CASE REPORT

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

The influence of sepsis on erythrocytes morphology: case report and literature review

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Abstract

This paper highlights a clinical case of sepsis caused by soft tissue infection. Peripheral blood smear, plasma value of inflammatory biomarkers and the white blood cells count were performed. Significant morphological changes were revealed through peripheral blood smear test two days after patient admission. Patient developed septic shock after the third day in intensive care unit (ICU). Laboratory results showed major morphological changes (erythrocytes deformity, abnormal neutrophils); these were correlated with elevated plasma value of interleukin-6 and procalcitonin.

Keywords: sepsis, erythrocytes, morphological changes.

Introduction

Sepsis has been recently defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection" [1]. This response particularly refers to the alteration of tissue microcirculation [2–4], which has an impact on oxygen delivery and consumption at tissue level [5]. The decrease in membrane deformability and red blood cells (RBC) morphological changes has been proved to be a possible cause of microvascular dysregulation [6, 7].

The erythrocytes membrane has got rheological properties such as deformability, aggregation, and viscosity. The membrane deformability allows the RBC to pass through small capillaries. The experimental studies on animal induced sepsis, showed erythrocyte membrane changes [8, 9] consisting of decreased membrane deformability [10], detected within the first 24 hours through ultrafiltration method. These findings could be an early indicator of sepsis [11]. The resulting RBC membrane rigidity leads to a capillary flow maldistribution regarded as the hallmark of sepsis. As a consequence of this phenomenon, local tissue hypoxia occurs and could be a cause of organ dysfunction syndrome [12, 13].

The changes which revealed the alteration of RBC morphology are detected later after the first 24 hours of induction of sepsis [14, 15]. Finally, the presence of disintegrated erythrocytes and also RBC aggregates were observed [16]. These last modifications are considered by some authors as an additional factor, which can also alter tissue microcirculation causing organ dysfunction [17, 18].

The fundamental role of erythrocyte is the transportation of oxygen from the lungs to the peripheral tissues. The process of tissue oxygen delivery is characterized by the oxygen dissociation curve (ODC), which depends on several factors (acidity, fever or 2,3-bisphosphoglycerate) and shows hemoglobin (Hb) affinity for oxygen [19–21]. Different data studies about sepsis showed that the RBC ODC shifted to the left [21–23], increasing the affinity of Hb for oxygen and thus leading to tissue hypoxia [24].

Sepsis is considered a syndrome of inflammatory systemic response, based on immune cells activation, the neutrophils are particularly involved in this process. These cells exert their role by converting oxygen into free radicals (superoxide, hydrogen peroxide) known as reactive oxygen species (ROS). The role of ROS is to destroy bacteria, which have been engulfed by neutrophils and macrophages [25–27]. Some authors suggest that the activated neutrophils in contact with RBC release ROS, which subsequently damage these cells [28–30]. As a consequence, this phenomenon reduces antioxidant status in sepsis and also cellular protective role. The association between reduced antioxidants status and sepsis has been proved through various clinical studies [31–33].

For the correction of this reduced status, antioxidants treatment with vitamin C or vitamin E is required and it either improves the RBC membrane deformability or it inhibits cell destruction [34, 35].

Moreover, Hb oxidation to methemoglobin or other Hb oxidation products was proved, and it has a negative impact on the transportation of oxygen to the peripheral tissues [36, 37]. This process of Hb oxidation is considered to be produced by ROS, after the diffusion of these radicals across the RBC membrane [38].

Aim

Our aim was to highlight membrane deformability and morphological alterations of RBCs in sepsis. We also correlated these morphological changes with other inflammatory biomarkers to demonstrate that these morphological alterations can be used as a reliable tool for septic cases diagnostic confirmation.

Case presentation

This study was conducted at the Intensive Care Unit (ICU), Emergency County Hospital, Arad, Romania, on an admitted 55-year-old female patient with septic shock from October 20–25, 2023. The current study (clinical case report) received approval from the Ethics Committee of the Emergency County Hospital, Arad, and consent form from the patient. This study was based on extensive studies of specialized literature using *PubMed*, *Google Scholar*, *Scopus*, and *MEDLINE* databases to highlight the influence of rheological properties of the blood in sepsis.

Upon admission to ICU, the patient presented sacral pressure ulcer stage 4 (patient was bed ridden for approx. two months as a result of musculoskeletal complication) and subsequent systemic inflammatory syndrome. The patient was placed on large spectrum antibiotics (Meropenem 1 g every eight hours and Vancomycin 1 g every 12 hours) and rehydration therapy (colloid and crystalloid solution). Wound culture showed *Pseudomonas aeruginosa* as the causative germ for sepsis and the targeted antibiotic therapy (Meropenem 1 g every eight hours) commenced. We noticed only atrial fibrillation from the medical past and the medication composed of digitalis, anticoagulants and blocking agents' drugs. Patient clinical evolution three days after intensive care therapy was unfavorable thus leading to septic shock, which required vasoconstrictor drugs. Initial dose of noradrenaline was administered (0.1 μg/kg/min).

