PATIENT WITH UNDETERMINED FULMINANT SYSTEMIC INFLAMMATORY RESPONSE SYNDROME: CLINICAL IMPLICATIONS FROM CASE REPORT

DOMINIK BURSA[1,2], MARCIN PACIOREK[1,2], DAWID POROWSKI[1,2], AGNIESZKA BEDNARSKA[1,2]
[1]Department for Adults' Infectious Diseases, Medical University of Warsaw, Warsaw, Poland - [2]Hospital of Infectious Diseases, Warsaw, Poland

ABSTRACT

Introduction*: Severe systemic inflammatory response syndrome (SIRS) is commonly related to sepsis but rare autoimmunological or hematological diseases can provide similar conditions: adult-onset Still's disease (AOSD), systemic lupus erythematous (SLE), hemophagocytic limphohistiocytosis (HLH), macrophage activation syndrome (MAS). These diseases cause cytokine storm and trigger extreme hyperferritinemia, thus they are called hyperferritinemic syndromes.*

Case presentation*: We present a case of a 55-year-old female who had fever, rash and arthralgia. She was admitted to the Hospital of Infectious Diseases in Warsaw with SIRS initially attributed to bacterial infection and suspicion of sepsis. During diagnostic management the patient developed overwhelming SIRS with hyperferritinemia. Broad-spectral antibiotics with short course of steroids were administered for the suspected autoimmunological syndrome. The response to treatment was quick. None syndromes met diagnostic criteria. After vancomycin infusion the second exacerbation appeared with acute kidney injury. Methylprednisolone pulses provided improvement. The patient met HLH criteria a few days after the second exacerbation. Slow, complete remission was achieved with immunosuppressive therapy (steroids and methotrexate). MAS was recognized due to AOSD.*

Conclusion*: The clinical presentation of patients with SIRS is nonspecific. They require thorough assessment because similar symptoms may occur in other several non-infectious conditions, such as autoimmune or hematological disorders.*

Keywords*: sepsis, systemic inflammatory response syndrome, hemophagocytic limphohistiocytosis, macrophage activation syndrome, adult-onset Still's disease, red man syndrome.*

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Introduction

Systemic inflammatory response syndrome (SIRS) is a non-specific immune system stimulation that has different sources. An infection is a common etiology of SIRS forming sepsis. Sepsis and septic shock are major healthcare problems affecting millions of people around the world each year, killing one in four (and often more) and increasing in incidence[(1)].

However, severe SIRS can occur in other rare conditions as well; particularly in connective tissue diseases: adult-onset Still's disease (AOSD), systemic lupus erythematous (SLE) or may arise from pathological immune system activation in hematological diseases: hemophagocytic limphohistiocytosis (HLH) and macrophage activation syndrome (MAS)[(2, 3)]. Both sepsis and above mentioned diseases, collectively called hyperferritinemic syndromes[(3)], are marked with similar symptoms, pathogenesis and present simultaneous hyperferritinemia. Of the great importance is the fact that these autoimmunological and hematological diseases, although very rare in incidence, imitate sep-

sis and can present as fulminant as sepsis course of disease but require different therapy. Their treatment is based on high doses of immunosuppressive agents not recommended or even potentially harmful in infectious etiology.

HLH is an uncommon syndrome associated with numerous conditions, such as neoplastic, infectious, autoimmune, or hereditary diseases. The disease is seen in all ages and has no predilection for race or sex[4]. HLH is probably significantly under-recognized in many adult critical care units mostly due to overlap between HLH and sepsis[2]. HLH is caused by a defect in inflammatory signals that results in uncontrolled hypercytokinemia, usually in a setting of congenital or acquired defective natural killer (NK)/T-cell function in the cytotoxic pathway. HLH should be suspected in cases of an unexplained, sudden onset of SIRS including fever, malaise, hepatosplenomegaly, jaundice, generalized lymphadenopathy and cytopenias[5, 6]. MAS is a rare syndrome, a subtype of HLH related to autoimmune disease, characterized by a mortality rate of 10-22%[2, 7, 8]. However, the total mortality in patients with acquired HLH syndrome exceeds 50% and can reach 100% without treatment[5].

