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Haematologic Abnormalities and Coagulopathies in Sepsis Associated with Community Acquired Pneumonia

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ABSTRACT

Acute organ dysfunction, haematologic changes and changes in coagulation are present in virtually all patients with sepsis associated with community acquired pneumonia. We were able to diagnose sepsis linked to community acquired pneumonia in 218 patients, based on typical symptoms and changes in laboratory values from the period of 2012–2020. We examined the frequency and severity of anaemia, quantitative and qualitative changes of leukocytes, numerical abnormalities of platelets, and clinical and laboratory signs of coagulopathy. We diagnosed anaemia of variable severity in 149 cases with sepsis and in 161 patients with leukocytosis. Extremely severe leukocytosis was diagnosed in 6 patients. Variably severe decreases in the number of leukocytes (leukopenia, agranulocytosis) were detected in 33 cases. Leukemoid reaction with increased leukocyte count, myelocytes, metamyelocytes and some atypical myeloid cells in the peripheral blood was diagnosed in 3 patients. Based on platelet counts we detected thrombocytopenia in 82 patients. Myelodysplastic bone marrow characteristics was revealed in one patient after performing biopsy with a Jamshidi needle. Disseminated intravascular coagulation was diagnosed in 6 patients based on typical clinical signs and laboratory tests of the coagulation system.

Keywords

Community acquired pneumonia, Sepsis, Quantitative and qualitative hematologic abnormalities, Disorders of the coagulation system.

Abbreviations

CAP: Community acquired pneumonia, CRP: C-reactive protein, CURB-65: Confusion, BUN, respiratory rate, blood pressure, age, DIC: Disseminated intravascular coagulation, WBC: White blood cell, HUS: Haemolytic uremic syndrome, ISTH: International Thrombosis and Haemostasis Society, MODS: Multi-organ dysfunction syndrome, PSI: Pneumonia severity index, qSOFA: quick Sequential organ failure assessment score, SOFA: Sequential organ failure assessment score, SIRS: Systemic inflammatory response syndrome, TTP: Thrombotic
thrombocytopenic purpura, RBC: Red blood cell.

Introduction

Sepsis is the result of an infection between an infectious microorganism and the immune, inflammatory and coagulation systems of the organism infected by said microorganism [1,2]. The reactions of the organism in response to the infection and the inflammatory effect of the pathogen involved are pathogenetic factors of major importance in the development of sepsis [1]. The pathogens invading the organism do not directly cause sepsis, instead they act by promoting the increased production and release of endogenous mediators affecting macrophages, leukocytes, monocytes and microvascular endothelia [1-4]. Next, complex pathological events result in damage to the microvasculature of parenchymal organs potentially leading to multiorgan dysfunction syndrome (MODS) or, in more severe pathologies, to the development of the symptoms of multiorgan failure [1,2,5]. In addition to and concomitantly with the multiorgan dysfunction syndrome, fundamental changes occur in all the constituents of the hematopoietic and coagulation systems, potentially indicating the severity of sepsis, affecting its severity and course as well as the recovery potential of the affected organism [4]. In this study, we retrospectively assessed 1826 patients with confirmed CAP treated in our department. In addition to analysing the characteristic abnormalities in CAP, we also examined the

frequency of the association between sepsis and pneumonia as well as the characteristics and severity grades of septic disease processes. The qualitative and quantitative characteristics of haematologic abnormalities and the pathological changes of the coagulation system in patients with sepsis have been analysed and evaluated. In our earlier publications we have reported our experiences with the clinical presentation of sepsis [2] and haematologic abnormalities associated with pulmonary infections [6]. The present communication dissects the characteristics and coagulopathies of haematological anomalies in sepsis associated with CAP.