We measured the plasma value of Hb, white blood cells (WBC), values of inflammatory biomarkers: procalcitonin (PCT), C-reactive protein (CRP), and interleukin-6 (IL-6). The laboratory tests were carried out every 24 hours simultaneously with the microscopic analysis of the peripheral blood smear.

CRP is an acute phase protein produced by the liver as an inflammatory or infectious response. The quantitative determination of the CRP was performed through immuno-turbidimetry method, the analysis that measure the level of CRP in patient blood. CRP binds to antibodies to form a complex which will cause turbidity in solution that can be measured by spectrophotometry. The amount of turbidity is proportional to the level of CRP. Normal values: <0.5 mg/dL.

PCT determination is necessary in the diagnosis of bacterial infection or sepsis and also determines whether antimicrobial treatment should be used or not. PCT level reflets the degree of systemic inflammatory response. PCT assay is based on a latex enhanced immunoturbidimetric method (serum samples). Normal values: <0.5 ng/mL.

IL-6 belongs to a larger group of proteins called cytokines and is considered a proinflammatory cytokine. IL-6 test is used to scrutinize inflammatory responses of the body. The IL-6 level was determined by the chemiluminescent enzyme-linked immunosorbent assay (ELISA) method. Normal values: <7 pg/mL.

Hb is a complete blood count parameter, which was determined automatically through hematology analyzer from anticoagulated blood. Normal values: 12–14 g/dL.

WBC count, also a complete blood count parameter, was determined through automatically hematological analysis. Normal values: 4–10×10^3/μL.

The laboratory findings are presented in Table 1.

Table 1 – ***The laboratory results of this clinical case***

Laboratory parameters	Day			
	1	*2*	*3*	*4*
Hb [g/dL]	8.6	8.7	9.6	8.5
WBC [×10^3/μL]	31.6	15.7	15.6	20
PCT [ng/mL]	4.6	1	0.8	16.4
CRP [mg/L]	109	137	113	48
IL-6 [pg/mL]	174	138	123	5000

CRP: C-reactive protein; Hb: Hemoglobin; IL-6: Interleukin-6; PCT: Procalcitonin; WBC: White blood cells.

The peripheral blood smear was performed 10 minutes after the blood sample was drawn. The May-Grünwald–Giemsa (MGG) staining was used for the sample, then microscopic examination was performed, initially at low power (with the objective of 10×/20×) for appreciation of cell staining and distribution. The number of leukocytes can be estimated, as well as the presence of abnormal cellular elements (blasts, erythroblasts), platelet aggregates, erythrocyte agglutinates/rolls. The method of examination of peripheral blood smears was carried out by optical microscopy 40×, 50×, 100× with immersion and MGG staining, 20 slides (peripheral blood smears) were examined, out of which 10 were included in this study, with ID 31773 and four best images are presented in this paper. Microscopic analysis results can be seen in Figures 1–4.

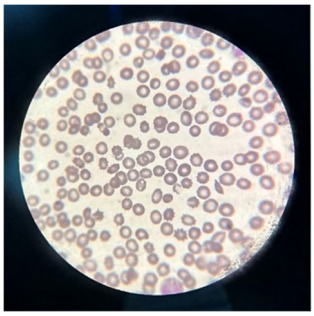

Figure 1 – ***Hypochromia, spherocytes (first day of admission). MGG staining. Immersion objective, ×100.***

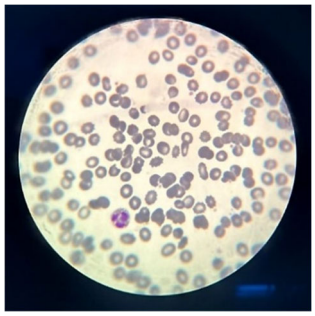

Figure 2 – ***Erythrocytes of different sizes, anisocytosis, anisochromia, poikilocytosis (stomatocytes, ovalocytes, acanthocytes, elliptocytes and crenated RBCs), segmented neutrophil (third day of admission). MGG staining. Immersion objective, ×100.***

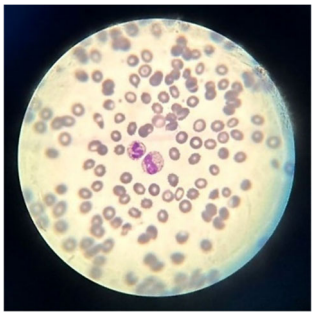

Figure 3 – ***Erythrocytes of different sizes and non-segmented neutrophils with toxic granules (seen first day of septic shock). Acanthocytes, rouleaux formation – RBCs show clumping or aggregation. MGG staining. Immersion objective, ×100.***

