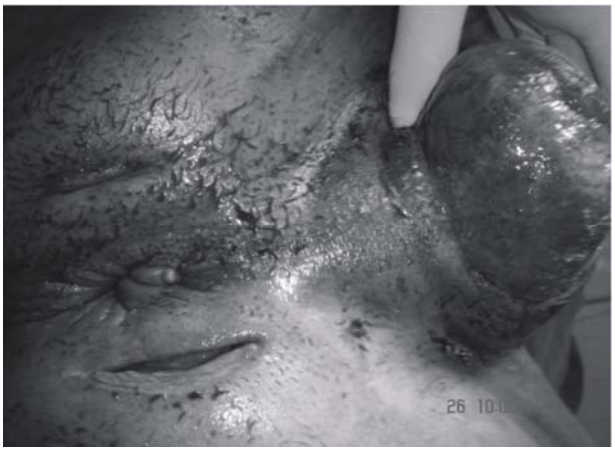

Fig 2. Cancer rectum complicated by extensive Fournier's gangrene (healing stage) and perineal fistulae.

The patients received their management in the surgery departments (within the Isolation unit-that had special barriers, aprons, masks, gowns and gloves under Mansoura University Microbiology Diagnostics and Infection Control Unit) unless complicated with septic shock or SIRS "mild & sever" (defined and staged according to the American College of Chest Physicians and Society of Critical Care Medicine Consensus Panel in 1991 after Sharma et al.[10] when they were transferred to surgical intensive care unit.

The medical treatment: was stepwise resuscitation and 3rd generation cephalosporisn together with metronidazole, then specified according to culture and sensitivity.[11]

The surgical treatment involved:

1. Aggressive excision of all non viable tissues every 48 hours under short time anesthesia "when indicated" till all remaining tissues were adherent and viable, only skin grafts were required in 6 patients.[12]
2. Resection of gangrenous testes (2 patients) and gangrenous penis (2 patients).
3. Suprapubic cystostomy for urinary extravasations (2 patients).
4. Colostomy in morbid obese (2 patients)," had massive anorectal infection protracted from defecation."

The metabolic study: estimated at admission serum albumin, hemoglobin and creatinine.

The bacteriologic study: involved (a) sample collection as pus from the wound depth or wound edges swabbing, (b) direct Gram film staining and solid media culture (5% sheep blood, chocolate agar) aerobic & anaerobic in gas pack jar,[13] (c) colony identification morphologically, Gram stain and antibiotic sensitivity testing using disc diffusion method.[14]

The immunologic study: entailed (a) Blood sample collection during the first 12 hours, that centrifuged at 1800 rpm for 20 minutes and serum storage at –70°C till assay. (b) Detection of serum interleukin-2 (IL2)called T cell growth factor as a measure of CD4 T-helper,[15] gamma interferon (γIFN)a marker of Th2 immune response, (16) intercellular adhesive molecule-1 (ICAM-1) an indicator of T cell homing at the infection site (4) using the enzyme linked immunosorbent assay.[15] The kits are supplied from Diaclone E research company, France, E mail: info@ Diaclone.com. Results are expressed as picogram per milliliter (pg/ml). (c) Detection of T-lymphocytes activity (This is an index for T cell function)[18] using in vitro peripheral lymphocytes culture with phytohaemagglutenin mitogenic stimulation, that stimulation is studied by measuring DNA synthesis as evidenced by titrated thymidine uptake of the proliferating cells. The results are expressed as count per minute (CPM).[19]

The patients outcome was: morbidity rate {local (L) massive anorectal infection protracted from defecation & urinary extravasations& gangrenous testes & gangrenous penis, systemic (S) Septic shock, SIRS (mild & sever)=, local & systemic (L+S)} and the finite end point was the in-hospital mortality {survive – died}.

Data were computed using Microsoft statistical software package version 10 {SPSS, 10}, for comparison the Chi-square, student t-test and one way ANOVA test were used, and the binary logistic regression for prediction, $P \leq 0.05$ is significant.

