SLE Manifesting as AIHA and Gut Lupus in a Male Patient

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KEYWORDS

Systemic Lupus Erythematosus, Autoimmune Hemolytic Anemia, Intestinal Pseudo-Obstruction, Corticosteroids

ABSTRACT

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that predominantly affects women but rarely manifests in males. This report presents a rare case of SLE in a 20-year-old male with autoimmune hemolytic anemia (AIHA) and intestinal pseudo-obstruction, complicated by septic shock. The patient exhibited hematologic and gastrointestinal (GI) manifestations, including anemia, malar rash, and abdominal distention. Early evaluation revealed severe anemia with hemolysis confirmed by positive Coombs tests and reduced complement levels. Imaging identified intestinal pseudo-obstruction. The primary objective was to manage hematologic and GI symptoms effectively. Methylprednisolone and cyclosporine were administered alongside antibiotics to address septic shock. Initial management included leukoreduced blood transfusion and fluid therapy. The patient demonstrated significant clinical and laboratory improvements within days, including normalized bowel function and stabilized hemoglobin levels. This case emphasizes the importance of early diagnosis and multidisciplinary management in rare male presentations of SLE. The findings also highlight the challenges of diagnosing SLE-related intestinal pseudo-obstruction due to its rarity and overlapping symptoms with other conditions. Prompt treatment with corticosteroids and immunosuppressants resulted in favorable outcomes, avoiding complications such as unnecessary surgical interventions. This study underscores the significance of considering SLE in differential diagnoses for young males presenting with hematologic and GI symptoms. Further research is necessary to explore the pathophysiology and optimal treatment approaches for rare SLE manifestations. Early intervention is critical to reducing morbidity and improving quality of life for patients with atypical presentations.

INTRODUCTION

Systemic lupus erythematosus is a multisystem autoimmune disease with various autoantibodies. A complex interplay of genetic susceptibility, gender, and environmental exposures serves as the basis of the SLE mechanism. Autoantibodies are the main effectors of the onset of disease in SLE, which is followed by activation of complement and/or other mediators of inflammation, and a series of events that include chemotaxis for lymphocytes and phagocytic mononuclear cells, and release of cytokines, chemokines, and proteolytic enzymes, as well as oxidative damage (Yazdany and Dall'Era, 2013).

SLE usually occurs in females with a ratio of female to male of 9:1. One of its female predisposition reasons is hormonal because sex differences in susceptibility are largest during reproductive years. Estradiol probably prolongs the life of autoreactive B and T lymphocytes. The other reasons could be microchimerisms and hypomethylated regions of inactivated X chromosomes in women (Hahn, 2013).

Manifestation of SLE differs from one patient to the other patient. Mild to severe manifestation and multiorgan systems could happen. Hematological manifestations of SLE include anemia, leucopenia, and thrombocytopenia. One of the prevalent causes of anemia in SLE is AIHA. Gastrointestinal (GI) symptoms are rarely reported as manifestations of SLE. Abnormal liver function test results were obtained in 23%–79% of cases and hepatomegaly in 39%–40% cases. When secondary causes are excluded, lupus can be attributed as the underlying cause. Meanwhile, intestinal pseudo-obstruction secondary to systemic lupus erythematosus (SLE) is a rare syndrome described in recent decades. Over 30 published cases have been reported, which are primarily associated with renal and hematological disease activity (García López et al., 2014).

Recognition of both hematological and gut involvement is paramount, allowing appropriate management, leading to a better prognosis, and avoiding unnecessary surgery and complications. In this paper, we report a case of SLE manifesting as AIHA and gut lupus in a male patient.

CASE STUDY

A 20-year-old male came to the ER with complaints of general weakness for 1 month, which worsened in the last four days before being admitted to the hospital. Symptoms of anemia (palpitations and pallor) were identified without mucocutaneous bleeding. The patient denied previous complaints of weakness and bleeding disorders.

The patient has not defecated since 5 days ago and feels bloated. Nausea was felt, but no vomiting was reported. There was a decrease in appetite, eating only half portions thrice per day for the past 3 days before admission. Urinary tract symptoms, shortness of breath, and fever were denied.

The patient claimed joint pain in both elbows and ankles since 1 month ago, remitting and relapsing. Red rash on the face, specifically on both cheeks and ear since 1 month ago, which felt itchy. He also suffered from hair loss, but no canker sores were observed. Symptoms of chronic liver and kidney diseases were not identified.

No history of previous hospitalization or blood transfusion was recorded. Previous liver, muscle, and autoimmune diseases were denied. The patient was a student and had not married yet. He lived only with his father because his parents were divorced. The patient's father said that the patient had looked gloomy for the last month because he missed his mother. The patient himself was an introverted person, and he did not tell his father much.

During the physical examination, hypotension of 80/60 mmHg with a regular heart rate of 88 bpm and respiratory rate of 24 times per minute were recorded, while other vital signs were unremarkable. Important findings were anemic conjunctiva, malar rash, discoid rash, and hair fall. A distended abdomen and reduced bowel sounds were found. The patient's hands were warm, wet, and pale. The color of urine collected in the urine bag was dark yellow. Reduced general motoric strength was recorded without focal neurologic deficit.

Laboratory findings at admission showed reduced hemoglobin, reticulocytosis, elevated indirect bilirubin, and high LDH levels (Table 1). A peripheral blood smear revealed hypochromic microcytic anemia with anisopoikilocytosis and spherocytes. High transaminases were found with elevated creatinine serum and blood urea nitrogen (BUN). Later, AIHA was confirmed by positive polyspecific direct and indirect Coomb's test (Table 1).