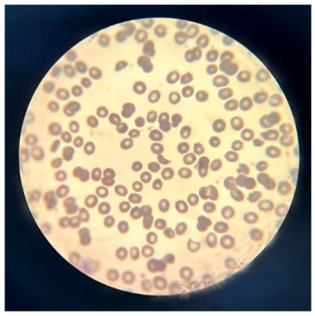

Figure 4 – ***Erythrocytes of different sizes and shapes: Anisocytosis, anisochromia, burr cells, elliptocytes, stomatocytes (seen first day of septic shock). MGG staining. Immersion objective, ×100.***

Peripheral blood smear interpretation described the platelet morphology, RBC and WBC. Platelet morphology: isolated platelets in small groups, platelet anisocytosis with micro-platelets and macro-platelets. Slide shows normal platelet number. RBC morphology: erythrocyte anisocytosis with microcytes and macrocytes, erythrocyte anisochromia, hypochromic erythrocytes, rare polychromatophilic RBC, poikilocytosis, with the presence of elliptocytes, spherocytes, rare codocytes, acanthocytes, burr cells (crenelated erythrocytes/echinocytes), ovalocytes, rouleaux formation – RBC show clumping or aggregation. WBC morphology: 93% segmented neutrophils; 4% lymphocytes; 1% monocytes; 1% eosinophils; 1% basophils; unsegmented neutrophils with toxic granules.

Discussions

The first image of blood smear showed minor morphological changes of erythrocytes. We were unable to perform rheological membrane test of RBC through ultrafiltration method [39]. Decreased membrane deformability, according to some studies, is the first indicator of sepsis [40]. We can observe only hypochromia (Figure 1), while mild anemia can be seen on lab results, this explains the presence of sepsis [41, 42]. We can exclude the iron deficiency anemia based of normal values of average erythrocyte volume, mean corpuscular Hb, average Hb concentration and also normal value of transferrin. We also found a high value of red cell distribution width (RDW) parameter, which is considered by some studies as independent risk factor of mortality in sepsis [43, 44]. Sepsis-induced anemia is a possible cause of this phenomenon [45]. RDW was calculated by automatic analyzer depending on the presence of frequency anomalies relative to certain levels of discrimination. RDW is normally used for the differential diagnosis of anemia [46].

The lab results (Table 1) also showed high value of leukocytes, which is considered an immunological response caused by infection and the high value of CRP, which reveals the inflammatory response [47]. The high PCT value on admission to ICU confirms the presence of sepsis [48, 49] and the significant increase which occurred on the fourth day of ICU treatment, confirm the septic shock. IL-6 is a proinflammatory cytokine, an intercellular messenger, the high plasma level of this parameter demonstrates the activation of innate immune system [50]. Finally, we also found a very high level of this cytokine that can be correlated with the significant increase of PCT.

Erythrocytes of different sizes, anisocytosis, anisochromia, poikilocytosis (stomatocytes, ovalocytes, acanthocytes, elliptocytes and crenated RBC), segmented neutrophils were observed on the third day of ICU stay (Figure 2). These changes, typical for sepsis, can be explained by damaged RBC membrane [51, 52] and can be correlated with the data of other studies. Thrombocytopenia (lab results) with platelet anisocytosis was present as well. Thrombocytopenia is considered a complication of sepsis rather than the side effect of low dose digitalis treatment [53].

The presence of erythrocytes of different sizes and non-segmented neutrophils with toxic granules were observed by optical microscopy 100× immersion objective and MGG staining and also acanthocytes, rouleaux formation (Figure 3). These morphological modifications are an indicator of septic shock [54]. The appearance of toxic granules is a result of cytokine activation and highlights a short time maturation of the neutrophils precursor. The significant high value of IL-6 (the fourth day) sustains this hypothesis, our finding is consistent with data of other studies [55, 56].

Oxidative stress is a consequence of innate immune activation and is a major cause of erythrocyte cytoskeleton destruction. This is a complex reaction depending on the severity of the sepsis. The last slide showed the presence of erythrocytes of different sizes and shapes: anisocytosis, anisochromia, burr cells, elliptocytes, stomatocytes (Figure 4); these major morphological alterations, according to some studies, are typical for septic shock state [57, 58] and could be a consequence of oxidative stress.

Conclusions

A wide range of RBC morphological changes were described in sepsis. In our clinical case report, the first major changes were shown on the third day in ICU. These findings can be used, in some circumstances, as a diagnostic tool for the confirmation of sepsis. Significant alterations of RBC morphology and other blood cells deformity were observed in septic shock state. These last changes can be well correlated with the increased values of IL-6 and PCT and it is thus recommended for patient prognostic evaluation.

Conflict of interests

The authors declare that they have no conflict of interests. The authors are responsible for the content and writing of the papers.

Authors' contribution

Cristian Mircea Nicolescu and Silviu Daniel Moldovan have equally contributed to this manuscript.

Acknowledgments

We would like to express our gratitude to our patient for agreeing to publish this case report.

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Received: November 3, 2023

Accepted: February 10, 2024