Clinical Characteristics of Community-Acquired Pneumonia Associated with Sepsis and Analysis of the Constituents of the Hematopoietic System

We have analysed the data of patients hospitalised with community-acquired pneumonia (CAP) diagnosis in our department during the period between 2012 and 2020. Based on retrospective assessments, 1826 patient histories were eligible for data processing. In all cases, bidirectional chest X-rays were used to confirm the presence of CAP. Table 1 summarises the abnormalities visualised on the X-ray images, showing that in most of our patients extensive pneumonia was confirmed. Among the general clinical symptoms, fever, dyspnoea, chest pain, coughing and debilitating weakness were found to be the most frequent (Table 2). Table 3 summarises the typical clinical symptoms and laboratory abnormalities: among them, hypotension, tachycardia, tachypnoea, decreased oxygen saturation, elevated blood glucose and CRP levels and leukocytosis were the most frequent. When diagnosing pneumonia we concurrently determined the severity grade of the disease processes based on the CURB-65 and PSI scores [2,7]. Based on the PSI, 708 patients were classified as moderately severe Grade II–III stage (70–90 points), while 1128 cases were classified as unfavourable Grade IV–V stage (91–130 points). The 1826 patients have undergone a total of 436 computer tomographic angiography scans due to elevated D-dimer value, haemoptysis, sinus tachycardia and atrial fibrillation tachyarrhythmia. Acute, non-massive pulmonary embolism was confirmed in 184 cases. The remaining 1102 patients with CAP were further analysed.

The severity of the condition of patients with sepsis was previously determined using the SIRS definition characterised by hyperventilation (PaO2 <32 mmHg), tachycardia, high fever, and leukocytosis or leukopenia [8]. This previous recommendation distinguished between three pathologies, namely sepsis consisting of SISR plus infection; severe sepsis consisting of SISR plus infection plus organ dysfunction; and septic shock consisting of severe sepsis plus hypotension (even with adequate fluid replacement) [9,10]. According to the recommendations ("Sepsis=3") of the international consensus conference held in 2016, sepsis can be divided into local infection (a disease process accompanied by acute inflammation); sepsis (infection plus organ dysfunction) and septic shock (sepsis plus resistant hypotension plus elevated serum lactate level) [11]. The diagnosis of multiorgan dysfunction is recommended to be based on the evaluation of qSOFA criteria (respiratory rate > 22/min, altered mental state and hypotension) and the SOFA assessment [10,11]: the SOFA score assesses and classifies respiratory, cardiovascular, hepatic, renal, nervous and coagulation system dysfunctions [10].

Table 1: Abnormalities detected on chest X-ray images in community acquired pneumonia (n=1826).

Radiological abnormalities	Number of patients (n/%)
Unilateral involvement, single lobe	426/23
Unilateral infiltrate, multiple lobes	372/20
lateral infiltration, multiple lobes	315/17
Complete unilateral lung opacity	268/14
Presence of pleural fluid	213/5
Cavitation	96/5

Table 2: General clinical symptoms in our patients with community acquired pneumonia.

General clinical symptoms	Number of patients (n = 1826)
Age	66.8 (44–82)
Sex	female: 873, male: 951
Fever	1588
Chills	690
Chest pain	1324
Coughing, expectoration	1382
General symptoms (weakness, weight loss, lack of appetite)	1296
Disorientation	395

Table 3: Typical clinical symptoms in our patients with community acquired pneumonia (n=1826).

Clinical symptoms and laboratory abnormalities	Results
Fever, °C	38.8 (38.6–39.6)
Heart rate (BPM)	118 (94–132)
Systolic blood pressure (mmHg)	108 (69–138)
Diastolic blood pressure (mmHg)	68 (64–86)
Respiratory rate (/min)	28 (22–36)
Oxygen saturation (%)	86 (80–92)
Blood glucose level (mmol/L)	9.6 (6.6–14)
Urea nitrogen level (mmol/L)	12 (9.4–17.0)
White blood cell count (/μL)	13,400 (11,000–17,600)
Haemoculture positivity	n=367

