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Serum Procalcitonin and Neutrophil Toxic Granules Guided Management of Post-Operative *K. pneumoniae* Septic-Shock in Laminectomy—A Case Report

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ABSTRACT

Introduction: We still rely on clinical diagnosis for initiating empirical antibiotic therapy and await blood culture for confirmation of infection, species identification and drug sensitivity. Differential blood cell count (WBC and neutrophils) and recording of toxic granules in the neutrophils are established methods for indirect diagnosis of infection though they are not used in the diagnosis of sepsis per se. Serum Procalcitonin is considered as a good biomarker in the management of sepsis. **Materials and Methods:** Whole blood and serum were used for laboratory analysis. We have combined the detection of toxic granules in the peripheral blood smear and serum PCT levels for diagnosis and monitoring the recovery of a patient with septic shock. A 63 year old laminectomy patient was transferred 2 days after the surgery to our hospital with several co-morbidities and complications. He was in septic shock and was put on Continuous Renal Replacement Therapy, with ionotropic support and IV fluids via nasogastric feeding and administration of Activated Protein C. Blood culture and daily measurements of serum Procalcitonin, differential blood cells count, and observation of toxic granules in neutrophils were done. **Results:** The blood culture showed infection due to *K. pneumoniae* resistant to carbapenems. WBC and Neutrophil counts were quite variable and showed incoherent response to treatment. Serum PCT was 24.57 ng/mL on the next day of admission and it peaked at 30.2 ng/mL on day 3. Its level started decreasing from the 4th day. Toxic granules disappeared when serum PCT levels reached < 1 ng/mL. The patient responded well to treatment and he was discharged on the 16th day upon request. **Conclusion:** This case is presented as an example of managing sepsis with a combination of a conventional hematology marker and a modern biomarker. Resource poor hospitals with inadequate microbiology services, may evaluate and use these two biomarkers not only for the total management of sepsis but also to reduce the cost of critical care.

Keywords: Sepsis; Procalcitonin; Toxic Granules

1. Introduction

Sepsis is the most common cause of death in noncoronary Intensive Care Units (ICU) with a reported mortality of 29% in the US and 27% in Europe [1], particularly in elderly, immuno compromised/suppressed and critically ill patients. Approximately, 46% of critical care patients and 53% of hospital based patients die due to severe sepsis in India [2].

Many laboratory results are indistinguishable between patients with Systemic Inflammatory Response Syndrome (SIRS) and sepsis or septic shock with multi organ failure. Differential diagnosis of infection and inflammation is very difficult in the absence of culture results. Conventional laboratory indicators for infection, like WBC/ neutrophils count and serum C-reactive protein (CRP), are non-specific and are often influenced by factors other than infection. Therefore, their status may not directly correlate to either progression or control of infection. Recent reports indicate that absolute neutrophil counts and morphological changes like toxic granules may be better indicators of systemic infection than band count [3]. Since it is desirable to have high sensitivity we used two markers, a biomarker and hematology marker for detecting and monitoring systemic infection (sepsis). Resource poor countries may not have a well equipped microbiology laboratory to do blood culture. Hence, there is an urgent need for biomarkers for a cost-effective and reliable management of sepsis.

Procalcitonin (PCT) has been proposed as a more specific and better prognostic marker than differential blood

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cell count and CRP in the management of sepsis [3-6]. Serum PCT based algorithm has been designed and used to guide the management of sepsis in many countries in Europe and the USA [7-10]. Several formats are available for the determination of serum PCT, 1) a semi quantitative lateral flow rapid test device called PCT-Q (> 0.5 $ng \cdot ml^{-1}$); 2) a fairly sensitive (>0.2 $ng \cdot ml^{-1}$) Lumino Immuno Assay (LIA) and 3) a highly sensitive (<0.1 $ng \cdot ml^{-1}$) Kryptor™ Procalcitonin assay (all manufactured by BRAHMS Diagnostica GmbH, Thermo Scientific Inc) in several countries including India. Procalcitonin test has been introduced in India only a couple of years ago and there have not been many studies to evaluate its usefulness in the diagnosis or management or stratification of sepsis in India. In India, quantitative serum PCT assay (LIA) has been evaluated in infectious pyelonephritis [11] in children, infective febrile conditions in intensive care units [12] and a semi-quantitative rapid test device was used in two other studies [13,14]. Though serum PCT levels are not elevated in viral infections [15], it is significant that this study demonstrates that serum PCT responds strongly in a HIV positive patient who had secondary bacterial infection.

2. Case Presentation

63-year-old male, was presented in the emergency of Global Hospital, Hyderabad with hypotension (60/40 mmHg) and hypoglycemia (60 mg/dl), urinary retention (dysuria), consciousness but with slurred speech. The patient had history of laminectomy + decompression C2 - C7, Coronary Artery Disease with Tri Vascular Disease, hypertension, Diabetes Mellitus, HIV + and he was being transferred and admitted in ICCU of Global Hospitals due to complications, for further evaluation and treatment. The treatment included Continuous Renal Replacement Therapy, with ionotropic support and IV fluids via nasogastric feeding and administration of Activated Protein C. Regular monitoring was done for septic-shock. His hospital stay was uneventful and he was discharged on the 16th day.

Whole blood in EDTA was collected for hemogram analysis. The WBC and neutrophil counts increased continuously and so did the serum creatinine during early part of his stay. The blood culture showed *K. pneumoniae* resistant to carbapenams and he was treated with antibiotics Tigecyclin, Colistin. Results of the laboratory investigations are summarized in **Table 1**.

