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sTREM-1 as a severity marker in patients with septic shock with abdominal surgery

Abstract

Background: The triggering receptor 1 expressed on the surface of myeloid cells (TREM-1) is up- regulated by the interaction of bacterial and fungi products with TLRs; and a soluble form of TREM-1 (sTREM-1) is released to the circulation. Hence the sTREM-1 may act as a biological marker of bacterial or fungal infection as has been shown for sepsis, pneumonia and bacterial meningitis. The aim of the study was to evaluate sTREM1 as a marker of severe infection in patients with abdominal surgery.

Methods: Blood samples were obtained from patients with abdominal surgery without infection, with sepsis and septic shock. White blood cell (WBC) count, TREM-1 expression in monocytes and neutrophils, and soluble TREM-1 in sera were measured by flow cytometry and ELISA respectively. TREM-1 and sTREM1 sere compared using ANOVA, and Spearman correlation was used for TREM- 1 cellular expression and sTREM1 in sera.

Results: The plasma concentration of sTREM-1 was higher in the group of septic shock compared to the other groups (p= 0.009). In addition, the expression of TREM-1 in neutrophils was lower in patients with septic shock compared to patients with abdominal surgery without sepsis (p=0.002). Finally, there was a trend to a negative correlation between sTREM-1 and the expression of TREM- 1 in neutrophils.

Conclusion: This study suggests that the plasma concentration of sTREM-1 is a good severity marker in patients with septic shock who had an abdominal surgery. It is possible that serum sTREM- 1 comes from the cleavage of TREM-1 in neutrophils.

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Introduction

Abdominal sepsis is a life-threatening disease with reported mortality rates ranging from 20 to 30%.[1] The causes of secondary peritonitis are anatomical defects of bacteria-containing hollow organs and a surgical intervention is the basis for the treatment. Standard surgical care consists of a laparotomy to eliminate the source of infection, and in most cases a surgical lavage of the abdominal cavity to minimize the abdominal bacterial load.[2] Identification of patients with secondary peritonitis or recurrent peritonitis after the initial emergency laparotomy and selection of patients for a second laparotomy is complex.[3]

Innate immune cells are key players in the recognition of invading pathogens during tissue damage, especially in abdominal sepsis. The magnitude of inflammation relies on the activation of pattern recognition receptors (PRR). One family of PRRs is the family of Toll-like receptors (TLRs), which are well-known for their role in innate immunity during infectious and non infectious diseases. Currently, 10 TLRs have been characterized in humans and can be divided into two groups; TLR1, TLR2, TLR4, TLR5, TLR6 and TLR11 are located within the cell membrane and recognize the components of the microbial cell wall, while TLR3, TLR7, TLR8 and TLR9 are expressed in compartments such as endosomes and lysosomes where they bind to nucleic acids of microbial origin.[4]

Recently, it was described that a member of the immunoglobulin superfamily receptor interacts with TLRs and influences the development of the inflammatory response: the Triggering Receptors Expressed on Myeloid cells.[5] The triggering receptor 1 expressed on myeloid cells (TREM-1) is a cell surface protein expressed by neutrophils and a subset of monocytes and macrophages.[6] Its expression is up-regulated by the interaction of bacterial and fungi products with TLRs. Together with the up-regulation of a membrane-bound TREM-1, a soluble form of TREM-1 (sTREM-1) is released to the circulation and to other body fluids. Hence the sTREM-1 may act as a biological marker of bacterial or fungal infection as has been shown for sepsis, pneumonia and bacterial meningitis.[7-9] TREM-1 contributes to the pattern recognition of bacterial PAMPs (especially LPS), and this may represent an important biological role of TREM-1. This receptor amplifies TLR signalling to promote the production of proinflammatory cytokines, neutrophil degranulation and phagocytosis.[6,10]

TREM family receptors recognize bacterial ligands[11] and it has been reported that TREM-1 co- localize with the TLR4-LPS receptor in human neutrophils and LPS primes the effects induced by TREM-1 engagement in these cells.[10] In the case of abdominal surgical patients, it could be a severity marker for septic shock. However, the proinflammatory effect of TREM-1 and its implication in the pathogenesis of inflammatory diseases and the mechanisms are still poorly understood. The aim of the study was to determine if sTREM1 in sera could be a severity marker by comparing the plasma sTREM-1 levels and TREM-1 expression in neutrophils and monocytes in patients who underwent abdominal surgery without infection, with abdominal sepsis without septic shock and abdominal sepsis with septic shock.

