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Case Report Open Access

Syndrome of Inappropriate Secretion of Antidiuretic Hormone and Severe Thrombocytopenia in an Immunosuppressive Systemic Lupus Erythematosus Patient: A Case Report

Arman Ahmadzadeh[1], Samad Nazarpour[1*], Elahe Jandaghi[1]

[1]Department of Adult Rheumatology, School of Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

SLE (Systemic Lupus Erythematosus) is an autoimmune disorder with a range of symptoms and an unclear cause. Infections, which are one of the leading causes of death in SLE patients, are made more possible by immunosuppressive medications. It is yet unclear how Cytomegalovirus (CMV) infection affects SLE. Clinically, differentiating between an infection and a lupus flare-up is critical. For this reason, we discuss the case of a 56-year-old woman who was hospitalized to Loghman Hospital's rheumatic clinic with SLE and CMV infection.

Keywords: Inappropriate ADH syndrome, Severe thrombocytopenia, Systemic Lupus Erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease marked by an increase in autoreactive cells and autoantibodies. Skin, joints, vessels, nerves, and many internal organs are all affected by SLE [1]. Skin rash, oral ulcer, butterfly-shaped malar rash, hemolytic anemia, arthritis, and nephritis are clinical signs of SLE's inflammatory reaction and their severity ranges from no apparent signs to substantial and irreversible tissue damage, and eventually death [2]. The pathophysiology of SLE remains uncertain and hard to describe, however, it mostly depends on the interaction of genetic, environmental, and hormonal variables [3]. Water and electrolyte imbalances, such as hypokalemia, hyper/hyponatremia, calcium disruption, and acid–base disorders, are all related to SLE. The majority of these problems are caused by medication side effects, with the direct impacts of lupus disease playing a smaller role. For example, electrolyte disturbances may happen due to lupus nephritis, which becomes more difficult with tubulointerstitial damage [4]. Hyponatremia is a rare occurrence in lupus patients. In terms of prevalence, etiology, and relationship to disease activity, hyponatremia in lupus is poorly understood [5]. Hyponatremia has been linked to increased disease activity, and fatigue development, in lupus patients, according to a recent study [4].

Infection is responsible for 25% to 50% of total mortality in SLE [6]. Cytomegalovirus (CMV) has appeared as one of the most serious opportunistic infections in the immunocompromised population [7]. CMV is a herpesvirus usually acquired throughout childhood and causes self-limiting or no manifestations [8]. CMV seroprevalence rates in healthy persons have been found to range between 40% and 100% [9, 10]. In a study of CMV infection in individuals with SLE, Dubey *et al.* discovered considerably increased seroprevalence of CMV Immunoglobulin M (IgM) antibodies in comparison to healthy controls, implying possible reactivation due to immune modulation [11]. In the hematological or transplant setting, CMV infection is usually a concern [12]. CMV can induce systemic and organ-specific pathology through inflammatory mechanisms as well as viral replication's cytopathogenic impact [13]. CMV promotes suppression in its host's immune system by inhibiting natural killer (NK) cell function, adenomatous polyposis coli (APC) formation, and T cell proliferation while evading the immune system [14]. CMV infection can mimic a lupus flare or show up as gastrointestinal hemorrhage or lung infiltrates in certain organs [15]. Disseminated intravascular coagulation (DIC) has been seen more commonly in immune-compromised patients with severe CMV infections [16],

*Corresponding Author: Samad Nazarpour., Department of Adult Rheumatology, School of Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, tehran, iran, E-mail: nazarpoor.s@lums.ac.ir , Telefax: +98-921-418-1998.

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while early CMV infection is typically clinically asymptomatic in immunocompetent individuals [17].

Numerous studies have been conducted on CMV infection in individuals who have had organ or hematopoietic stem cell transplants, as well as those who have been infected with the human immunodeficiency virus [18]; there is a lack of data on the association of hyponatremia with CMV infection in patients with lupus. We describe a 56-year-old woman who referred to a rheumatology unit of Loghman Hospital with SLE and CMV infection.