Among 1102 patients, 32 patients had confirmed septic shock based on the severity grade, they were transferred to the Central Intensive Care Unit for continued therapy. 218 cases showed clinical symptoms and laboratory values of typical sepsis. In addition to general clinical symptoms (fever, chest pain, dyspnoea, coughing, debilitating weakness, malaise), characteristics indicating the development of sepsis were observed (Table 4): among them hypotension, high respiratory rate, decreased oxygen saturation, and elevated CRP and plasma procalcitonin values were the most frequent. Samples for haemoculture were taken before initiating antibiotic treatment and 86 patients with

sepsis were confirmed to have been infected by a pathogenic microorganism, most frequently by Streptococcus pneumoniae (n=38), Haemophylus influenzae (n=13) and Staphylococcus aureus (n=11). In the rest of the cases, infections caused by Pseudomonas aeruginosa, Moraxella catarrhalis and Legionella pneumophyla were shown with almost equal frequency. We have also analysed the presence of comorbidities in our septic patients. In the group of 218 patients, 149 had previously diagnosed and treated conditions: the most frequent among them were various cardiovascular conditions (n=36), COPD (n=32), and previously treated malignancies (n=22). Less frequent comorbidities included diabetes mellitus (n=20), liver disease (n=15) and neurological disorders (n=17).

Table 4: Typical clinical symptoms and laboratory abnormalities in our patients with community acquired pneumonia complicated by sepsis (n=218).

Clinical symptoms	Number of patients (n = 218)
Fever > 38.5 °C	179
Hypothermia < 36 °C	14
Heart rate > 90/min	189
Tachypnoea: respiratory rate > 30/min	176
Hypotension: systolic BP < 90 mmHg	138
Hypotension: diastolic BP < 60 mmHg	92
Arterial hypoxemia: PaO2 < 80 mmHg	159
C-reactive protein (mg/L)	168 (112–220)
Plasma procalcitonin (µL)	4.6 (1.6–10)
Serum urea nitrogen (mmol/L)	14 (10–19.6)
Blood glucose (mmol/L)	10.8 (8.2–18.9)
Altered mental status	97
Positive haemoculture *	86

• For details see the body of the text.

Haematologic abnormalities were examined in the 218 patients with sepsis; in all cases the following values and characteristics were evaluated at least twice a week: haemoglobin and hematocrit values, RBC counts, qualitative and quantitative changes in WBCs, changes in platelet counts, as well as the laboratory values indicating the function of the coagulation system (prothrombin time, partial thromboplastin time, serum fibrinogen, and D-dimer). In cases of severe haematologic abnormalities, more frequent, daily monitoring was instituted. Serum iron, folic acid and vitamin B12 levels, total iron binding capacity and transferrin levels were determined and both direct and indirect Coombs tests were performed.

For patients with sepsis, choosing the correct antibiotic therapy is of crucial importance; when choosing antibiotic therapies for our patients a key aspect of the choice was to use an empiric therapy that was effective against both Gram-positive and Gram-negative pathogens as well as "atypical" microbes. Targeted antibiotic therapy was used in cases where the haemoculture gave positive results. Additional measures included fluid and electrolyte supplementation, correction of carbohydrate metabolism, non-invasive oxygen therapy, correction of acid-base imbalance, and preventive LMWH therapy. Temporary renal replacement therapy was required in four cases.

Haematologic Abnormalities in Patients with Clinical Signs and Symptoms of Sepsis

Based on the tests performed in our septic patients, anaemia was the most frequent abnormality (n=159, 73%) (Table 5). Marked anaemia, characterised by haemoglobin values in the range of 83–100 g/L was detected in the majority (n=91) of the cases. Normochromic normocytic type anaemia was detected in 112 patients, while 72 patients had hypochromic microcytic anaemia with low serum iron values (2–5 µmol/L). In 11 cases, vitamin B12 and folic acid deficiencies also contributed to the development of anaemia. In 21 patients, anaemia was worsened by occult gastrointestinal bleeding (ulcerative oesophagitis or ventricular erosions). Haemolytic anaemia was confirmed in 2 cases.

