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CASE REPORT PERIOPERATIVE MEDICINE

Undetected intraabdominal sepsis due to prolonged corticosteroid therapy in systemic lupus erythematosus: a case report and literature review

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ABSTRACT

Gastrointestinal manifestations are not included in the criteria for diagnosing systemic lupus erythematosus (SLE) by the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) 2019, however, gastrointestinal disorders are one of the potentially fatal complications of SLE. Mesenteric vasculitis and thrombosis are the two main mechanisms that cause gastrointestinal disorders in SLE patients. Long-term immunosuppressants used by SLE patients might alter the immune system's response to infection, leading to immunoparalysis. The delay in recognizing might cause sepsis, thus increasing the mortality risk.

A 47-year-old woman with a history of SLE complained of hematochezia. The patient had been consistently consuming 12 mg of methylprednisolone every day for the past five years without doctor's supervision. Past medical history of congestive heart failure (CHF) caused by coronary arterial disease (CAD). After 24 days hospitalized for observation of hematochezia, an emergency laparotomy was performed due to deterioration caused by peritonitis. Intraoperative, 60 cm of jejunal necrosis was identified and intestinal resection was done. The patient's condition improved in two days after emergency laparotomy and intensive treatment. The undetected intraabdominal sepsis caused by jejunal infarction and gut necrosis due to long-term use of corticosteroid that masked the manifestations of severe infection in the gastrointestinal tract infarction and necrosis.

Abbreviations: NLR - neutrophil to lymphocyte ratio; SGOT - serum glutamic oxaloacetic transminase; SGPT - serum glutamic pyruvic transminase; eGFR - estimated glomerular filtration rate; PT - prothrombin time; APTT - activated partial thromboplastin time; INR - international normalized ratio

Keywords: Systemic lupus erythematosus, Intraabdominal sepsis, Immunoparalysis, Corticosteroid

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1. INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that has potential to cause multiorgan damage. The formation of antigen-antibody complexes cause inflammation that affect all organs.[1,2] The most affected organs are the musculoskeletal, hematopoietic, cardiopulmonary, and integumentary systems. While gastrointestinal manifestations are less common, it is one

of the most noteworthy complications of SLE, that can be life-threatening if not treated promptly.

So far, several mechanisms have been suggested that cause gastrointestinal manifestations, which generally include mesenteric vasculitis and thrombosis.[1] It is challenging to identify the incidence of infections in SLE patients that have been put on long-term immunosuppressant therapy. The compromised immune system may lead to delay in early recognizing signs and symptoms of infection and subsequent sepsis, thus increasing the mortality risk due to the delayed treatment. The infection-related mortality rate in SLE is known to be five times higher than in the general population.[3]

In this case, we noticed that long-term administration of corticosteroid medications in SLE patients may result in immune system collapse, thus masking the manifestations of infection and necrosis in the gastrointestinal tract.

2. CASE REPORT

A 47-year-old woman came to the emergency department at Fatmawati General Hospital with complaints of hematochezia one week before her admission to the hospital. The patient had a history of SLE with a positive anti-nuclear antibody (ANA) test with a homogeneous nuclear pattern with a titer above 1:1000 and a decrease in C3 and C4 complement. The patient had been consistently consuming 12 mg of methylprednisolone every day for the past five years without doctor's supervision. Past medical history included admission to another hospital two weeks before for congestive heart failure (CHF) caused by coronary artery disease (CAD) with an ejection fraction (EF) of 24%. The patient still experienced intermittent chest pain and shortness of breath during activities.

On admission at the emergency department, the patient was conscious and vital signs were stable. The blood examination indicated normochromic normocytic anemia with hemoglobin level of 9.6 g/dL. The electrocardiogram (ECG) showed a non-ST-elevation myocardial infarction (NSTEMI), with increased troponin T (29 ng/L). The patient was diagnosed with hematochezia; SLE with mucocutaneous, musculoskeletal, cardiac, and renal manifestations (albuminuria (+3)), proteinuria (2936.0 mg/24 h); and stable angina pectoris (Figure 1). The fluid resuscitation with 0.9% NaCl 500 mL was administered every 24 h, 40 mg of esomeprazole injection per 12 h, 500 mg of tranexamic acid injection per 8 h, and 2 packs of packed red cell (PRC) transfusion. The patient was hospitalized for gastrointestinal tract bleeding observation. Further