Table 1. Initial Laboratory Findings

Lab Test	Admission	Normal Range*
Hemoglobin	1.7 g/dL	11,0-14,7g/dL
MCV	116.7	86.7-102.3 fL
MCH	56.7	27.1-32.4 pg
Reticulocyte (%)	6.6%	0.80-2.21%
Reticulocyte (#)	0.02	0.034-0.100.10^6/uL
WBC	14520	3370-10000
Neutrophil/Lymphocyte	92.9%/5.3%	39.8-70.5%/ 23.1-49.9%
Platelet	181000	150-450. 10^3/uL
Direct Bilirubin	0.96 mg/dL	<0.20 mg/dL
Total Bilirubin	2.28 mg/dL	0.2-1.0 mg/dL

Lab Test	Admission	Normal Range*
AST	3249 U/L	0-37 U/L
ALT	1918 U/L	0-55 U/L
LDH	1373.2 U/L	100-190 U/L
Coombs test Direct/Indirect	Positive/Positive	Negative/Negative
Albumin	2.65 g/dL	3.4-5.0 g/dL
Random Blood sugar	94 mg/dL	<200 mg/dL
PT/aPTT	13.9 s/ 33.9 s	9-12s/ 23-33 s
BUN	37 mg/dL	10-20 mg/dL
Creatinine serum	1.6 mg/dL	0.5-1.2 mg/dL
HBsAg	Nonreactive	Nonreactive
Anti-HCV	Nonreactive	Nonreactive
Peripheral blood smear	Hypochromic microcytic anisopoikilocytosis (spherocyte+, agglutination+), atypical lymphocyte+, giant platelet+	

The source of infection was thoroughly searched. Chest x-ray showed patchy consolidation parahilar (Figure 1). Abdominal x-ray (BOF/LLD) concluded our suspicion of gut involvement with abnormal distribution of bowel gas in the left abdominal area (Figure 2). Abdomen ultrasound showed liver with AP diameter +/- 13.7 cm, sharp corners, flat edges, parenchymal echo intensity appears to increase homogeneously,no IHBD/EHBD widening is visible, and the conclusion is parenchymal liver disease. Abdominal CT was not done in this patient due to clinical improvement following therapy.

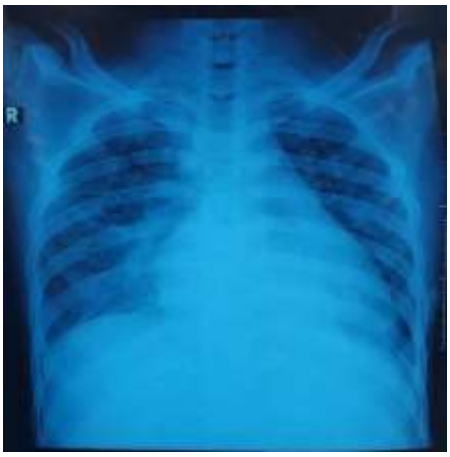

Figure 1. Chest Xray showing bilateral patchy consolidation

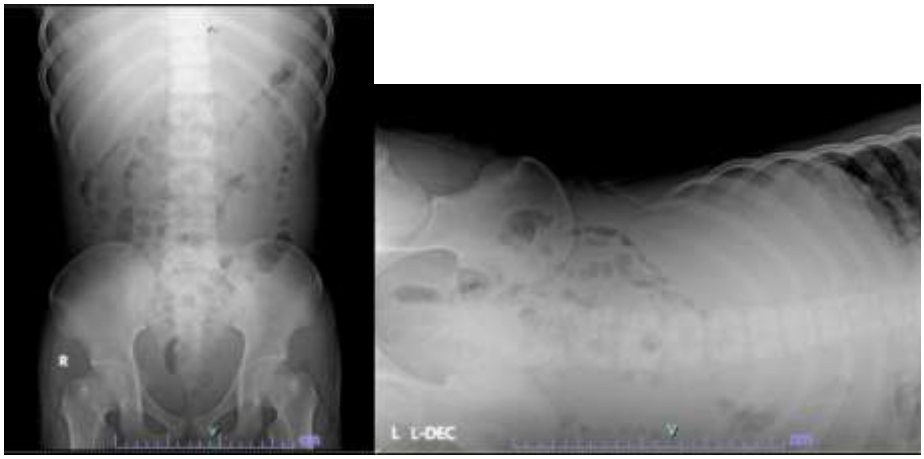

Figure 2. Abdominal x-ray consists of BOF (left) and LLD (right) showing abnormally distributed bowel gas

This patient was initially diagnosed with Autoimmune Hemolytic Anemia (AIHA). Complication of septic shock due to pneumonia was also observed. There is also an increase in transaminase (OT 3249 PT 1918), Hypoalbumin (2.65) , Hypotonic hypovolemic hyponatremia (132) and Fully compensated metabolic acidosis (high anion gap (23.9), Def bic 228).Our first goal was to reduce oxygen demand through leukoreduced PRC transfusion alongside intravenous steroids for the AIHA. We started methylprednisolone 1 mg/kgBB/day, not pulse therapy, due to septic shock. Fluid therapy, vasopressor (norepinephrine 50 mcg/kgBB/min with goal MAP $\geq$ 65mmHg), and empirical antibiotic therapy (ceftriaxone 2 g/day) were done as a part of sepsis bundle therapy.

Clinical improvement was observed on days two and three, with improvement in motoric strength (the patient started to sit alone). Blood pressure was normal (100/60 mmHg with MAP of 73 mmHg) without vasopressor. Other vital signs were unremarkable. He started to feel improvement in his bowel movements on day 4 when he could defecate and did not feel bloated anymore.

An investigation of secondary causes of AIHA was made. ANA test returned positive (Elisa method), and reduced C3 and C4 complement levels were recorded. Ds-DNA level was above the normal range (positive), but the ANA profile was not examined due to cost constraints. We excluded the possibility of myopathy by checking creatinine kinase and electromyography (as the patient complained of proximal inferior extremity weakness), but it came back normal. The possibility of lupus nephritis was rejected because only mild proteinuria (+1) was found (Table 2).

An effort was made to find the differential causes of elevated transaminases, excluding autoimmune hepatitis, through an ASMA test, which came back negative. Gamma-glutamyl transferase (GGT) was mildly elevated with normal alkaline phosphatase (ALP) levels. Electrophoresis serum did not show an increase in gamma fraction. The total serum IgG test was not done due to facility limitations. Then, this patient was diagnosed with systemic lupus erythematosus (SLE) with hematologic (AIHA) and gut (possibly intestinal pseudoobstruction, which we could not prove yet) manifestation (with cutaneous lupus, which we did not discuss further).