Case presentation

A 56-year-old woman with a 7-year history of SLE and Sjogren disease was admitted to the rheumatology unit of Loghman Hospital on 18 April 2021, for weakness, lethargy, anorexia, nausea, vomiting, delirium, lack of cognition, dizziness, and progressive weight loss of about 10 kg and an increase in serum creatinine to 2.5 mg/dl and Platelet 49000 with possible diagnosis of lupus nephritis flare and TTP. With a respiratory rate of 18 breaths per minute, a blood pressure of 130/80 mm Hg, and a heart rate of 90 beats per minute, the patient was completely conscious. Examination revealed several round ulcers in the oral cavity measuring approximately 1-cm with well-delineated borders.

Previously, she was admitted to the hospital in 2017 for hematuria and proteinuria, as well as a rise in creatinine to 3.4, for which she underwent a kidney biopsy (16.9.2018). According to the pathological report, class IV was recognized by glomerular scarring and proliferative, necrotizing, and crescentic lesions affecting more than half of the glomeruli. The first treatment was intravenous cyclophosphamide pulse, which was eventually discontinued due to hemorrhagic cystitis and replaced with rituximab. In order to continue the patient's maintenance treatment, mycophenolate mofetil 1000 mg/12 hours as well as a daily dose of hydroxychloroquine 200 mg and prednisolone 5 mg were prescribed. Regarding the development of cytopenia, because of the treatment, bone marrow biopsy was performed. Due to the detection of mild myelofibrosis, the patient's cytopenia was controlled by reducing the dose of cellcept to 500 mg / 12 hours. Additionally, she was admitted to the hospital again in January 2020 with proteinuria (3370 mg/24 hours), anemia (hemoglobin: 7.8 g/dl), and gross hematuria, which was treated with three pulses of intravenous methylprednisolone 1g, prednisolone 50 mg daily, and cellcept 500 mg/12 hours. The patient was discharged with a creatinine of 1.2 mg/dL.

Furthermore, examination of the heart and lungs was normal, and the patient had no abdominal pain or digestive problems. No abnormalities were found on abdominal and pelvic sonography. Echocardiography showed mild pericardial effusion EF:55% and mild tricuspid regurgitation (TR) and normal pulmonary artery systolic pressure (PASP). Brain and lung computed tomography (CT) was not remarkable. The patient did not have skin rash, arthritis, or limited mobility in the joints. Primary laboratory tests revealed serum creatinine: 2.5 mg/dL, peripheral leukocyte count: 7300/ml, hemoglobin: 14.3 g/dl, platelets: 49×10^9 /l; and sodium (Na) 117 mmol/L, potassium (K) 4.9 mmol/L, lactate dehydrogenase (LDH): 848 IU/L, calcium (Ca):8.8 mg/dL, Uric Acid: 10.1 mg/dL, Erythrocyte Sedimentation Rate (ESR): 2 mm/hr, C-reactive protein (CRP): 2.2 mg/L, triglycerides (TG): 154 mg/dL, and total cholesterol: 189 mg/dL. In addition, a peripheral blood smear revealed no schistocytes. A urine dipstick test was positive for leukocytes (3-4), blood (1+), Red Blood Cell Count (RBC) (8-10), and protein (1+). Urine Na value was 70 mEq/L in a random urine sample. In this regard, maintenance therapy was initiated, mycophenolate mofetil (MMF) was discontinued, and she received prednisolone (1 mg/kg/day) and intravenous saline with Na supplementation. Daily plasmapheresis was initiated for the patient on 5/13/2021 on suspicion of thrombotic thrombocytopenic purpura (TTP). Owing to increased LDH and thrombocytopenia, the patient received daily plasmapheresis for five days. Despite the decrease of LDH, her platelets did not rise. Therefore, plasmapheresis was stopped and a daily dose of 400 mg/kg/day of Intravenous immune globulin (IVIG) was started and was continued for five days with no benefit. A hematology consultation was conducted, and a bone marrow biopsy was conducted on the patient. Additionally, CMV PCR (polymerase chain reaction) was ordered on suspicion of CMV infection. Considering the patient's high dose steroid medication, the hyponatremia was not linked to Addison's disease, according to the endocrinologist. Owing to hyponatremia resistant to treatment, nephrology consult was ordered. The nephrologist did not relate the hyponatremia to a concurrent tubulopathy with salt-losing nephropathy based on serum and urine electrolytes. The possibility of abnormal release of antidiuretic hormone syndrome was also examined, possibly as a result of persistent hyponatremia, high urine sodium excretion (70 mEq/L), and normal to high blood pressure, leading to the possibility of simultaneous infection or neoplasia. Urinary Na was randomly evaluated and furosemide was initiated at a low dose of 20 mg / BD with restriction of water intake, on suspicion of Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH). A bone marrow sample revealed no neoplasia, and a total body computed tomography (CT) scan revealed no abnormalities. Additional infectious tests, such as broncho-aleolar lavage, revealed no signs of infection. The patient had a CMV antigenemia with a positive viral load by PCR (352755 copies/ml) after a thorough serologic and infectious work-up. The patient was prescribed i.v. gancyclovir, which resulted in a gradual remission of symptoms and stabilization of white blood count (WBC), platelet count, serum sodium, aspartate aminotransferase (AST), and alanine transaminase (ALT) level. Proteinuria and active sediment, however, remained after high-dose steroid treatment, indicating active renal lupus. Then, she was only given tapering CS, tacrolimus, valganciclovir, and hydroxychloroquine, with gradual regularization of proteinuria but slow worsening of renal function (creatinine 2.1 mg/dl with Glomerular Filtration