RESULTS

The evaluated thirty four=(34) male patients had their mean age 40.5 ± 14.7 years (range 3 – 67) and the mean duration till presentation was 3.7 ± 1.8 days (range 1–8). Seventeen patients (50%) had co-morbid diseases mainly diabetes as thirteen (76.5%) out of the seventeen (50%) were diabetics, and the predisposing illness was commonly anorectal sources; 13 (38.2%), while the necrotizing process extent was mainly limited;[19] (55.9%) Table 1. & (Fig 1).

Table 1. Patients "clinical data".

		No.	%
Co-morbid disease	**+ve**	**17**	**50**
	Diabetic	13	38.2
	Cardiac	4	11.7
	Hepatic	4	11.7
	Renal	4	11.7
	-ve	**17**	**50**
Disease source	**Idiopathic**	**6**	**17.6**
	Known	**28**	**82.4**
	Ano-rectal	13	38.2
	Uro-genital	9	26.5
	Dermatologic	6	17.6
Disease extent	Isolated	9	26.5
	Limited	19	55.9
	+ Extensive	6	17.6

17 patients were co morbid diseases –ve, 17 patients were co morbid diseases +ve [12 patients had single Co- disease & 4 patients had two Co- diseases&1 patients had three Co- diseases].
Anorectal source: Haemorrhoidectomy (5), Fistulectomy (3), Abscess (3), Cancer rectum (2)
Urological: Post TUR (4), Hydrocele surg (1), Varicocelectomy (3), circumcision (1).
Dermatologic:Perineal laceration (2), scrotal hematoma (2), Burn (1), IM injection (1) + Extensive:ant.abdominal wall (2), Thigh (2), buttocks (2).(Mansoura CRSU score).

The bacteriologic study defined 86 isolates [aerobic (4) patients, anaerobic (7) patients and mixed (23) patients] with E coli & group A streptococci predominance each;15 patients (44.1%).The isolates per case were 2–3 organisms ranked as 2 organisms in 10 patients {5 identical-5 different] &3 organisms in 18 patients{10 identical-8 different] &4 organisms in 15 patients{3 identical-12 different}&5 organisms in single patient , Table 2.

Table 2. Patients" bacteriologic study".

		No	%
i) Aerobic	E-coli G –ve	15	44.1
	Group A strept G +ve	15	44.1
	Pseudomonas G –ve	9	26.4
	Staph aureus G +ve	6	17.6
	Citrobacter G –ve	6	17.6
	Klebsilla pneumonia G –ve	6	17.6
	Proteus mirabilis G –ve	3	8.8
ii) Anaerobic	Bacteroids fragilis	8	23.5
	Clostridium	6	17.6
	Lactobacillus	6	17.6
	Peptostreptococus	6	17.6

Isolates = 86: 2 organisms in 8 patients & 3 organisms in 10 patients & >3 organisms in 16 patients. Aerobic (4) patients, anaerobic (7) patients and mixed (23) patients.

The patients had low serum albumin level (mean ± SD 3.3 ± 0.6 mg/dl),but statistically in the Fournier's gangrene patients the serum levels of IL-2 , ICAM-1 γIFN tended to be greater (P = 0.0001) with lowered T cell function (P = 0.0001) compared to control group (Table 3).

Table 3. Comparison of immunological parameters between cases and controls.

		Cases (n=34) Mean ± SD	Controls (n=18) Mean ± SD	P value
T cells	(CPM)	11347.1 ± 3332.3	18255.1 ± 1641	0.0001*
ICAM-1	pg/ml	35.9 ± 5.7	10.5 ± 0.7	0.0001*
IL-2	pg/ml	309.6 ± 34.1	93.3 ± 1.3	0.0001*
δ IFN	pg/ml	368.4 ± 11.3	131.1 ± 2.1	0.0001*

Student t test is used.

Patients with co- morbid diseases had more extensive disease compared to those without (P = 0.02), otherwise the clinical, bacteriologic and immunologic data were insignificant. Surgical debridements were performed 61 times (mean was 1.8, range 1-5), 15 patients required single

debridement and 19 patients required multiple debridements (mean was 2.4, range 2-5).