Table 2. Follow up Laboratory Findings

Lab Test	Admission	Normal Range*
Gamma-glutamyl transferase	73.6 U/L	5-40 U/L
Creatinine Kinase	139 U/L	7-4267 U/L
IgM anti-HAV	Nonreactive	Nonreactive
Alkaline phosphatase	117 U/L	40-150 U/L
ANA	367.0 AU/mL	≥ 40.0 = positive
C3	15 mg/dL	82-185 mg/dL
C4	5 mg/dL	15-53 mg/dL

Lab Test	Admission	Normal Range*
Anti- ds-DNA	166.0 IU/mL	≥ 30.0 = positive
ASMA	Negative	Negative
Procalcitonine	26.39 ng/mL	≥ 10 = septic shock
Proteinuria	1+	Negative
Electrophoresis serum	Reduction in albumin and beta globulin fraction; Elevated alpha1 and gamma globulin fraction with beta gamma bridging	

Laboratory improvement was observed, with continually increased hemoglobin (Figure 3), progressively reduced transaminases, infection parameters, and creatinine serum. The final laboratory parameter can be seen in Table 3.

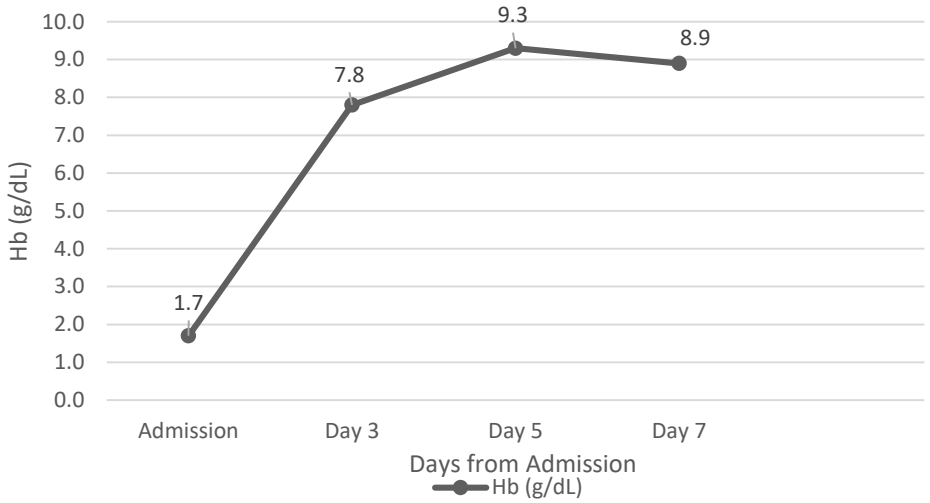

Figure 3. Hemoglobin Levels during Hospitalization (with blood transfusion)

Table 3. Laboratory Findings during Hospitalization and Outpatient

Lab Test	Admission	Day 3	Day 5	Day 7	Outpatient (Day 39)
Hemoglobin	1.7 g/dL	7.8 g/dL	9.3 g/dL	8.9 g/dL	12.4 g/dL
WBC	14520	14270	13250	6440	15230
Neutrophil	92.9%	93.3%	89.1%	72.8%	87.5%
Lymphocyte	5.3%	0.1%	4.8%	16.9%	8.7%
Platelet	181.10^3/UL	154.10^3/UL	148.10^3/UL	101.10^3/UL	291.10^3/UL
AST	3249 U/L		289 U/L	64 U/L	11 U/L
ALT	1918 U/L		663 U/L	258 U/L	29 U/L
BUN	37 mg/dL		22 mg/dL		17 mg/dL
Creatinine serum	1.6 mg/dL		0.8 mg/dL		0.7 mg/dL
Procalcitonine	26.3 ng/mL		5 ng/mL	0.57 ng/mL	0.57 ng/mL

After day four, steroid therapy was tapered down to oral (methylprednisolone 16 mg, thrice a day), and an immunosuppressant was given (cyclosporine oral 25 mg/day). Hydroxychloroquine 200 mg/day was given from day 2. The patient was discharged on day six with no symptoms. Symptomatic therapy including proton pump inhibitor and prokinetic was also given.

The patient visited the outpatient setting on day nine and d-39 and did not report any symptoms on both occasions. No weakness was felt, and no bloating or nausea was reported. Laboratory exam revealed increased hemoglobin and platelet along with improvement in liver transaminases (**Table 3**). Erythrocyte sedimentation rate (ESR) was normal (6 seconds). Corticosteroid was tapered down to 40 mg/day of methylprednisolone, given concurrently with cyclosporine oral 50 mg/day and hydroxychloroquine 200 mg/day.

DISCUSSION

Systemic lupus erythematosus is a multisystem autoimmune disease with various autoantibodies. Clinical symptoms can vary from mild symptoms such as symptoms on the skin and joints, to life-threatening symptoms such as manifestations in the kidneys and lungs. Symptoms from one person to another can vary (Yazdany and Dall'Era, 2013). In our cases, SLE manifests as hematological and gastrointestinal symptoms.

The development of SLE occurs in a long period of predisposition to autoimmunity. An interplay of genetic susceptibility, gender, and environmental exposures, and then (in a small proportion of those predisposed) development of autoantibodies usually precede clinical symptoms by months to years (Figure 1). A proportion of individuals with autoantibodies demonstrate clinical SLE, often starting with the involvement of a small number of organ systems or abnormal laboratory values and then evolving into enough clinical and laboratory abnormalities to be classified as SLE. Finally, over a period of many years, most individuals with clinical SLE experience intermittent disease flares and improvements (usually not complete remission), and compile organ damage and comorbidities related to genetic predisposition, chronic inflammation, activation of pathways that damage organs (such as renal tubules), and/or induce fibrosis, to therapies, and to aging (Hahn, 2013). Our patient is a male, still studying in high school, and had not yet checked the presence of autoantibodies. Nevertheless, he had not had any symptoms or flares previously.