Material and methods

Study population and procedures

A prospective cross sectional study was performed from March 2018 to June 2019 at the Intensive Care Unit (ICU) and the Department of

Surgery, Hospital General de Mexico "Dr. Eduardo Liceaga" (HGM). The study was approved by the Ethics and Research Committees of the HGM and the Facultad de Medicina, Universidad Nacional Autónoma de México. The patients were invited to participate in the study or those who were unconscious their relatives or guardians were invited to have their relative included in the study. Written informed consent was obtained from all the subjects or their relatives. The study was conducted following the Good Clinical Practices and the International Conference of Harmonization standards. Adults with abdominal surgery without complications (not infected), with abdominal sepsis and with septic shock were included in the study. The patients were diagnosed with sepsis or septic shock, according to the current guidelines.[12] The exclusion criteria included: age younger than 18 years, other infectious process at the day of recruitment, peritonitis related to dialysis catheter, peritonitis in patients with cirrhosis and ascites, disseminated malignant disease, pregnancy, AIDS or immunosuppressive treatment and lack of consent.

Clinical data was recorded in a special format designed for the study and included age, gender, main diagnosis, admission category, mortality, the length of mechanical ventilation and ICU stay, outcome.

at discharge, Brussels score, Simplified Acute Physiology Score version 3 (SAPS-3), sequential organ failure assessment (SOFA) score, routine blood test and body temperature. Blood samples were taken at admission, at day 2 in uncomplicated surgical patients and at days 2 and 5 in sepsis and septic shock. Pheripheral blood was drawn and centrifuged, sera was stored at −70 °C until analysis, another tube with EDTA was taken for cell analysis on the same day.

Detection of TREM1 in sera and cells

The concentration of sTREM-1 was measured by duplicate in sera using a commercially enzyme- linked immunosorbent assay (ELISAs; Human TREM-1 Quantikine ELISA Kit) and quality control of ELISA assays was made according to the manufacturer's instructions. The minimal level of detection of ELISA assay for sTREM-1 was 4.5 pg/ml. The peripheral blood mononuclear cells (PBMCs) were isolated by Fycoll-paque; the TREM-1 expressed in the membrane of monocytes and neutrophils was determined with the fluorescence-conjugated mouse anti-human antibodies anti-CD64-PeCy7, CD66b-FITC, CD16-PeCy5 and CD354-PE (Biolegend, San Diego, CA, USA) and the fluorescence was detected by flow cytometry using the Attune-NxT cytometer, acquired data was analyzed using the FlowJo X software (TreeStar) at the Infectious Diseases Research Laboratory, Facultad de Medicina, UNAM.

Statistical analysis

Univariate analysis was used for descriptive variables. The comparison of the clinical characteristics, the expression of TREM-1 on the cell surface of neutrophils, monocytes and the concentration of sTREM-1 was made using the ANOVA test. A Spearman correlation analysis was performed between TREM-1 and sTREM-1 to determine a relation between the receptor expressed in the cell membrane and the one secreted in the patients sera. A $p < 0.05$ value was considered significant. The analysis was carried out with the statistical package SPSS 22nd edition.

Results

Demographic characteristics

Twenty-eight patients without infection who underwent elective surgery, 10 patients with abdominal surgery and sepsis and 21 patients with abdominal surgery and septic shock were included. The mean age + SEM in surgical patients was 45+2 years old, in septic shock 50+3 years old, and sepsis 38+4 years old (p=0.1), a higher percentage of females was observed in elective surgery patients without infection (89% female) compared to septic shock (62% female) and sepsis (50% female) (p=0.02). There were no significant statistical differences in weight, height and body mass index among groups (Table 1).

Table 1 Demographic and clinical characteristics

	Not infected n= 28	Sepsis n=10	Septic shock n=21	*p*
Demographic characteristics				
Age (years), x ± EE	45 ± 2	38 ± 4	50 ± 3	0.1
Female, n (%)	25 (89)	5 (50)	13 (62)	0.021
Male, n (%)	3 (11)	5 (50)	8 (38)	
Weight (kg), x ± EE	69 ± 2	81 ± 6	72 ± 4	0.1
Height (m), x ± EE	1.55 ± 0.01	1.61 ± 0.03	1.59 ± 0.01	0.1
BMI, x ± EE	28 ± 0.9	31 ± 2.2	29 ± 1.6	0.5
External consult, n (%)	28 (100)			
Emergency department, n (%)		10 (100)	7 (33)	<0.001
Surgery ward, n (%)			14 (67)	
Clinical characteristics				
Leucocytes (Hospital admission), x ± EE	7.6 ± 0.3	17.8 ± 1.6	16.6 ± 2.4	<0.001

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Table continued...