MAS like HLH is a phenomenon characterized by cytopenia, organ dysfunction and coagulopathy associated with inappropriate activation of macrophages and uncontrolled hypercytokinemia. The epidemiology of MAS in autoimmune diseases remains an open question in many cases[7, 13]. However, among connective tissue diseases, MAS occurs most notoriously in AOSD even in the 12-14% of cases[9]. AOSD, the most common among presented diseases, remains a rare condition in general population. In the Japanese and the European populations, the reported prevalence rates range from 1 to 34 cases per 1 million persons. Women seem to be more often affected than men representing up to 70% of the patients[10]. Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder analogous to the systemic form of juvenile idiopathic arthritis. The clinical manifestations of this disease range from spiking fevers, arthritis, salmon rash, elevated liver enzymes, lymphadenopathy, hepatosplenomegaly, and serositis[9].

Case Presentation

A 55-year-old woman, previously healthy, was admitted to the Hospital of Infectious Diseases in Warsaw with suspected sepsis. She suffered from irregular fever averaging 38-39 degrees Celsius, sore throat, arthralgia, papular rash of the whole body, especially during fever peaks. On physical examination her condition was considered moderate, with tachycardia 105/min, with reddened throat, cervical lymphadenopathy and urticarial rash. Blood results revealed elevated inflammatory indicators such as leukocytosis, high concentration of C-reactive protein (CRP) and slightly increased liver enzymes (Table 1).

Medical presentation was in line with systemic inflammatory response syndrome attributed to suspected bacterial infection. Prior to antibiotic therapy with penicillin, ceftriaxone and non-steroid anti-inflammatory drugs (NSAIDs) blood cultures had been taken. In the first 3 days of hospitalization she displayed partial improvement - body temperature dropped to 37 degrees Celsius, heart rate returned to norm, white blood cells (WBC) decreased to 12.7 thousand/mL. Upon the 4th day of hospitalization fever returned in the evenings, laboratory tests showed normal WBC and continuously elevated CRP. While treatment the blood cultures were negative, abdominal ultrasound showed spleen enlarged to 13 cm, chest X-ray and echocardiography showed no deviations. Diagnosis for viral etiology was negative. Based on teeth x-ray, a maxillofacial surgeon removed one tooth as a potential source of infection but no improvement was obtained. Antinuclear antibodies panel, antineutrophil cytoplasmic antibodies, rheumatoid factor, lupus anticoagulant and anticardiolipin antibodies were negative. Biopsy of the skin lesion with muscle tissue revealed poor inflammation of connective tissue consisted of mononuclear cells, neutrophils and eosinophils with dissection of single blood vessels, but without necrosis. Besides infection in differential diagnosis, AOSD was taken into consideration.

On the 10th day of hospitalization, patient's general condition deteriorated from the morning hours, massive diarrhea occurred, body temperature rose to 40 degrees Celsius, heart rate to 130/min, respiratory rate increased to 30/min, oxygen saturation decreased to 90%. A stool immunoassay was negative for Clostridium difficile. The blood results showed signs of overwhelming SIRS with hyperferritinemia and coagulopathy (Table 1).

At this stage, four causes of exacerbation (life-threatening progression of SIRS) were taken into consideration:

1) severe sepsis as a result of the present infection progression

	On admission	10th day of hospitalization. 1st exacerbation				27th day of hospitalization. 2nd exacerbation			
Day of hospitalization	**0**	10th	11th	13th	17th	27th	28th	30th	33th
Laboratory results:									
PCT [N: <0,05 ng/ml]	0,05	44,35	11,51	1,44		100,39	50,26		0,39
Lactic acid [N: 0,7-2,1 mmol/l]	2,15	2,63	1,77			1,45	1,13	0,94	0,94
urea [N: 2,5-7,1 mmol/l]	5,25	6,24	8,61	8,74	6,43		20,45	16,67	11,14
creatinine [N: 46-92 umol/l]	59	91	63	45,4	36		260	159	82
eGFR [N: >60ml/min/1,73m2]	>60	56	>60				17	29	>60
ALT [N: 10-52 U/l]	129	130	136	222	111	91	73	63	59
AST [N: 10-36 U/l]	65	229	169	133	28	88	38	22	16
CRP [N: <10 mg/l]	263	389	212	42	14	289	250	80	16
D-DIMER [N: <500 ng/ml]	2023	93589	>200000	7827	1408	13622	9797	9119	810
Hb [N: 11,5-16,5 g/dl]	12	10,1	10,1	9,3	10,5	11,5	10,5	*8,8*	9,9
PLT [N: 128-348 G/l]	356	95	79	18	222	157	104	*62*	134
WBC [N: 4-10 tys/ml]	17	7,5	9,2	5,4	5,5	5,8	7,3	2,7	3
LDH [N: 313-618 U/l]	861	4932				1992		1245	
ferritin [N: 25-280 ng/ml]		>12000			815	2959			
IL-6 [N: <7 pg/ml]		138,6	5,2						
Total cholesterol [N: <5 mmol/l]						5,76			
Cholesterol LDL [N: <2,5 mmol/l]						3,45			
Cholesterol HDL [N: ≥1,2 mmol/l]						1,49			
Triglyceride [N: <1,7 mmol/l]						4,09			
Blood smear:									
Immature neutrophils [N: 0-5 %]	15	81	76	22	7	44	60	35	7
Neutrophils [N: 40-70 %]	68	11	15	54	80	42	30	50	67
Monocytes [N: 5-12 %]	6	0	1	3	4	3	1	2	2
Mielocyte [%]	1	3	1	0	0	1		0	0
Metamielocyte [%]	0	0	2	0	0	1	2	0	0

Table 1: Results of laboratory examination: on admission and during the first and second exacerbation. On admission results indicated SIRS, first and second exacerbations presented overwhelming inflammation with deteriorating coagulopathy and cytopenia. Abnormalities turned out to be hints of HLH, but HLH criteria[6] were met not until the 4th day of second exacerbation (i.e. 30th day of hospitalization): Hb 8.8 g/dL, PLT 62 G/L. Abbreviations: PCT - procalcitonin; eGFR - estimated glomerular filtration rate; ALT - alanine aminotransferase; AST -aspartate transaminase; CRP - C-reactive protein; Hb - hemoglobin; PLT - platelet count; WBC - white blood cells; LDH - lactate dehydrogenase; IL-6 - Interleukin 6; LDL - low-density lipoprotein; HDL - High Density Lipoprotein.

2) severe sepsis as a result of a new infection (healthcare-associated infection, HAI)

3) progression of suspected connective tissue disease (i.e. AOSD)

4) pathological immune reaction (i.e. HLH, or MAS resulting from AOSD).

Vancomycin, meropenem and methylprednisolone (3x80 mg) were administered intravenously with a quick improvement of general condition.

On the 2nd day of exacerbation body temperature and heart rate were normalized, however, d-dimer reached the highest concentration (>200000 ng/mL), whereas on the 4th day of exacerbation the lowest hematological parameters were observed (Table 1). Clinically she remained stable, without complaints and with normal vital signs (body temperature, heart rate, respiratory rate).

The manifestation of the observed disease, additional tests results and treatment effects indicated hyperferritinemic syndrome, however the patient did not meet criteria of any entities included in that syndrome. Seven days after antibiotic withdrawal, methylprednisolone gradually was replaced by oral prednisone (1mg/kg/d). The patient remained in a good, general condition with normal inflammatory parameters.

On the 25th day of hospitalization (15 days after the first exacerbation) fever with chills appeared, CRP rose moderately. Blood cultures were taken from peripheral vain and central catheter. A methicillin-resistant Staphylococcus haemolyticus was isolated from central blood. Central catheter was removed and treatment with vancomycin started. During the infusion of the first dose of vancomycin the patient developed a "red man syndrome" accompanied by fever and general deterioration. Blood results again indicated sever inflammation, but additionally with acute kidney injury (Table 1.) The patient developed the second exacerbation.

However, at that stage, only non-infectious causes of severe SIRS were considered. Five-day pulses of methylprednisolone at a dose of 1000 mg were applied obtaining a quick clinical improvement and a gradual reduction of inflammatory indicators, serum creatinine and urea concentration. It was not until the 4th day of the second exacerbation that the patient's laboratory abnormalities met the criteria of HLH-2004 (Figure 1). Eventually, she was diagnosed with MAS following AOSD.