Rate (GFR) 43, and 24 hours proteinuria 350 mg at the last visit, with a stable CMV viral load of about 700 copies/ml).

The clinical laboratory data during hospitalization is detailed in Table.1.

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Table1. Clinical laboratory data obtained during hospitalization

Urinalysis		**Blood chemistry analysis**	
Cr	2.5- 1.8-1.6-1.4-1	AST	29-30
Urea	165-71	ALT	52- 47
Urine Na random	70-	ALP	185-175
Uric Acid	10.1-12.4-9.8-6-5.8-5	Total Bilirubin	0.9-0.5
Urine 24 hr pro	2400 mg	LDH	828-944-956-644-743-650-608-597-536
Hematological analysis		CPK	135
Red blood cell		TIBC	302-486
Hemoglobin	14.3-11.2-9.1-7.5- 8- 8.1-....10	Fe	62-76
Hematocrit		Ferritin	285- 150
White blood cell	7300-3700-2200-700-400-1300-2800-....6570	CRP	2.2-2.4 – ……..1.3
reticulocyte count	1.2-1.5-0.5	ESR	2-5-54- …..10
Platelet	49000-35000-45000-24000-……..225000	Na	117-125- 122- 125-128-125-132-135-……142
PT	12.5-11.3	P	4.8
Ca	8.8	K	4.7……4
Immunological analysis			
HBsAg		Neg	
HCV Ab		Neg	
Coombs Direct & Indirect		Neg	

Discussion

Patients with SLE who have been managed with corticosteroids and/or immunosuppressants may experience gastrointestinal issues (diarrhea, hepatitis, ascites), as well as recurring lymphopenia and hyponatremia in blood/serum investigations [19]. Although hyponatremia has been documented in SLE, only a few case reports were found in literatures on hyponatremia in SLE [20, 21]. Studies have linked antidiuretic hormone (SIADH) to neuropsychiatric lupus. Hyponatremia is linked to renal dysfunction and the use of medications like cyclophosphamide in SLE patients. There is no well-known link between hyponatremia and SLE, except renal illness causing a decrease in renal tubular Na uptake and Na loss because of chronic inflammation [22]. According to Park *et al.,* SIADH causes hyponatremia in renal epithelial cells by blocking the activity and lowering the expression of the apical epithelial Na channel and/or Na/K adenosine triphosphatase [23].

Serious infections occur in half of SLE patients, and they account for more than 20% of hospitalizations [24]. In SLE, defensive mechanisms against bacteria, viruses, and fungi are weakened when excessive immunological reactivation affects various organs with systemic signs [25]. Ramos-Casals *et al.* studied 25 cases of viral infections in newly diagnosed SLE individuals, with various viruses being involved. The majority of these individuals had nonspecific symptoms, such as fever, arthralgia, malaise, and cutaneous rash, more than SLE-related symptoms. They reported that antinuclear antibodies (ANA) and Anti-double stranded DNA antibody (anti-dsDNA) were found in >90% of cases, leukopenia and/or thrombocytopenia in >80% of cases, and antiphospholipid antibodies (aPL) in 50% of cases, according to the SLE criteria. These data highlighted the close relationship between viral infection and cytopenia, or the generation of autoantibodies [15]. In the immune-compromised host, CMV infection causes severe organ-specific consequences. CMV infection can manifest as CMV related-retinitis, colitis, or pneumonitis in SLE patients, which can cause a systemic inflammation that mimics SLE [26]. Although it appears to be a link between Epstein-Barr virus or parvovirus B19 infection and SLE, the interplay between CMV infection and SLE progression is still under question [27]. The link between SLE and CMV infection has been studied before, with increasing