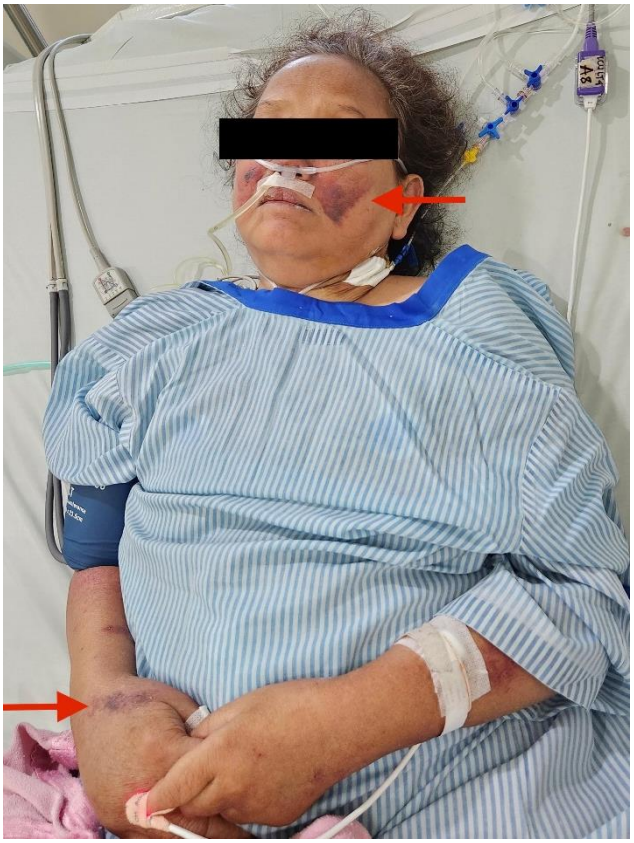

Figure 1: Mucocutaneous manifestation of SLE as butterfly rash (red arrows)

examination with endoscopy and colonoscopy did not reveal any abnormalities.

During hospitalization, after 24 days the patient's condition deteriorated. She suffered from abdominal distention and decreased level of consciousness. The hemodynamic was stable with the blood pressure of 160/100 mmHg, heart rate of 99 beats/min, respiratory rate of 18 breaths/min, the body temperature of 36°C, and no signs of infection. On the other hand, the laboratory findings showed C-reactive protein (11.78 mg/dL) and procalcitonin (10.56 ng/mL) levels were significantly increased. There was also renal dysfunction with an increase in blood urea (133.8 mg/dL) and creatinine (1.28 mg/dL) levels. The abdominal CT-scan showed thickening of the ileum wall of the right lower hemiabdomen regarding an indication of obstruction and dilatation of the small intestine, symmetrical thickening of the long segment of the caecum wall up to the ascending colon regarding an indication of colitis, and ascites (Figure 2).

Emergency laparotomy was performed due to abdominal distention with signs of peritonitis. Intraoperative, 60 cm of jejunal necrosis was identified and resection was

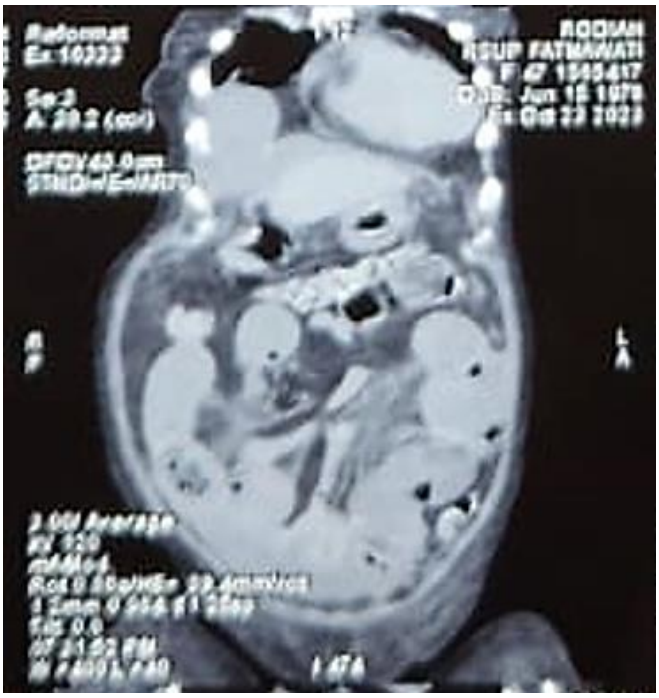

Figure 2: Abdominal CT-scan showing a thickening of the ileum and caecum up to the ascending colon

done. The tissue was sent for histopathological examination. The result showed inflammatory cells,

including lymphocytes, plasma cells, eosinophils, and neutrophils in the lamina propria and stroma to the serosa, indicating active chronic inflammation and hemorrhagic infarction in the jejunum.