	Not infected n= 28	Sepsis n=10	Septic shock n=21	p
Leucocytes (day 2), x ± EE		11.7 ± 1.4	16.3 ± 2.5	0.13
Leucocytes (day 5), x ± EE		8.7 ± 1.6	8.7 ± 2.2	0.29
Hemoglobin (Hospital admission), x + EE	14.1 ± 0.2	14.3 ± 0.8	9.8 ± 0.3	<0.001
Lactate, x ± EE			4.4 ± 0.6	
SAPS III, x ± EE			59 ± 3.3	
NEMS, x ± EE			286 ± 54	
SOFA (ICU admission), x ± EE		1 + 0.8	8.6 + 1	0.002
Brussels (ICU admission), x ± EE		1 + 0.8	6 + 0.8	0.003
Days of ICU stay, x ± EE			8 ± 6	
Type of surgery				
Laparoscopic colecystectomy, n (%)	28 (100)	2 (20)		<0.001
Appendectomy, n (%)		7 (70)	4 (19)	
Dehiscence repair, n (%)			2 (9)	
Closure of primary peforation, n (%)			5 (24)	
Intestinal resection, n (%)		1 (10)	9 (43)	
Biliperitoneum, n (%)			1 (5)	
Complications				
None, n (%)	28 (100)	10 (100)	14 (67)	0.006
Massive bleeding, n (%)			4 (19)	
Trans-surgical cardiorespiratory arrest, n (%)			1 (4.7)	
Deaths, n (%)			5 (24)	

Clinical characteristics

All the patients with elective surgery without infection had a laparoscopic cholecystectomy; septic shock patients had appendectomy in 19%, dehiscence repair in 9%, primary perforation closure in 24%, intestinal resection in 43% and biliperitoneum in 5%; and sepsis patients had laparoscopic cholecystectomy in 20%, appendectomy in 70% and intestinal resection in 10%. At hospital admission, leukocyte count was higher in the septic shock group (16.6 + 2.4 x 103) and sepsis (17.8+ 1.6 x 103) compared to patients who underwent elective surgery without infection who had normal leukocyte count (7.6 + 0.3 x 103), p <0.001. After 5 days, the leukocyte count decreased to normal levels in sepsis and septic shock. The hemoglobin in g/dL at admission was normal in elective surgery patients (14.1+0.2) and sepsis (14.3+0.8), but was low in the septic shock group (9.8+0.3) <0.001. SOFA (8.6+1 vs 1+0.8, p=0.002) and Brussels (6+0.8 vs 1+0.8, p=0.003) scores were higher in the Septic shock group compared to the sepsis group, respectively. Lactate of admission day (mean+SEM) was 4.4 + 0.6, SAPS III 59 + 3.3 and NEMS 286 + 54 in patients with septic shock (Table 1). No complications were described in the elective surgery uninfected patients and the septic patients, in septic shock patients massive hemorrhage (bleediing more than 500 ml. during surgical procedure) presented in four patients (19%) and cardiorespiratory arrest during surgery presented in one patient (4.7%). Five of the septic shock patients died (Table 1).

Sera s-TREM1 and TREM1 expression in cells

A slightly higher expression of TREM1 in monocytes was observed in surgical patients (79+11) compared to septic patients (60+11) p=0.03, no differences were observed in TREM1 expression with septic shock patients (82+18) in monocytes. On the contrary, a lower level of TREM1 expression was observed in septic shock patients (30+27, p=0.002) and septic patients (15+13, p=0.002) compared to uninfected surgical patients (81+14) in neutrophils (Figure 1A).

A higher level of serum sTREM1 was observed in the patients with septic shock (Md 129.5 pg/ml), compared to elective surgery uninfected patients (Md 14.5pg/ml) and sepsis patients (Md 17 pg/ml)

p=0.009 (Figure 1B). In the Spearman correlation analysis, although not satistically significant, a trend for an inverse relationship between the expression of TREM1 on the surface of neutrophils and the sTREM1 serum levels was observed (Figure 2).