The examination of the qualitative and quantitative changes in white blood cells showed variable degree leukocytosis (WBC counts 12,000–19,000/µL) in a significant proportion of the cases (n=151, 69%). Among them, 6 patients had extreme leukocytosis (WBC > 50,000/µL) and the qualitative analysis of peripheral blood showed marked left shift changes. Leukemoid type changes in the qualitative blood counts were confirmed in the case of 3 patients: In 3–5% myelocytes and metamyelocytes were detected and sporadically single myeloid cells of atypical form were also observed. In these cases the WBC counts exceeded 20,000/µL. Leukopenia (WBC <1,800/µL) and agranulocytosis (WBC <500µL) was detected in 29 patients and 4 patients, respectively. In the case of one patient with sepsis, crista biopsy according to the Jamshidi method was performed due to severe pancytopenia and the results of the histological examination confirmed myelodysplastic type changes in the bone marrow.

Moderate increases in platelet counts (400,000–600,000/µL) were detected in 58 patients during the initial stages of the septic disease processes. However, only a few days after the development of the initial symptoms of sepsis thrombocytopenia (40,000–80,000/µL) of varying severity was confirmed in 82 patients. No haemorrhagic complications of internal organs with direct connection to thrombocytopenia were detected.

Six of the 218 septic patients were diagnosed with DIC (Table 5). In all of the cases the development of coagulopathy was detected during a period when the clinical presentation of the sepsis was at its most severe. Persistent bleeding originating from puncture sites drew attention to the development of coagulopathy. Symptoms of gingival bleeding, epistaxis, hemoptysis and haematuria were detected. Characteristic deviations in laboratory parameters (very low platelet count: < 10,000/µL, prolonged prothrombin and activated partial thromboplastin time, elevated D-dimer value, low serum fibrinogen level) confirmed the development of DIC.

Causes Leading to the Development of Anaemia in Sepsis

The inflammatory response induced by the infectious agent has a key pathogenetic role in the aetiology of anaemia that frequently

develops in sepsis [3]. Systemic inflammation leads to a decrease in the production of erythropoietin, the sensitivity of the RBC precursor cells in the bone marrow to erythropoietin decreases, leading to diminished differentiation and proliferation potential as well as a shortened life span for these cells [4,12]. Sepsis leads to a decrease in the deformability of RBCs which in turn increases viscosity, and worsening microcirculation and tissue perfusion are accompanied by the impairment of oxygen transport [12]. Anaemia developing in sepsis can be exacerbated by quite commonly occurring occult gastrointestinal bleeds which lead to a further decrease of serum iron levels [13]. Chronic conditions (liver and kidney diseases, immunological processes, long-term steroid therapy, cancers, and diabetes mellitus) diagnosed and treated before the manifestation of sepsis also contribute to the exacerbation of anaemia [3].

The degree of anaemia detected in our septic patients could be correlated with the severity of sepsis. Significant degree anaemia almost exclusively occurred in patients with severe clinical stage (category IV–V) according to PSI. Clinical experience and literature data confirm that causal treatment of the septic disease processes and supplementation of missing factors required for RBC production (iron, folic acid, and vitamin B12) lead to the alleviation and later resolution of anaemia. The administration of RBC suspension is only indicated and necessary in cases of very severe anaemia (Hgb < 85 g/L).

Qualitative and Quantitative Abnormalities of White Blood Cells in Sepsis

Quantitative WBC abnormalities are dominant during the pulmonary inflammatory processes induced by severe infections: the very frequently observed variable degree leukocytosis is a consequence of enhanced bone marrow cell activity [14]. In the bone marrow, the maturation process of myeloid precursor cells is accelerated and proliferation multiplies, thus, in addition to the mature WBCs, great numbers of immature myeloid cells are also released into the peripheral circulation, leading to marked left shift blood count characteristics [3,14]. Significantly increased numbers of WBCs (50,000/μL) are detected during extreme leukocytosis. Leukemoid reaction is identified in cases when the left shifted blood counts contain both relatively immature WBC precursor cells (myelocytes and metamyelocytes) and a low percentage of cells with atypical morphology [3,14]. In spite of the diverse and in some cases seemingly bizarre peripheral blood counts the bone marrow counts are intact and no pathological cell proliferation can be confirmed. It seems that an unfavourable disease course should be anticipated both in the case of a decrease in peripheral WBC counts (leukopenia, agranulocytosis) and the appearance of myeloid precursor cells [14].