After surgery, the patient was admitted to the intensive care unit (ICU) on mechanical ventilation support. She was treated with a combination of meropenem, amikacin, and fluconazole. Continuous furosemide was infused to increase the urine output. The patient's condition improved after two days of intensive treatment, she became conscious and then was extubated in stable hemodynamics. The renal function also improved and the patient was transferred to the high-dependancy unit (HDU).

3. DISCUSSION

The diagnosis of SLE in this case was made according to the criteria from the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) in 2019. The ANA test showed a positive result with a homogenous nuclear pattern and a titer >1:1000. Furthermore, the ACR also determines the additional seven clinical criteria, e.g., constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal, and three immunologic criteria, e.g., antiphospholipid antibodies, complement proteins, and SLE-specific antibodies. Patients are classified by at least one criterion and ≥10 points.[4] Clinical criteria that were observed in this patient during her medical care included leukopenia, autoimmune hemolysis, oral ulcers, acute cutaneous lupus, pleural effusion, pericarditis, joint involvement, proteinuria, and low complement C3 and C4. Antiphospholipid antibodies and SLE-specific antibodies tests were not performed on this patient.

Gastrointestinal disorders are one of the complications of SLE that could be potentially life-threatening, if not managed appropriately. The small intestine, predominantly the jejunum or ileum, seems to be the most commonly involved. In this case, the patient experienced abdominal distention along with a history of hematochezia. The abdominal CT-scan examination revealed thickening of the ileum wall in conjunction with small intestine dilatation and obstruction. This may represent a manifestation of chronic intestinal pseudo-obstruction (CIPO) with its complications. CIPO is a condition resulting from autoimmune inflammation of the visceral smooth muscle and enteric nervous system. CIPO is characterized by ineffective intestinal propulsion.[1] The underlying mechanism is vasculitis, which causes chronic ischemia of intestinal smooth muscle that leads to muscular destruction and hypomotility. Another possibility is dysmotility of the muscularis propria.[5]

In this case, the patient was hospitalized for 24 days and developed signs of peritonitis, thus underwent an emergency laparotomy. Intraoperative, jejunal infarct and necrosis were identified. Intestinal infarction or necrosis is a complication of CIPO, that was undetected. Ischemic enteritis of the small intestine is a trigger of intestinal infarction or necrosis, regarded as a manifestation of lupus mesenteric vasculitis (LMV), that is associated with CIPO mechanism.[1,5] LMV constitutes one of the causes of acute abdominal pain in SLE patients. LMV is classified into acute ischemic enteritis associated with the small intestine and chronic multiple ulcers in the colon.

Approximately 8-40% of SLE patients experience acute abdominal pain during the active phase of the disease, however LMV is an uncommon condition in SLE patients, yet may result in severe complications. The prevalence of LMV in SLE patients in Asia ranges from 2.2-9.7%, while the prevalence of LMV in America is much lower (0.9%). Patients with intestinal infarction and necrosis tend to have a poor prognosis of SLE, that