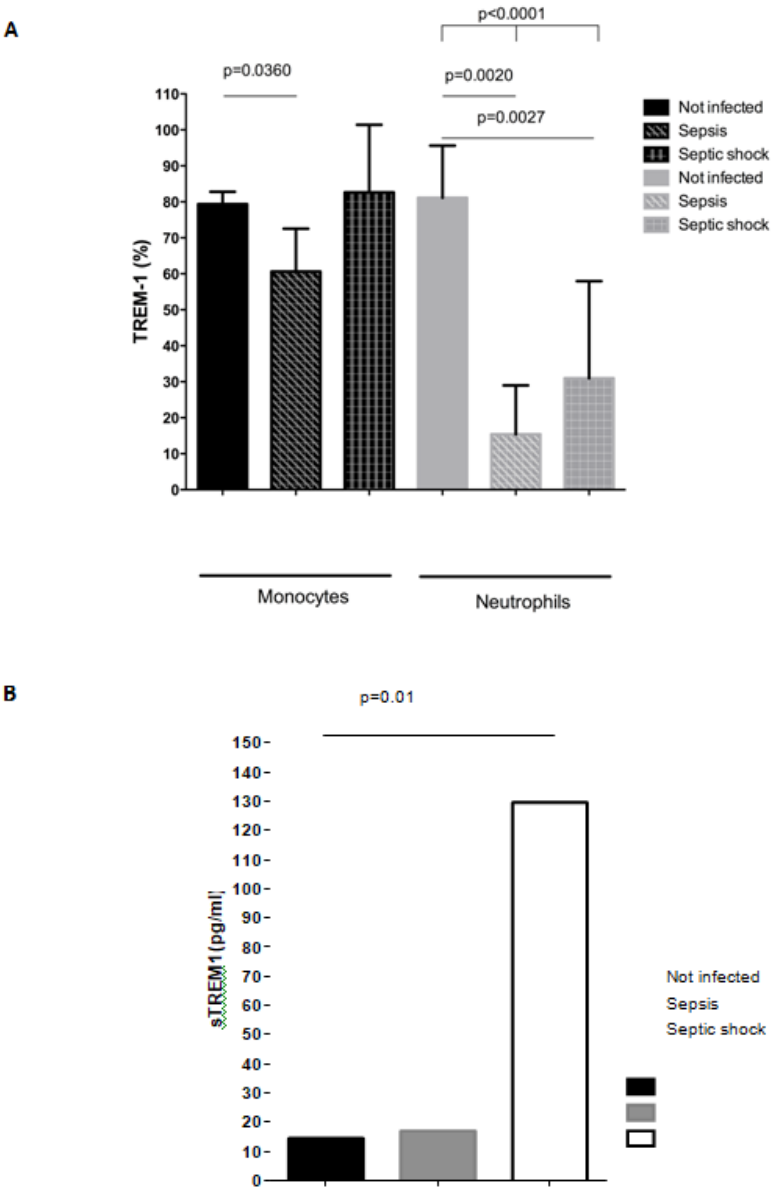

Figure 1 TREM1 and sTREM1 detection. Expression of TREM 1 (%) in the surface of monocytes and neutrophils (A) and detection of sTREM1 (pg/ml) in sera (B) in patients who had abdominal surgery without infection, with sepsis and with septic shock (% of TREM1 is expressed in medians).

Discussion

The patient survival is determined by a proper diagnosis, administration of adequate antibiotic therapy and supportive measures; but in clinical practice, there are many limitations. The identification of severity markers of infection could help to implement an earlier and more aggressive intervention in order to reduce the mortality in this patient population. sTREM-1 has been proposed as a useful diagnostic tool to predict infectious pneumonia and sepsis.[13] In response to sepsis, TREM-1 amplifies the infection-induced inflammatory response signals; sTREM-1 is the soluble form of TREM- 1 that lacks the transmembrane and intracellular domains. These two domains probably are cleaved from TREM-1 on the membrane surface by proteolysis.[14] This study shows that serum sTREM-1 levels are increased in patients with abdominal surgery with septic shock compared to patients with abdominal sepsis without septic shock and with patients with abdominal surgery without sepsis. This observation as shown in other infectious diseases, suggests that the serum level of sTREM-1 is a good marker of severity in patients who underwent abdominal surgery and develops an infection, as reported by Song et al.[15] It is not known the source of the sTREM-1 in sera; the finding in this study that sTREM-1 increases in serum while TREM-1 decreases in neutrophils and the inverse correlation in

neutrophils in abdominal surgical patients with septic shock, suggests that the protein could be cleaved from the neutrophils as a source for the soluble form in sera, as suggested previously[14] or that the elevated serum concentration of sTREM-1 in these patients produces a down-regulation in the expression of TREM-1 in the neutrophils. Another finding was that the serum levels of sTREM-1 matched with high scores of SOFA and Brussells severity scores in the group of abdominal surgery with septic shock, which indicates that the higher the level of serum sTREM-1 the greater the risk of multiple organ failure and therefore the greater the risk of death, as was observed in this group with a 24% mortality. However, the sample size for this study was small and more studies are needed.