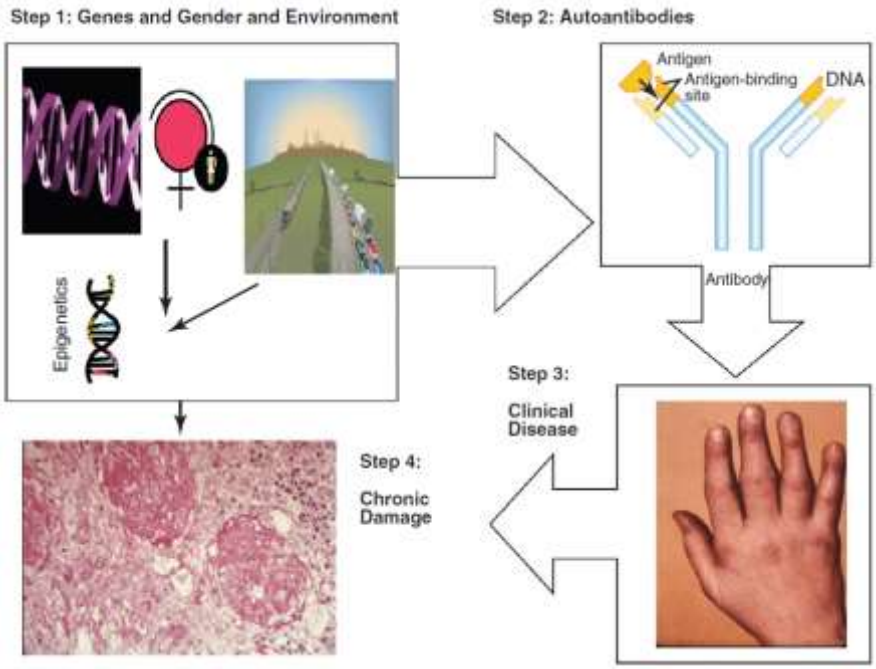

Figure 1. Development of SLE (Hahn, 2013)

Autoantibodies are the main effectors of the onset of disease in SLE (Figure 2). In humans, they are probably necessary for disease, but not sufficient. That is, their deposition must be followed by activation of complement and/or other mediators of inflammation, and a series of events that include chemotaxis for lymphocytes and phagocytic mononuclear cells, and release of cytokines, chemokines, and proteolytic enzymes, as well as oxidative damage, must occur for organ inflammation and damage to be severe. In nearly 85% of patients with SLE, autoantibodies precede the first symptom of the disease by an average of 2 to 3 years—sometimes as long as 9 years. The autoantibodies appear in a temporal hierarchy, with

antinuclear antibodies (ANAs) first, then anti-DNA and antiphospholipid, and finally anti-Sm and antiribonucleoprotein (anti-RNP). (Hahn, 2013)

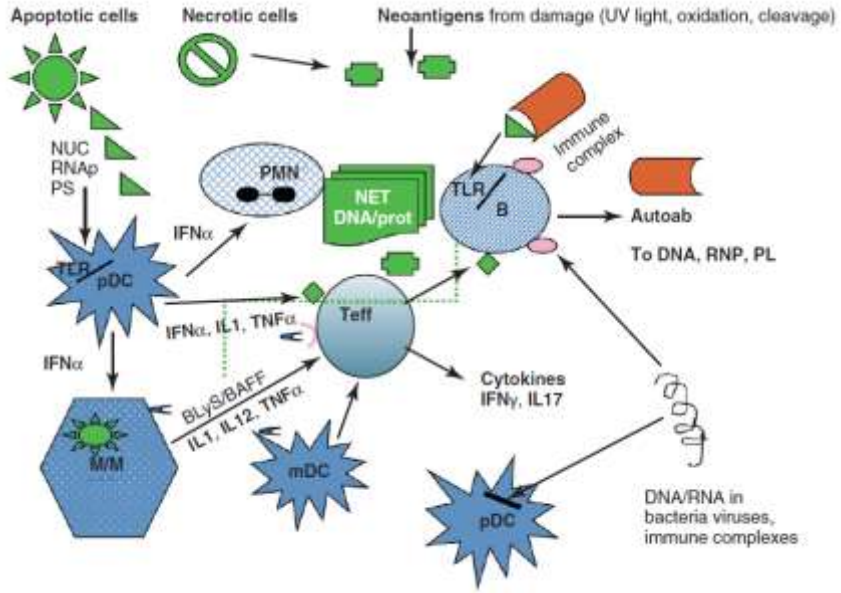

Figure 2. Autoantibodies production through the interaction of innate and adaptive immune systems (Hahn, 2013)

SLE is most often found in women of reproductive age between 13-40 years. Prevalence was found to differ according to ethnicity. SLE is found in 5.8/100,000 white people, 17/100,000 Asian people, and 11/100,000 Aboriginal people. In Asian countries themselves, differences in prevalence were found, with China, Japan, and the Philippines having a higher incidence than India and Pakistan. This is possible due to differences in data collection methods and ethnic differences in the sample population. The SLE mortality was found to be 5 times higher than the normal population, especially if it affects vital organs such as the brain, lungs, heart, and kidneys. SLE mortality rate at RSUD Dr. Soetomo was reported to be as high as 22.5% (Yuliasih, 2020).

It is very rare for lupus to affect males, as in our case, since gender influences on disease susceptibility are of major importance because there are nine women for every man with SLE. The most important impact may be hormonal because sex differences in susceptibility are largest during reproductive years. Estradiol probably prolongs the life of autoreactive B and T lymphocytes. In contrast, testosterone has been shown to have an immunosuppressant effect. Women exposed to oral contraceptives, or to hormone replacement therapy regimens containing estrogenic compounds, have a small but statistically significant increased risk for the development of SLE. Prospective, randomized, blinded, controlled trials showed that administration of one hormone replacement therapy containing conjugated estrogens and progesterone significantly raised the risk of mild/moderate disease flare in women with established SLE. However, other features of the female gender may also be important in predisposing to SLE: microchimerism in most women after pregnancy from their fetuses might set up lupus-like graft-versus-host–type immune reactions, and the X chromosome and its loci and methylation status make women predisposed to SLE because their inactive X chromosome is enriched in hypomethylated regions. The CpG in these regions can be bound by TLR9, thus activating innate immune responses and increasing the risk for autoimmunity. Lupus-predisposing genes located on the X chromosome include *TLR7/9* (where copy number seems important), *IRAK1*, and *TREX1*. Whether their location on X in humans is important in their effects remains to be determined. Additional evidence for the importance of the X chromosome

in SLE includes the observation that phenotypic men with an extra X (XXY, Klinefelter syndrome) have a significantly higher prevalence of SLE than men who are XY (Hahn, 2013).