Table 1: The laboratory results

Parameters	Normal values	At admission	Pre-operative	Post-operative
Hemoglobin (g/dL)	11.7-15.5	9.6	10.5	11.9
Leukocytes ($\times10^9$/L)	5.0-10.0	4.6	12.7	11.0
Platelets ($\times10^9$/L)	150-440	240	171	111
Absolute Lymphocytes (/µL)	≥1500	906	635	635
NLR	4.0	3.3	17.7	14.6
SGOT (U/L)	≤ 32	42	39	15
SGPT (U/L)	≤ 33	24	42	21
Ureum (mg/dL)	16.6-48.5	28.9	-	133.8
Creatinine (mg/dL)	0.51-0.95	0.72	-	1.28
eGFR (mL/min/1.73m^2)	≥ 90	100.04	47,64	49.90
Albumin (g/dL)	3.5-5.2	-	2.01	2.01
HS Troponin T (ng/L)	≤ 14	29	-	-
PT (sec)	11.7-15.1	12.4	12.5	18.3
APTT (sec)	25.0-33.0	27.8	20.1	34.9
INR		0.89	0.9	1.34
Fibrinogen (mg/dL)	176-444	-	-	275
D-Dimer (ng/mL)	< 500	-	-	360
Sodium (mmol/L)	136-145	139	138	142
Potassium (mmol/L)	3.5-5.1	4.2	4.3	3.5
Chloride (mmol/L)	98-107	113	108	109
Magnesium (mmol/L)	1.6-2.6	-	-	2.0
Calcium ion (mmol/L)	1.00-1.15	-	-	1.07
Blood glucose level (mg/dL)	70-140	79	-	89
C-reactive protein (mg/dL)	< 0.5	-	-	11.78
Procalcitonin (ng/mL)	< 0.5	-	-	10.56
Lactate (mmol/L)	0.5-2.2	-	-	1.7
Amylase (U/L)	13-53	-	52	-
Lipase (U/L)	13-60	-	75	-
pH	7.37-7.44	-	7.46	-
PCO_2 (mmHg)	35.0-45.0	-	34.7	-
PO_2 (mmHg)	83.0-108.0	-	138.9	-
HCO_3 (mmol/L)	21.0-28.0	-	25.1	-
Base Excess (mmol/L)	-2.5-2.5	-	1.1	-
Total CO_2	19.0-24.0	-	26.1	-
SaO_2 (%)	95.0-99.0	-	99.1	-

NLR, neutrophil to lymphocyte ratio; SGOT, serum glutamic oxaloacetic transminase; SGPT, serum glutamic pyruvic transminase; eGFR, estimated glomerular filtration rate; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen; SaO_2, oxygen saturation

somewhat is significantly associated with morbidity. Therefore, early diagnosis and treatment are critical in managing this condition.[5]

In this case, the patient had never presented with any signs suggestive of acute abdominal pain and intraabdominal sepsis. We suspected that the patient had been experiencing immunoparalysis related to long-term uncontrolled consumption of corticosteroid (methylprednisolone). The use of anti-inflammatory agents is correlated with downregulation in both the innate and adaptive immune capabilities. This condition masked the manifestation of intraabdominal sepsis.[6]

Corticosteroids modulate the host's defense response at almost all levels and suppress the hyperactivity of the host's immune system. Free corticosteroid molecules pass through the plasma membrane into the cytoplasm and bind to a specific receptor, the glucocorticoid receptor (GR). Upon hormone binding, the GR complex shifts to the nucleus and inhibits the inflammatory genes' transcription, including nuclear factor (NF)-κB and activator protein-1, which are activated by extracellular inflammatory signals received by cell surface receptors.[7]

NF-κB is a crucial transcription factor that stimulates the inflammatory response to infection. Activation of NF-κB entails activation of IκB kinase which rapidly phosphorylated IκBα in response to various pro-inflammatory signals, such as endotoxins, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, oxidants, bacteria, viruses, and phorbol esters. Following its release, NF-κB translocates into the nucleus and binds to the target gene's promoter region to initiate the transcription of several cytokines, including TNF-α, and IL-1β, IL-2, and IL-6, as well as chemokines, including IL-8, cell adhesion molecules, growth factors, interferons, receptors involved in immune recognition, antigen presentation receptors associated protein required for neutrophil adhesion and migration, and inflammation-related enzymes. TNF-α and IL-1β activate and are activated by NF-κB by forming a positive regulatory loop that enhances and maintains inflammation.[7]

Corticosteroids inhibit NF-κB and inhibit the transcription of related cytokines, including IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, TNF-α, and granulocyte-macrophage colony-stimulating factor. Corticosteroids likewise have an inhibitory effect on fibrinogenesis, and act as antagonists of the IL-1 receptor and the anti-inflammatory cytokines IL-4, IL-10, and IL-13 in synergy to control the host defense response. Glucocorticoids stimulate apoptosis of T cells, eosinophils, and monocytes, and inhibit neutrophil activation.[7] The use of corticosteroids that trigger the production of immunosuppressant chemicals induces programmed death 1 (PD1) and its ligand (PD-L1) increases in antigen-presenting cells, subsequently inhibiting the activation of T lymphocytes. Furthermore, adaptive immunity will be suppressed by an increase in immunosuppressive T-cell subpopulations, including myeloid-derived suppressor cells and CD4+ and CD25+ T-regulatory cells (Treg).