percentages of SLE patients testing positive for CMV DNA [27, 28]. Moreover, increased titers of IgG and IgA antibodies against CMV pp52, an initial lytic cycle antigen required for lytic viral replication have been found in patients with SLE [29]. According to Paulo Santos *et al.,* the incidence rate of positive CMV antigen (CMV-Ag) in individuals with autoimmune rheumatic disorders was % 4.97. Due to their study, the mortality rate was 45.5%, and increased dosages of daily oral corticosteroids and a smaller number of lymphocytes being associated with a higher mortality rate. Lung (45.5%), bone marrow (40.9%), and gut (40.9%) were the most common CMV locations in their investigation (27.3%) [30]. Similarly, Tsai *et al*. examined how CMV infection affected the clinical outcomes of hospitalized patients with auto-immune disorders, mainly SLE. It was discovered that patients with autoimmune disorders detected with CMV infection had a considerably greater mortality rate than patients without autoimmune disease. According to their research, individuals with CMV infection underwent a higher dosage of corticosteroid and an increased amount of azathioprine administration before admission compared to patients without CMV [31].

The literature suggests a causal link between CMV and SLE. However, a definitive link between CMV seropre-valence and illness has yet to be identified. Emerging evidence shows that CMV can interplay with the host immune system in different ways, potentially contributing to flare-ups and causing SLE-related characteristics, including secondary APS and Raynaud's phenomenon [32]. During active infection, CMV shows the ability to significantly alter host T cell activity. Phosphoprotein 65 (pp65422–439), UL44, US31, and La (SS-B) protein are some of the main viral proteins that promote immune-pathogenic processes of CMV-induced autoimmunity. To further understand its impact on disease progression, population-based, long-term prospective investigations are required [32].

Because of significant advances in both diagnostic tests and medications in the last few years, rheumatologists have been able to better control CMV infection. To identify CMV reactivation, diagnose infected people for therapy, and evaluate antiviral therapy reaction, a precise and rapid quantitative PCR technique is required [33].

Patients with rheumatic disorders are more vulnerable for CMV infection because of their underlying immune system dysfunction and their treatment regimens, which frequently involve corticosteroids and other immune-suppressive medicines [34]. As such, in individuals with SLE, corticosteroids at a prednisolone equivalent dose (7.5 to 10 mg/day), corticosteroid pulse therapy, and a high-dose cyclophosphamide are all risk factors for infection [35]. Cyclophosphamide, as an alkylating drug, is utilized in critical signs of SLE, including lupus nephritis and mesenteric vasculitis and can inhibit the immune system [36]. A larger cyclophosphamide dosage was linked to an increased rate of infection, and leucopenia following cyclophosphamide administration [37]. Corticosteroids are well-known for increasing infection susceptibility due to the immunosuppressive impact which is amplified in higher doses and extended periods of time [38]. The effect of immunosuppressive medications on the consequence of CMV infection is critical for rheumatic patients' overall prognosis [39]. CMV infection generally coincides with a rheumatic disease flare-up, making antiviral treatment more challenging. When it comes to CMV treatment, many medical institutes start antiviral when a certain, predetermined positive threshold is observed [33]. Thereby, immunosuppressive medicines increase the risk of typical bacterial infections and opportunistic illnesses in patients with Rheumatoid arthritis (RA). In a patient with severe RA treated by multiple immunosuppressants, continuous monitoring and a high index of caution seem essential [40, 41].

Conclusion

Since managing immunocompromised patients with CMV infection remains a critical problem, a consistent method for CMV screening in subjects with active rheumatic diseases, particularly in patients receiving rising immunosuppressive medication, is valuable. To promote early diagnosis of viral infection in SLE patients, clinicians should assess the pharynx, eyes, skin, and genitalia, and consider serological and molecular tests. The case presented here demonstrates the importance investigating CMV infection in SLE patients using immunosuppressive medicines. When these medications are administered concurrently, infectious events should receive notably close consideration.

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Conflict of interest statement

None.

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