The disease morbidity were 22 events (63.4%) (Occurred only in twenty patients) [Septic shock; 4, 11.7%&mild SIRS; 6, 17.6% & sever SIRS; 4, 11.7% & local; 8, 23.5%] and by its grades (L, S, L+S) achieved significant difference with T cell function (P = 0.0001), serum IL-2 (P = 0.0001) and γIFN (P = 0.0001), also with serum albumin P = 0.0001 Table 4.

Table 4. Morbidity association with the immunologic parameters and serum albumin.

	Systemic (n=14)	Local (n=8)	Systemic & Local (n=2)	No Morbidity (n=14)	P value
T cells (CPM)	10192.3 ± 2863.6	12700.0 ± 226.7	5200.0 ± 130.9	13976.9 ± 530.8	0.0001*
ICAM-1 pg/ml	36.3 ± 0.8	36.2 ± 1.3	36.2 ± 0.4	35.3 ± 9.2	0.94
IL-2 pg/ml	297.3 ± 23.2	307.5 ± 11.0	252.5 ± 17.1	340.0 ± 17.3	0.0001*
δ IFN pg/ml	364.2 ± 7.1	368.7 ± 4.4	348.0 ± 6.2	378.8 ± 2.9	0.0001*
Albumin mg%	2.8 ± 4.0	2.6 ± 0.1	1.9 ± 8.8	3.7 ± 0.2	0.0001*

One way ANOVA test P ≤ 0.05 is significant.

The mortality rate was 6 patients, 17.6% [4 patients due to multi-organ dysfunction syndrome " MODS" and two due to single organ dysfunction syndrome " SODS" acute liver cell failure]

Patients who survived were younger [mean ± SD, 36.17 years ± 12.18] than those who died [mean ± SD, 60.66 years ± 5.28] (P = 0.0001), similarly the difference in duration before consultation between both groups was significant (P = 0.0001). Also the statistically significant parameters for bad prognosis were extensive disease (P = 0.0001), local complications (P = 0.01), septic shock (P = 0.0001) and sever SIRS (P = 0.0001). Survived patients had higher serum albumin, serum IL-2 [3.3 ± 0.5 mg/dl, 321.5 ± 22.1 pg/ml respectively] compared to those died [1.9 ± 0.1 mg/dl, 251.6 ± 14 pg/ml] and the differences were statistically significant (P = 0.0001) Table 5.

Table 5. Significant survival factors.

		Survivors (n=28)	Dead (n=6)	P value
Age (years)	+	36.17 ± 12.18	60.66 ± 5.28	0.0001*
Time till consultation (days)	+	3.00 ± 1.11	7.00 ± 1.04	0.001*
Disease extent	‡			
	Isolated	8	1	
	Limited	18	1	0.0001*
	Extensive	2	4	
Disease morbidity	‡			
	Local	4	4	0.0001*
	Septic shock	2	2	0.01*
	Severe SIRS	1	3	0.001*
Metabolic	+ Serum albumin **mg%**	3.30 ± 0.47	1.93 ± 0.11	0.0001*
Immunologic	+			
Serum IL-2 pg/ml		321.96 ± 22.12	251.66 ± 14.03	0.0001*

+ Data expressed as mean ± SD, student t test is used. ‡ Chi-square test.
4 patients due to "MODS" and two due to "SODS" acute liver cell failure.

Neither the bacteriologic typing nor the frequency of surgical debridement {survivors underwent 1-3 times, the mean was 2.6, single attack in 12 & two attacks in 13 & three attacks in 3 and non survivors underwent 1-5 times, the mean wasv2.3, single attack in 3 & three attacks in 2 & 5 attacks in single patient .P=0.68} had affected the outcome, also the logistic regression of the studied parameters was insignificant.