Women with SLE also have low plasma androgens, including testosterone, dihydrotestosterone, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate. The concentrations of androgens correlate inversely with disease activity. Low concentrations of plasma testosterone and raised luteinising hormone (LH) values have been found in some men with SLE. Thus, excessive oestrogenic but inadequate androgenic hormonal activity in both men and women with SLE might be responsible for the alteration of the immune responses. The opposite effects of oestrogens and androgens on the immune system, coupled with unbalanced oestrogenic and androgenic hormonal activity in patients with SLE, may help explain some of the immune aberrations seen in this disease (Mok and Lau, 2003).

The diagnosis of SLE is obtained through clinical judgment. Existing classification criteria are used to guide the diagnosis, but not to confirm the diagnosis. The first classification criteria for SLE were developed by the American Rheumatism Association (ARA) in 1971 which consisted of 14 criteria; four or more of the 14 criteria had to be fulfilled in order for a person to be classified as having SLE. Importantly, the criteria could occur simultaneously or serially over any period. The criteria heavily emphasized mucocutaneous features by including malar rash, discoid rash, photosensitivity, and oral ulcers as independent criteria. Notably, the criteria incorporated the presence of LE cells and a false positive syphilis test result, but did not include tests for autoantibodies such as an antinuclear antibody (ANA) test and anti–double-stranded DNA antibody (anti-dsDNA) because these tests were not widely in use at the time the criteria were developed. The revised criteria for the classification of SLE were published in 1982 3 which were composed of 11 elements. Consistent with the 1971 criteria, a patient had to fulfill 4 out of 11 criteria to be classified as having SLE. Five of the elements were composites of more than one variable: serositis, renal disorder, neurologic disorder, hematologic disorder, and immunologic disorder. New potential variables were put forward, such as serologic tests and skin and kidney histopathology. In 1997, the criteria for the classification of SLE were revised for a second time in order to incorporate advancing knowledge about the association of antiphospholipid antibodies with SLE. Under the criterion “immunologic disorder,” the decision was made to exclude LE cells and insert antiphospholipid antibodies. Antiphospholipid antibodies were defined as the presence of immunoglobulin (Ig) G or IgM anticardiolipin antibodies, a positive lupus anticoagulant test result, or a false-positive serologic syphilis test result (Yazdany and Dall’Era, 2013).

Because of the limitations of the criteria previously described, Systemic Lupus International Collaborative Clinics (SLICC) classification criteria was made to further revise the ACR classification criteria. It consisted of 11 clinical and 6 immunologic elements. A patient is classified as having SLE if he or she (1) has biopsy-proven lupus nephritis with a positive ANA or anti–double-stranded DNA antibody test result or (2) fulfills four of the criteria including at least one clinical criterion and one immunologic criterion (Yazdany and Dall’Era, 2013).

The 2019 EULAR/ACR classification criteria for SLE include positive ANA at least once as obligatory entry criterion; followed by additive weighted criteria grouped in seven clinical (constitutional, haematological, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal) and three immunological (antiphospholipid antibodies, complement proteins, SLE-specific antibodies) domains, and weighted from 2 to 10. Patients accumulating ≥10 points are classified. In the validation cohort, the new criteria had a sensitivity of 96.1% and specificity of 93.4%, compared with 82.8% sensitivity and 93.4% specificity of the ACR 1997 and 96.7% sensitivity and 83.7% specificity of the Systemic Lupus International Collaborating Clinics 2012 criteria (Aringer et al., 2019). We used the newest EULAR/ACR 2019 classification criteria for our patient. Entry criteria was met, as our patient show high titer

of ANA test (though it is by ELISA and not IF method). Hematologic domain (autoimmune hemolysis) and mucocutaneous domain (acute cutaneous lupus in form of malar rash) were found as clinical domain along immunological domain (low C3, low C4, and positive anti ds-DNA antibody) with total score of 16. Lupus diagnosis was made based on clinical judgment reinforced by supporting classification criteria.

One of the hematological manifestation of SLE is anemia. Anemia in SLE consisted of various types, with descending order of prevalence: anemia of chronic disease, iron deficiency anemia, autoimmune hemolytic anemia (AIHA), drug-induced myelotoxicity, anemia of chronic renal failure, and so on (Karpouzas, 2013). AIHA is a heterogenous disorder characterized by destruction of RBC through antibodies. AIHA is further classified based on autoantibody type or the underlying disease. Warm AIHA accounts for 48-70% of patients with AIHA. Warm autoantibodies are dominated by IgG that strongly react towards erythrocytes at temperature of 37^0C, causing extravascular hemolysis through FcγRIII or C3b receptors on macrophages (Jäger et al., 2020). These autoantibodies are invariably polyclonal and flawed during T-cell regulation of humoral immune system, hence distinction function between self and non-self is defected. Gene polymorphism for signal substance CTLA-4, which activates regulatory T cells (Treg cells), increases risk of autoimmunity (Berentsen, 2015). Therefore, it is not surprising if half of warm AIHA cases were secondary to lymphoproliferative disease (chronic lymphocytic leukemia) and other autoimmune-based conditions, particularly in this case, SLE. (Jäger et al., 2020)

Diagnosis of AIHA in SLE is through three steps (Figure 3). The first step is to demonstrate that the anemia is, in fact, hemolytic. Generally, hemolytic anemias are normocytic or macrocytic as a result of significant reticulocytosis or concomitant folate deficiency. Anisocytosis and spherocytes may be observed in the blood smear. Low serum haptoglobin and increased reticulocyte count indicate hemolysis. Increased indirect bilirubin, urine urobilinogen, and lactate dehydrogenase (LDH), albeit nonspecific, corroborate hemolytic anemia. LDH reflects the severity of hemolysis and serves as a marker of the therapeutic responses. The second step is the differentiation between immune and nonimmune Hemolysis. This is best predicated by the direct antiglobulin test (DAT), Coombs test. A positive test confirms the presence of bound antibodies (particularly IgG, but also immunoglobulin A [IgA] or immunoglobulin M [IgM]) and/or complement (C3d or C3c) on the surface of red cells through red cell precipitation, upon the addition of antihuman igG antibody. A positive DAT in the context of established hemolytic anemia (step one) generally confirms the diagnosis of AIHA. The third step is the responsible is the identification of the autoantibody type responsible for hemolysis. Based on previous explanation, AIHA in SLE is exclusively WA-AIHA. The DAT is positive with IgG in 20% to 66% of patients with IgG plus complement (C3d) in 24% to 64% and with complement alone in 7% to 14% of all patients. Our case met diagnosis element of AIHA, which is increased reticulocyte, LDH, and indirect bilirubin along with positive DAT (Karpouzas, 2013).