To the best of our knowledge we were the first to observe and verify myelodysplastic type bone marrow abnormalities in sepsis: a crista biopsy was performed due to the development of severe peripheral pancytopenia and the processing and analysis of this sample verified this abnormality. During the successful treatment of sepsis the peripheral blood counts slowly and gradually improved and then normalised. A second crista biopsy was performed to exclude "denovo" myelodysplastic syndrome; however, qualitative or qualitative type bone marrow abnormalities could no longer be confirmed in this second specimen.

Quantitative Abnormalities of Platelets in Sepsis and Analysis of Coagulopathies

In the initial stages of the septic disease processes, our cases have shown a temporary moderate increase in platelet counts; however, as the sepsis progressed the development of thrombocytopenia became more typical. Based on literature data, the prevalence of thrombocytopenia in sepsis is 20%; however, thrombocytopenia occurred with a prevalence of 35–59% in our cases with severe clinical symptoms [3,8]. As a consequence of sepsis, platelets binding to injured endothelium in the small vessels of parenchymal organs are destroyed and sequestered, accompanied by the formation of microaggregates [3,8,15]. The increased production of inflammatory mediators promotes the interaction between platelets and leukocytes, which is a pathological process that further decreases the life span of platelets [8,15]. The immune pathomechanism is also an important part of the development of thrombocytopenia: the auto-antibodies capable of binding to platelets further decrease platelet counts and life span through destruction [16].

Sepsis is often accompanied by coagulation abnormalities that further exacerbate the clinical condition of septic patients and unfavourably affect their recovery potential [17-20]. Among coagulopathies, the prevalence and significance of DIC development can be highlighted. Six of the 218 septic patients were diagnosed with DIC (Table 5). For all of these patients, the development of DIC was detected during a period when the clinical presentation of the sepsis was at its most severe. Without exception, persistent bleeding originating from puncture sites drew attention to the development of coagulopathy. Additionally, symptoms of gingival bleeding, epistaxis, hemoptysis and haematuria were detected in these cases. Among laboratory abnormalities, very low platelet counts (< 10,000/μL), significantly prolonged prothrombin and partial thromboplastin time, low fibrinogen level, and elevated values of fibrin/fibrinogen degradation products (D-dimer) were detected in our patients with DIC. According to the definition recommended by the ISTH, DIC is a marked intravascular activation of the coagulation system leading to the formation of multiple microthrombi in the small vessels of parenchymal organs [18-20]. As highlighted by the ISTH, in cases of severe decompensated DIC, multiorgan dysfunction induced by systemic intravascular coagulation and haemorrhagic events caused by the consumption of coagulation factors and platelets occur simultaneously [18-20].

A thrombotic shift in the haemostasis system includes contributions from both the inhibition of the fibrinolysis process and the impaired functioning of antithrombotic proteins (antithrombin, protein C, and protein S) [17,15,19].

Table 5: Haematologic abnormalities in our patients showing clinical symptoms of sepsis.

Haematologic abnormalities	Number of patients (n = 218)
Anaemia	
Haemoglobin < 120 (83–114)	159
Hypochromic microcytic	72
Normochromic normocytic	112
Blood loss induced	21
Vitamin B12 deficiency	11
Haemolytic	2
White blood cell abnormalities	
Leukocytosis: WBC > 12,000/μL	151
Extreme leukocytosis: WBC > 50,000/μL	6
Leukemoid reaction	3
Leukopenia: WBC < 1,800/μL	29
Agranulocytosis: WBC < 500/μL	4
Platelet abnormalities	
Thrombocytosis: PLT > 400,000/μL	58
Thrombocytopenia: PLT < 100,000	82
Bone marrow abnormality	
Myelodysplastic type bone marrow	
Coagulopathy	
Disseminated intravascular coagulation	