DISCUSSION

Fournier's gangrene (FG) is the most serious life threatening infection of the perineum and genital

organs,[21] mostly reported in an ever aging population,[20] and this study detected wide age range similar to[22] but our patients had lower average age as.[23]

Contradicting FG initial description, this study revealed co-morbid diseases conjugation similar to[24] and identifiable sources of infection like.[25]

In accordance with most studies,[26,27] the bacteriologic study found the disease polymicrobial and reflecting the source of infection 'E coli' (anorectal), 'group A streptococci' (urogenital).

Essentially this study declared novel observations which had not been previously reported (a) FG association with inadequate T cell function reflecting both poor microbial presentation and effector T cell tolerance related to T-cell anergy, apoptosis, decoy of interleukin receptors or inhibitory cytokines release.[28] (b) FG was consistent with immunologic dissonance marked as (i) high γIFN (stimulate innate and Th2 cytokines, Th2 subset of CD4 Th cells) (ii) raised ICAM-1 (T-cell recognition & co-stimulation, migration and homing) (iii) elevated IL-2 (clonal expansion of the committedCD4 Th cells).[29,30] Hence FG is a polarized Th2 immune response.

This study recorded high disease morbidity as reported by.[17] The systemic morbidity is related to the cytokines released, inciting wide spread endothelial and parenchymatous cell injury,[31] while the local morbidity is attributed to the malignant intravascular inflammation.[32]

The association of morbidity rate with serum IL-2, γIFN and T cell function might be related to maladaptive cascade mediators release acting autocrine & paracrine,[33] inciting auto destructive process through hypoxic & histotoxic hypoxia, apoptosis [anti- for inflammatory cells & pro- for host cells] and immune intolerance [Th1 suppression & Th2 excitation].[34]

Still the disease has an inherently high mortality reaching in our study 17.6%, that was less than previously reported (53%) by.[35]

The Triad for critical illness outcome is "patient" [co-morbid disease, its response to treatment], "disease" [nature & severity] and "treatment" given,[36] herein, significantly survivors were younger than who died as observed by,[37] = contradicting.[38] That's might be related to age associated immunesenescence, malnutrition and immobilization, also the survivors searched for medical consultation earlier than the unsaved. This also reported by,[39] of course early consultation enabled detection of early disease and co-morbid diseases management, But the necrotizing process in who died was extensive as reported by[40] but[41] found the association equivocal and[42] denied that association.

Statistically, the co-morbid diseases, infection sources and bacteriologic typing didn't affect the survival going with many reports,[43,44] but the systemic and local complications worsened the prognosis similar.[38]

In accordance with,[7] this study found survived patients had significantly higher serum albumin consequent to better patient's metabolic reserve.

Noteworthy, FG predilected with immune dysfunction, and survived patients had higher IL-2 level, that's might be related to its functional role[45] in preventing and combating this devastating infection to be formulated as a cutoff point and added to Laor score, FGSIS-IL2.

The frequency of surgical debridment did not affect the survival, but[18] found greater mortality with increased frequency so disease managing should be multidisplinary (Local & Systemic) as[46] suggested.

The risk adjusted analysis of the relevant survival factors in this study using the logistic regression analysis were insignificant predictors of the outcome, similarly not all the risk scoring system Fournier's gangrene severity index scoring=(FGSIS) items were statistically significant as serum creatinine, co-morbid diseases also other findings were significant as body surface area involved, serum IL-2, so surgical risk scale[mode of presentation, co-morbidity and procedure magnitude "sepsis related organ failure assessment SOFA"] together with the experience of the treatment team help to predict the outcome as no agreement as to the optimal approach{time &frequency of medical and surgical treatment} and judgment is required, that's determined by local expertise and preference.

In conclusion Fournier's disease represents a T helper 2 maladaptive immune response with local gangrenous process associated with unbalanced metabolic status. Patients with co-morbid diseases had more extensive gangrene compared to those without. Also the disease carried poor outcome and the studied parameters (immune-metabolic-local disease extent) are important for disease management and outcome, Decision making should be performed by senior expert multidisplinary teams as neither the risk adjusted analysis nor the risk scoring system (FGSIS) were valid outcome predictors but the surgical risk scale may be valuable.

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