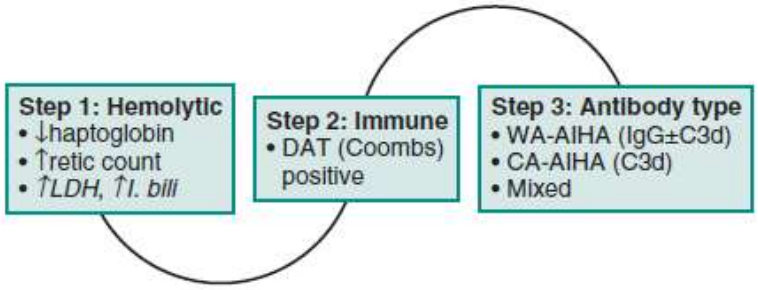

Figure 3. Three steps in determining AIHA in SLE (Karpouzas, 2013)

The first line management of AIHA is corticosteroid (prednisolone 1mg/kgBW/day or equivalent). During three weeks of steroid therapy, hemoglobin level is expected to increase. High-dose corticosteroid is given for severe AIHA or hemoglobin level <8 g/dL. Response monitoring is through increase level of hemoglobin and hematocrit with reducing level of reticulocyte. Second line therapy consisted of steroid pulse dose for three days (methylprednisoloone 1000 mg/day intravenous), azathioprine (until 2 mg/kgBW/day), cyclophosphamide (until 2 mg/kgBW) or splenectomy. Rituximab, IVIG, danazol, and mofetil mycophenolate also can be considered for refractory AIHA especially those combined with reticulocytopenia (Kalim et al., 2019). Our patient was given methyprednisolone 0.8mg/kgBW/day (equivalent to prednisolone 1 mg/kgBW/day with leukoreduced red cell transfusion due to severe anemia. Immunosuppressant then was given after resolution of infection with oral cyclosporine.

Gastrointestinal (GI) symptoms are rarely reported as manifestations of SLE and are rarely used as disease severity establishment (Malaviya et al.,2011). This may be because, on one hand, they are not assumed to be part of the diagnostic criteria of SLE (Petri et al., 2012). All GI tract and other related organs (the pancreas, liver, gallbladder, and pancreatic and biliary ducts) can be affected (Tian & Zhang, 2010). Although the GI symptoms in lupus are not predominant, the immune complex deposition in the gut of patients and mice with lupus is mentioned, partly due to the large surface area of the GI system. The gut immune complex deposition induces inflammatoryresponses and possibly facilitates gastrointestinal permeability defect with the translocation of pathogen molecules from the gut into the blood circulation. The reactions against pathogen-associated molecularpatterns (PAMPs) that are foreign to the host are usually more severe than the responses toward the host antigens, the presence of PAMPs in blood possibly induces a potentimmune activation, especially innate immune responses and acute and chronic inflammation is an exacerbating factor of lupus activity (Charoensappakit et al., 2022).

The liver can also be affected by SLE. Abnormal liver function test results were obtained in 23%–79% of cases and hepatomegaly in 39%–40% cases. The presence of oral ulcers, cytopenia, double-stranded DNA antibodies, and thyroid disease have all been associated with increased risk of liver involvement in lupus patients. Numerous causes can be attributed to this, including the use of aspirin, NSAIDs, azathioprine, methotrexate, fatty liver infiltration brought on by corticosteroid therapy, diabetes mellitus, obesity, viral hepatitis, and alcoholism. Takahashi et al identified liver dysfunction in 123 (59.5%) of 206 patients, with the following causes: drug-induced (30.9%), SLE-related (28.5%), fatty liver (17.9%), AIH (4.9%), PBC (2.4%), cholangitis (1.6%), alcohol (1.6%), and viral hepatitis (0.8%) (Takahashi et al., 2013). When secondary causes are excluded, lupus can be attributed as the underlying cause. In patient with abnormal liver enzymes, detailed serial examinations, full laboratory, radiography work, and even liver biopsy in some cases are needed to identify whether the underlying cause is lupus itself or something else. Treatment is adjusted according to the cause. Lupus hepatitis is a liver dysfunction related to lupus characterized by hypertransaminasemia owing to fluctuations in alanine transaminase levels, which is consistent with disease activity. According to previous reports, the lupus hepatitis progression rate to end-stage liver disease is low. Most patients with lupus hepatitis respond well to glucocorticoid therapy (Alharbi, 2022). This patient has elevated liver enzymes without a history of consuming previous drugs, no history of consuming alcohol, not obese, no fatty liver on ultrasound, negative hepatitis virus markers, and negative ASMA test. So we concluded that this liver enzyme abnormality was lupus hepatitis. After administration of steroids, the transaminase enzyme progressively decreases.

Intestinal pseudo-obstruction may be the initial manifestation in association with other organs, presenting in this manner in up to 50% of the cases (Tian & Zhang, 2010) and

representing a diagnostic challenge for the clinician as well as for the surgeon (Perlemuter et al., 1998). It is a serious disease that may compromise the life of the patient when not detected in a timely manner (Chng, 2010). Patients may present symptoms of recurrent abdominal pain associated with bloating, nausea, vomiting and intolerance to oral feeding, noting that symptoms may precede the diagnosis of lupus from 11 to 66 d and even up to 2 years (Chng, 2010). The majority of the cases reported in the literature are young females, half of whom had a prior diagnosis of SLE (Kim,2011) and who presented with a subacute progression of the GI symptoms associated, for the most part, with renal, hematological and generalized symptoms. They were subjected to laparotomy during more than one occasion because of suspected surgical abdomen pathology, without revealing the cause of the symptoms. Our patient presented with bloating and distended abdomen associated with hematological symptoms, as with previous reported cases.