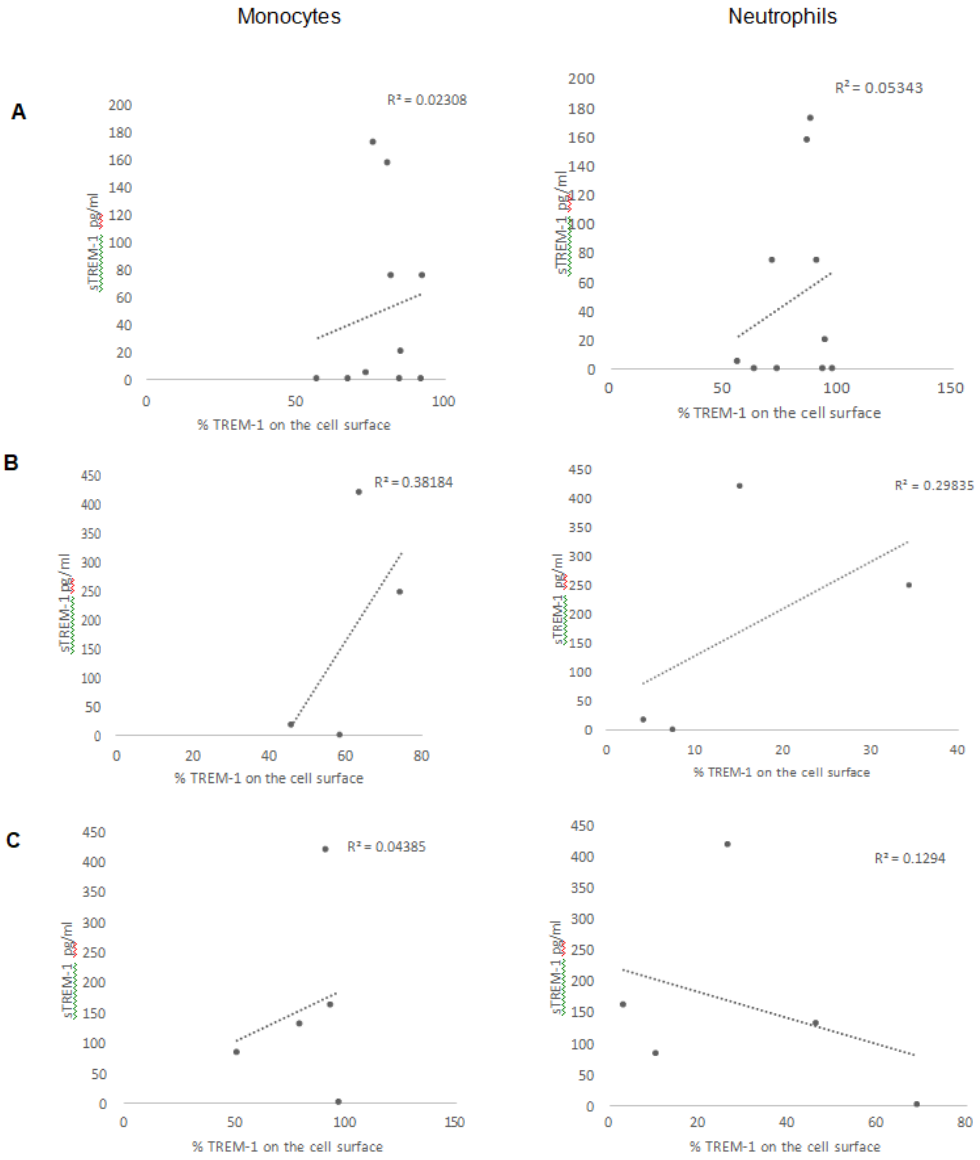

Figure 2 Correlation of sTREM1 (pg/ml) in blood with the percentage of TREM1 in the cellular membrane of monocytes (left column) and neutrophils (right column) in patients with abdominal surgery not infected (A), with sepsis (B) and with septic shock (C).

Conclusion

This study suggest that the serum level of sTREM-1 is a good marker of severity in patients with infection who underwent abdominal surgery. In addition, the inverse correlation in neutrophils with a high level of sTREM1 in sera and a low expression in neutrophils suggest that sTREM-1 might be cleaved from the neutrophils as a source for the protein in sera. Finally, the high level of sTREM-1 in the sera of patients with acute abdominal sepsis matched with the severity scales, as previously reported.[16-18]

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