1. Fever
2. Splenomegaly
3. Cytopenia
   hemoglobin <9 g/dL,
   or platelets < 100 G/L,
   or neutrophil count < 1000/mL
4. Hypertriglyceridemia or hypofibrinogenemia
   Fasting triglycerides ≥3.0 mmol/L, or fibrinogen < 1.5 g/L
5. Serum ferritin > 500 ng/mL
6. Hemophagocytosis in bone marrow, spleen, or lymph node
7. Low or absent NK cell activity
8. Soluble CD25 (soluble IL-2 rec) >2.400 U/mL

Figure 1: HLH-2004 Diagnostic Criteria[6]. At least five out of eight listed criteria to recognize HLH.

No additional tests (NK cells activity and CD25 concentration) were taken and bone marrow aspiration was not performed because the patient had already received pulses of methylprednisolone so the results would have been unreliable. Eventually, the dose of prednisone was increased to 1.5 mg/kg/d and methotrexate 15 mg/week was added. After being discharged from hospital the patient remained under observation for the next 12 months. Prednisone was gradually reduced to 5 mg/d, methotrexate was increased to 30 mg/week. The patient fully recovered and returned to professional and home activities.

Discussion

The presented case shows the difficulty in proceeding with a patient who during their fever diagnosis develops generalized inflammatory syndrome with multiple organ failure requiring immediate targeting of treatment. The greatest dilemma resulted from the occurrence of severe SIRS with hyperferritinemic syndrome simultaneously with negative history of chronic diseases, which could be a clue for the proceeding exacerbation. Ultimately, the first episode of exacerbation was interpreted as MAS due to newly diagnosed AOSD[7, 10, 11].

The second exacerbation was associated with the administration of vancomycin after finding a positive blood culture. During vancomycin infusion the patient presented a "red man syndrome" and high concentrations of acute phase proteins, d-dimer, creatinine and urea. Vancomycin is cited as one of the drugs which can induce MAS[12]. The "red man syndrome" often depends on the speed of vancomycin infusion. In the light of previous use of vancomycin without complications this mechanism seems to have played a part.

In the presented case, both the overall view of the illness and the coexistence of the laboratory abnormalities (listed below) deviating from typical to uncommon among septic patients suggested non-infectious background of severe SIRS:

1) Relatively low (<3 mmol/L) lactic acid concentration in the blood serum in comparison to high inflammatory parameters. Among patients with severe sepsis lactic acid concentration is typically greater than 4 mmol/L, which reflects the severity of the inflammatory reaction and anaerobic glycolysis.

2) Concentration of d-dimer at the level of 100000, 200000 ng/mL without concomitant disseminated intravascular coagulation should be interpreted as a sign of a serious inflammatory response syndrome due to MAS.

3) Hematological disorders:

a) the overwhelming percentage of immature forms of granulocytes on the first day of exacerbation, reaching 81%, implies a massive stimulation of bone marrow.

b) progressing cytopenia suggested the onset of MAS, although this may also occur in severe sepsis.

4) Hyperferritinemia (over 12000 ng/mL) pointed to a pathological inflammatory reaction, which deviates from the concentration reported in patients with sepsis[3, 5].

Conclusion

It should be remembered that there are patients manifesting ambiguous conditions related to rheumatology, hematology and infectious diseases. In case of patients with an acute sepsis ineffectively treated with antibiotherapy other origins of severe SIRS should always be suspected, such as hemophagocytic syndromes, hematological diseases or severe connective tissue diseases. In case of ambiguity one should follow the individual course of a disease, an overall clinical manifestation and laboratory deviations, as well as immediately expand antibiotherapy, introduce immunosuppressive therapy even if, as in the presented case, HLH/MAS criteria are not met.

A relatively low concentration of lactic acid despite remarkably high inflammatory markers (d-dimer and the percentage of immature neutrophils), especially in the early phase of HLH, is worth noting and requires further studies.

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Corresponding author
DOMINIK BURSA
7/6 Lecha st., 05-400 Otwock
(Poland)