Little is known about the pathogenesis of the disease. Etiologies such as the production of antibodies, smooth muscle myopathy, neurological involvement of the myenteric plexus and the autonomic nervous system, intestinal vasculitis with secondary ischemia, and immunocomplex deposits have been explored (Tian & Zhang, 2010) as well as irritation of the intestine due to the presence of ascitic fluid (Zhang, 2011) as probable mechanisms producing the disease. Intestinal sections most frequently affected are the jejunum or ileum and a high percentage of cases are associated with esophageal hypomotility (Chng, 2010). Some authors previously demonstrated smooth muscle motility disorders in phase III of the migratory motor complex (Perlemuter, 1998). This theory may be supported by the damage to the muscle layer caused by the immunocomplex deposit and secondary inflammation. Production of an antibody against the smooth muscle has been proposed (Ebert & Hagspiel, 2011) that could cause tissue destruction, although until now it has not been demonstrated (Cuchacovich, 2009). The hematological disorder manifested by cytopenia is associated with the presence of anticellular antibodies $TCD3^{+}$/TCR and anti-Ro antibodies as previously described (Chng, 2010); the latter have the capacity of altering the function of the myocytes and of the cell conduction systems, presumed to be another mechanism of injury (Tsokos, 2011).

Diagnosis of intestinal pseudo-obstruction consists of clinical picture, age and gender of the patient, together with imaging and laboratory studies. Plain X-ray of the abdomen may provide useful information of an obstructive process (Kahi&Rex, 2003) (air fluid levels, coffee ground loops, absence of air in the pelvic cavity, image of “stack of coins”); however, the noninvasive imaging study with the greatest diagnostic usefulness is abdominal computed tomography because it helps to rule out mechanical causes of the obstruction and identifies characteristic images such as target dilated loops of the jejunum and ileum, swelling of the intestinal walls, air fluid levels, pyelocaliectasis and, above all, ureterohydronephosis that may be present in up to 60% of cases (Chng, 2010). Panendoscopy and manometry have demonstrated esophagitis and disorders of esophageal motility (Perlemuter, 1998) as well as gastric and duodenal hypomotility (Chng, 2010). Invasive methods such as colonoscopy and double balloon enteroscopy provide information on portions of the small and large intestines that cannot be reached by other means, as well as the possible advantage of taking biopsies (Chen, 2005). However, it is not a method that is frequently used, given that there is currently no pattern or specific marker in the histopathological study in existence considered to be the gold standard (Chng, 2010). Abdominal x-ray of our patient showed dilated intestine with abnormal distribution, with normal left lateral decubitus x-ray. Unfortunately, we didn’t proceed to abdominal CT scan due to improvement of symptoms.

Treatment of intestinal pseudo-obstruction in SLE should be individualized (Tsokos, 2011). Among the recommendations for management of SLE issued by the European League Against Rheumatism and established by the ACR, there is no scheme suggested for GI manifestations (Petri et al., 2012). The most frequently described experience in disease

management is based on corticosteroids administered in pulses (methylprednisolone 500-1000 mg daily for 2-5 d) associated with other immunosuppressants (cyclophosphamide being the most used) (Tian, 2010). Cases have been reported where cyclosporine A, methotrexate, azathioprine (Ceccato, 2008), and tacrolimus were used (Maruoka, 2006). The use of prokinetics should be considered, preferably erythromycin because of its antimicrobial properties, although the use of metoclopramide, octreotide and neostigmine should be considered. Finally, use of parenteral nutrition should be individualized in cases where oral feeding is not possible. Human immunoglobulin has been used only in small cohorts with good results due to its high cost (Zandmann, 2009). Early directed treatment makes progression of the disorder highly reversible, avoiding the need for surgery and having an impact on survival, recovery of function and decrease in complication rates (Park, 2009). We managed our patient's GI symptoms along with his hematological symptoms through methylprednisolone 0.8 mg/kgBW/day with oral cyclosporine. Improvement was seen both for his hematological and GI symptoms. Prokinetic in form of metocloperamide was used.

CONCLUSIONS

This case describes SLE in male patients which is rarely occured. The patient suffered from hematologic and GI track manifestation in forms of AIHA and intestinal pseudo-obstruction, along with septic shock. Corticosteroid and immunossuppresant along with antibiotic were given and improvement was evident. Early diagnosis and prompt treatment are essential to lower mortality and morbidity, especially in reproductive age, which SLE predisposed on.

REFERENCES

Alharbi S. (2022) Gastrointestinal Manifestations in Patients with Systemic Lupus Erythematosus Open Access Rheumatol. Oct 17;14:243-253. doi: 10.2147/OARRR.S384256. PMID: 36281321; PMCID: PMC9587305.

Aringer M, Costenbader K, Daikh D, et al. (2019) 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Annals of the Rheumatic Diseases* 78(9): 1151–1159. DOI: 10.1136/annrheumdis-2018-214819.

Berentsen S (2015) Role of Complement in Autoimmune Hemolytic Anemia. *Transfusion Medicine and Hemotherapy* 42(5). S. Karger AG: 303–310. DOI: 10.1159/000438964.

Ceccato F, Salas A, Góngora V, Ruta S, Roverano S, Marcos JC, Garcìa M, Paira S (2008) Chronic intestinal pseudo-obstruction in patients with systemic lupus erythematosus: report of four cases. *Clin Rheumatol* 27: 399-402 [PMID: 17938989 DOI: 10.1007/s10067-007-0760-5]

Charoensappakit, A., Sae-khow, K., & Leelahavanichkul, A. (2022). Gut Barrier Damage and Gut Translocation of Pathogen Molecules in Lupus , an Impact of Innate Immunity (Macrophages and Neutrophils) in Autoimmune Disease.