PLT = platelets

Following the recommendation of the ISTH, the definition of SIC ("sepsis-induced coagulopathy") has become accepted in recent years [18,19,21]: it is characterised by thrombocytopenia, prolonged prothrombin time and SOFA severity degree covering primarily the development of respiratory, cardiovascular, hepatic and renal type dysfunction (Table 6). In DIC the total score reflecting the degree of severity is 5 or higher, while in SIC the same value is 4 or lower (Table 6). As the table and the score indicate, in SIC the focus of the pathological process is organ dysfunction, while DIC is characterised by coagulation system abnormalities (significant depletion of coagulation factors and platelets) [19]. The advantage and essence of the clinical use of SIC is that it shows a very marked sensitivity at the time of the development of the early initial abnormal symptoms of the coagulation system and it precedes the development of true typical DIC [18,19]: consequently, the targeted treatment of sepsis-associated coagulopathy (anticoagulant therapy, activated protein C) can be started in the early phase of the process and thus can prevent the development of DIC associated with even more severe sequelae [19,20].

In clinical practice it is important to distinguish between SIC and heparin-induced thrombocytopenia since there is an overlap between the appearance of clinical symptoms in the two pathologies [18,19]. Heparin-induced thrombocytopenia is the consequence of an autoimmune process, since the platelet activating antibodies produced in response to complexes of platelet factor 4 and heparin accelerate pro-coagulant processes and thus lead to the development of thrombophilia [19]. The platelet factor 4 dependent immunoassay is of diagnostic value in this condition [19,20]. When the development of heparin-induced thrombocytopenia is a real possibility in clinical practice, heparin therapy must be discontinued and switching to direct thrombin inhibitor (argatroban, bivalirudin) treatment is recommended [19].

Table 6: Characteristics of sepsis induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC) according to the recommendations of the International Society of Thrombosis and Haemostasis (ISTH) [19].

Laboratory abnormalities	Scores	SIC	DIC
Platelet count (x10/L)	2 1	< 100 > 100; < 150	< 50 > 50; < 100
FDP v. D-dimer	3 2 1	- - -	Significant increase Moderate increase Normal
Prothrombin time-INR	2 1	> 1.4 > 1.2; < 1.4	> 6 > 3; < 6
Fibrinogen (g/L)	1	-	< 1
SOFA severity index	2 1	> 2 1	- -
Total severity index		> 4	> 5

(FDP = Fibrinogen/fibrin Degradation Product; INR = International Normalised Ratio; SOFA= Sequential Organ Failure Assessment).

TTP and HUS are typical forms of thrombotic microangiopathies that only rarely occur in clinical practice and typically result in severe thrombocytopenia. The development of TTP is characterised by thrombocytopenia, haemolytic anaemia and extensive thrombus formation leading to microcirculatory damage [20]. TTP is an autoimmune disease where the decreased level and inhibited activity of the von Willebrand multimer cleaving specific protease, ADAMTS13 (disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) leads to platelet aggregation [18]. The decreased activity of the ADAMTS13 enzyme leads to inadequate cleaving of von Willebrand factor multimeric units and thus it cannot prevent the development of thrombophilia [20]. TTP can be successfully treated with daily plasmapheresis [18]. The development of HUS is characterised by intravascular haemolysis, thrombocytopenia and acute kidney failure [19]. Shiga toxin-induced HUS as a sequela of Escheria coli infection occurs in children, while the causal factor of the less common "atypical HUS" associated with sepsis is the activation of the complement system and it can be successfully treated by the administration of the complement activation inhibitor ecolizumab [19].

Conclusion

The development of the clinical symptoms of sepsis is caused by a complex inflammation induced by the infectious microorganism affecting the immune, inflammatory and coagulation systems of the host organism and the interactions between these systems. However, almost simultaneously with these complex pathological processes fundamental changes affect all the components of haematopoiesis: they are detected in the form of

anaemia, thrombocytopenia and the qualitative and quantitative abnormalities of white blood cells and these abnormal changes are correlated with the severity of the septic disease processes. The association of coagulopathies (DIC, SIC) and thrombotic microangiopathies with septic disease processes can be considered as acute, life-threatening complications that affect both the disease course and life prospects of the patients.

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