Serum was separated from clotted blood and serum procalcitonin was assayed every 24 h by BRAHMS LIA method. Hematology parameters like hemoglobin, hematocrit, MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin), MCHC (mean corpuscular hemoglobin concentration) were measured using automated 5 part hematology analyzer. Peripheral blood smears were stained with Leishman Stain and the toxic granules in the neutrophils viewed at 1000× magnification. Serum PCT was assayed in 11 consecutive 24 h samples (**Figure 1**). The patient was discharged on the 16th day on request and he was stable at the time of discharge.

3. Discussion

Our intention was to determine the association (if any) between serum PCT levels and neutrophil toxic granules and their usefulness as surrogate biomarkers in the management of septic shock. This case study mainly focuses on neutrophil toxic granules profile and the serum PCT levels during the course of septic-shock in an immunosupressed (HIV +) patient. Our data suggest that there is secondary systemic bacterial infection. Blood culture done on day 3 of admission confirmed carbapenam resistant *K. penumoniae* infection. Tigecyclin and Colistin were administered from day 3. Blood culture was not done on days 4 - 6. Blood culture done on 7th day showed "no growth". There was positive correlation between serum PCT and toxic granules. The toxic granules were present on all days and disappeared from 12th day when PCT levels reached 0.5 $ng \cdot mL^{-1}$. Serum PCT increased during first 3 days of admission and started decreasing immediately after administration of Tigecyclin and Colistin, indicating infection control (**Figure 1**). Serum PCT peaked on the 3rd day (30.32 $ng \cdot mL^{-1}$) and was associated with severe leukocytosis, thrombocytopenia, neutrophilia with shift to the left and increased levels of blood urea and creatinine indicating multi organ involvement. Clinical improvement in the patient from day 4 onwards was underlined by improvement in the PCT

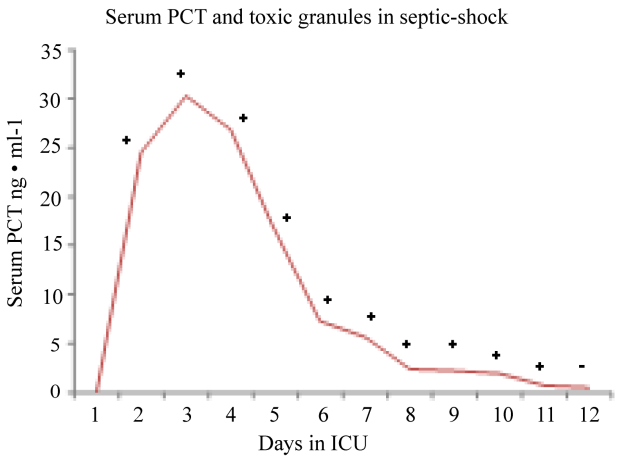

Figure 1. Association between serum PCT levels and toxic granules in septic shock (+) and (–) indicate presence and absence of toxic granules in neutrophils (Indira C *et al.* 2011).

Table 1. Laboratory data.

Day in ICU	BIO-MARKER	HEMATOLOGY					MICRO	BIOCHEMISTRY	
	sPCT ng/ml	Toxic Granules	Hb (gm%)	Platelets	WBC	Neut (%)	Culture	Urea (mg/dl)	sCreat mg/dl)
1	ND	(+)	10.2	1.38	25060	92	*K.p*	136	2.1
2	24.57	(+)	11.4	0.6	26480	89	CR	90	1.9
3	30.32	(+)	9.8	0.31	32050	88	ND	119	3.6
4	26.86	(+)	8.5	0.51	20500	88	ND	124	3.6
5	16.35	(+)	9	0.65	9970	82	ND	110	3.4
6	7.27	(+)	9.3	0.55	11020	80	ND	106	3
7	5.62	(+)	9.6	0.54	16390	86	No growth	92	2.2
8	2.37	(+)	11.4	0.55	18360	86	No growth	110	2.1
9	2.21	(+)	11.8	0.66	16240	83	No growth	118	1.8
10	1.93	(+)	10.1	0.34	12520	80	No growth	101	1.9
11	0.71	(+)	8.3	0.97	7010	66	No growth	85	1.6
12	0.5	(–)	7.3	1.18	6160	54	No growth	110	1.9
13	ND	(–)	7.5	1.59	6200	48	No growth	110	1.7
14	ND	(–)	7.6	2.27	8200	65	No growth	110	1.9
15	ND	(–)	7.7	2.85	7420	58	No growth	81	1.4
16	ND	(–)	7.1	3.13	6130	54	No growth	73	1.3

ND: Not Done; (+) Toxic Granules Detected; (–) Toxic granules Not Detected; Hb = Hemoglobin; ICU = Intensive Care Unit; sPCT: serum Procaocitonin; sCreat: serum creatinine; Hb: Hemoglobin; K.p: *K. pneumoniae*; Neut: Neutrophil.

levels, urea, creatinine and disappearance of the toxic granules on the 12th day. Serum PCT was not done beyond 12th day as there was no fever and to reduce the cost of investigations. The patient recovered completely and was discharged on the 16th day on request.

4. Conclusion

Surrogate biomarkers help to monitor changes at molecular level during infections. We compared the toxic granules in neutrophils with the levels of serum PCT every 24 h. The changes in the levels of serum PCT and the toxic granules represented more closely the status of infection (severity) in the patient compared to WBC and neutrophil counts. Toxic granules when scored and quantitated based on the density and distribution in the cytoplasm of neutrophils would enhance the predictive value. Serum PCT levels and toxic granules may be considered for early diagnosis, assessment of severity and for terminating antibiotic treatment in sepsis. It will be useful to investigate the outcome prediction for the patient when serum PCT and toxic granules are used regularly every 24 h to monitor response to treatment instead of culture. This may eventually help to improve outcome prediction and reduce the cost of critical care. Resource poor laboratories/hospitals where good microbiology facility is not available may find it viable to use serum PCT and toxic granules in the management of sepsis and septic shock.

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