Chng HH, Tan BE, Teh CL, Lian TY (2010) Major gastrointestinal manifestations in lupus patients in Asia: lupus enteritis, intestinal pseudo-obstruction, and protein-losing gastroenteropathy. *Lupus* 19: 1404-1413 [PMID: 20947549 DOI: 10.1177/0961203310374337]

Cuchacovich R, Gedalia A (2009) Pathophysiology and clinical spectrum of infections in systemic lupus erythematosus. *Rheum Dis Clin North Am* 35: 75-93 [PMID: 19480998 DOI: 10.1016/j.rdc.2009.03.003]

Ebert EC, Hagspiel KD (2011) Gastrointestinal and hepatic manifestations of systemic lupus erythematosus. *J Clin Gastroenterol* 45: 436-441 [PMID: 21422947 DOI: 10.1097/MCG.0b013e31820f81b8]

García López CA, Laredo-Sánchez F, Malagón-Rangel J, et al. (2014) Intestinal pseudo-obstruction in patients with systemic lupus erythematosus: A real diagnostic challenge. *World Journal of Gastroenterology* 20(32): 11443–11450. DOI: 10.3748/wjg.v20.i32.11443.

Hahn B (2013) The Pathogenesis of SLE. In: Wallace DJ and Hahn B (eds) *DUBOIS' Lupus Erythematosus and Related Syndromes*. 8th ed. Philadelphia: Elsevier.

Jäger U, Barcellini W, Broome CM, et al. (2020) Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting. *Blood Reviews* 41. Elsevier Ltd: 100648. DOI: 10.1016/j.blre.2019.100648.

Kahi CJ, Rex DK (2003) Bowel obstruction and pseudo-obstruction. *Gastroenterol Clin North Am* 32: 1229-1247 [PMID: 14696305 DOI: 10.1016/S0889-8553(03)00091-8]

Kalim H, Setyohadi B, Hidayat R, et al. (2019) *Diagnosis Dan Pengelolaan Lupus Eritematosus Sistemik* (Sumariyonoed.). Jakarta: Perhimpunan Reumatologi Indonesia.

Karpouzas GA (2013) Hematologic and Lymphoid Abnormalitis in SLE. In: Wallace DJ and Hahn B (eds) *DUBOIS' Lupus Erythematosus and Related Syndromes*. 8th ed. Philadelphia: Elsevier.

Kim J, Kim N (2011) Intestinal pseudo-obstruction: initial manifestation of systemic lupus erythematosus. *J Neurogastroenterol Motil* 17: 423-424 [PMID: 22148114 DOI: 10.5056/jnm.2011.17.4.423]

Malaviya AN, Sharma A, Agarwal D, Kapoor S, Garg S, Singh S, Rawat R (2011) Acute abdomen in SLE. *Int J Rheum Dis* 14: 98-104 [PMID: 21303489 DOI: 10.1111/j.1756 185X.2010.01581.x]

Maruoka H, Honda S, Takeo M, Koga T, Fukuda T, Aizawa H (2006) Tacrolimus treatment for refractory lupus cystitis. *Mod Rheumatol* 16: 264-266 [PMID: 16906381 DOI: 10.3109/s10165-006-0494-2]

Mok CC, Lau CS. (2003) Pathogenesis of systemic lupus erythematosus. J Clin Pathol 56(7):481-90. doi: 10.1136/jcp.56.7.481. PMID: 12835292; PMCID: PMC1769989.

Park FD, Lee JK, Madduri GD, Ghosh P (2009) Generalized megaviscera of lupus: refractory intestinal pseudo-obstruction, ureterohydronephrosis and megacholedochus. *World J Gastroenterol* 15: 3555-3559 [PMID: 19630114 DOI: 10.3748/wjg.15.3555]

Perlemuter G, Chaussade S, Wechsler B, Cacoub P, Dapoigny M, Kahan A, Godeau P, Couturier D (1998) Chronic intestinal pseudo-obstruction in systemic lupus erythematosus. *Gut* 43: 117-122 [PMID: 9771415 DOI: 10.1136/gut.43.1.117]

Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, Bruce IN, Isenberg D, Wallace DJ, Nived O, Sturfelt G, Ramsey-Goldman R, Bae SC, Hanly JG, Sánchez-Guerrero J, Clarke A, Aranow C, Manzi S, Urowitz M, Gladman D, Kalunian K, Costner M, Werth VP, Zoma A, Bernatsky S, Ruiz-Irastorza G, Khamashta MA, Jacobsen S, Buyon JP, Maddison P, Dooley MA, van Vollenhoven RF, Ginzler E, Stoll T, Peschken C, Jorizzo JL, Callen JP, Lim SS, Fessler BJ, Inanc M, Kamen DL, Rahman A, Steinsson K, Franks AG, Sigler L, Hameed S, Fang H, Pham N, Brey R, Weisman MH, McGwin G, Magder LS (2012) Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 64: 2677-2686 [PMID: 22553077 DOI:10.1002/art.34473]

Takahashi A, Abe K, Saito R, et al (2013) Liver dysfunction in patients with systemic lupus erythematosus. Intern Med. 52:1461–1465. doi:10.2169/internalmedicine.52.9458

Tian XP, Zhang X (2010) Gastrointestinal involvement in systemic lupus erythematosus: insight into pathogenesis, diagnosis and treatment. *World J Gastroenterol* 16: 2971-2977 [PMID: 20572299 DOI: 10.3748/wjg.v16.i24.2971]

Tsokos GC (2011) Systemic lupus erythematosus. *N Engl J Med* 365: 2110-2121 [PMID: 22129255 DOI: 10.1056/NEJMra1100359]

Yazdany J and Dall'Era M (2013) Definition and Classification of Lupus and Lupus-Related Disorders. In: Wallace DJ and Hahn BH (eds) *DUBOIS' Lupus Erythematosus and Related Syndromes*. 8th ed. Philadelphia.

Yuliasih (2020) Systemic Lupus Erythematosus. In: Yuliasih (eds) *Perkembangan Patogenesis dan Tatalaksana Systemic Lupus Erythematosus.* 1st ed. Surabaya.

Zandman-Goddard G, Blank M, Shoenfeld Y (2009) Intravenous immunoglobulins in systemic lupus erythematosus: from the bench to the bedside. *Lupus* 18:884–888.

Zhang J, Fang M, Wang Y, Mao J, Sun X (2011). Intestinal pseudo-obstruction syndrome in systemic lupus erythematosus. *Lupus* 20:1324–1328. [PMID: 21680640 DOI: 10.1177/0961203311405702]