Treg actively produces anti-inflammatory cytokines, including TGF-β and IL-10; downregulates the secretion of pro-inflammatory mediators; neutralizes cytotoxic T cells; and inactive monocytes. Immune cells will experience greater apoptosis, and subsequently, phagocytosis of apoptotic cells by circulating macrophages, which leads to the macrophages' transition to the M2 phenotype, characterized by increased production of the anti-inflammatory substances IL-10 and IL-1ra. In summary, these mechanisms include an increase in apoptosis that leads to decreased immune cells, loss of antigen presentation, reduced response to pathogen-associated molecular patterns (PAMPs), and decreased cellular energy production. All of these responses are the consequence of epigenetic changes that cause activation or deactivation of genes, involving the immune response over intervals of time, and the outcome of this phenotype is an intense inflammatory response or, contrary, immunoparalysis.[6]

Immune dysfunction plays a role in the increased risk of sepsis in patients on immunosuppressant therapy. Iatrogenic immune deficiency threshold in predicting sepsis risk includes neutropenia, absolute neutrophil count <500 cells/mm^3; monocyte deactivation or immune paralysis determined by monocyte human leukocyte antigen class II (HLA-DR) expression <30% or <8000-12000 molecules per cell; lymphopenia, absolute lymphocyte count <1000 cells/mm^3; and hypogammaglobulinemia, IgG level <500 mg/dL.[8] The absolute lymphocyte count in this case decreased significantly upon admission and preoperatively, going from 906 cells/mm^3 to 635 cells/mm^3.

A significant drop in absolute lymphocyte count correlated with an increase in CRP and procalcitonin might indicate the possibility of sepsis in the patient. However, in cases of iatrogenic immunoparalysis induced by the long-term use of immunosuppressants (corticosteroids), the compensatory anti-inflammatory response (CARS) dominates, resulting in loss of immune capacity and signs of sepsis which typically are assessed using sequential organ failure assessment (SOFA) disguised.

The mechanism underlying multiple organ dysfunction in sepsis is still unknown. However, it is now known that the gut microbiome plays a role in this mechanism. Microbiome imbalance, called dysbiosis, is the most commonly affected intestinal physiological issue. This has been observed that the gut microbiome influences the severe responses to sepsis and harms the outcomes. A prospective cohort study showed that intestinal dysbiosis with the accumulation of bacilli and their fermentation metabolites is involved in late-onset sepsis.[9] Based on this, we believe that the intestinal damage and necrosis in this case were also caused by dysbiosis.

Basic management of sepsis was implemented, including early resuscitation, use of vasopressors if necessary, and administration of appropriate broad-spectrum antibiotics and source control. Other supportive therapies such as monitoring of fluid balance, administration of anticoagulant, nutritional therapy, and other supporting medications in this case have proven to be effective, even in immunosuppressed conditions.[5,10] However, it is not recommended to give anti-inflammatory medications (such as high-dose steroids or anti-cytokine therapy) to septic patients with immunoparalysis, except in refractory shock. Adjuvant immunostimulatory therapy could be beneficial for septic patients with immunosuppression, however this has not been proven to be clinically convincing.[10]

4. CONCLUSION

The manifestation of SLE in each organ has its own complexity, especially in the gastrointestinal system. Poor outcomes might be associated with the complexity of SLE patient's condition as well as non-compliance with control and treatment. Continuous and long-term use of corticosteroids suppresses the immune system in SLE patients and subsequently causes an immune dysfunction that leads to immunoparalysis. This condition plays a crucial part which masks the deterioration of the disease and affects organ damage such as infarct and necrosis in the gastrointestinal tract, that leads into undetected intraabdominal sepsis.

5. Ethical approval

Ethical approval was not required for this study in accordance with local or national guidelines.

6. Consent to participate

The patient's biological daughter has given their written consent for the patient's clinical information and examination results to be reported in the journal.

7. Consent for publication

Written informed consent for publication was obtained from the patient's biological daughter for publication of this case report with any accompanying images.

8. Conflict of interests

The authors declare that they have no conflict interests. The authors declare that no funding was received for this study.

9. Author's contribution

VI, SKM: Conceptualization:.

YEL: Writing-original draft.

YEL, VI: Writing-review & editing:

All authors read and approved the final manuscript.

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