**Generalized Lymphadenopathy in the Presence of Acute Epstein Barr Virus Infection as the Initial Manifestation of Systemic Lupus Erythematous; a case report**

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**Abstract**

Lymphadenopathy could represent various etiologies including infections, malignancies, and rheumatologic diseases. Systemic lupus erythematous (SLE) is known as the great mimicker which could be presented with different first manifestations. We report a 42-year-old woman in the acute phase of Epstein Barr infection, admitted with polyarticular peripheral arthritis, sacroiliitis, and generalized lymphadenopathy. She had no similar history or taken unpasteurized dairy. Nodes were soft, mobile, tender without skin change on top. During the process, she was diagnosed with SLE and discharged with prednisolone 30 mg/day and hydroxychloroquine 400 mg/day. After two weeks of follow-up, all lymphadenopathy and symptoms were diminished. This case underscores the thousand faces innate of systemic lupus erythematous. Clinical awareness would lead to accurate diagnosis and early intervention.

**Keywords**

case report; Systemic lupus erythematous; lymphadenopathy; EBV

**Key Clinical Message**

Clinicians should carefully consider generalized lymphadenopathy, particularly post viral infections, as one of possible SLE first signs regarding unusual joint involvements such as sacroiliitis. Late diagnosis of this autoimmune inflammatory disease, could lead to irreversible morbidity and higher mortality.

1. **Introduction**

Systemic Lupus Erythematous (SLE) is a complex heterogenous disease with variable clinical presentations.1 Estimates indicate that SLE incidence rate was 5.1 per 100,000 about seven-fold higher in woman compared to men in the United States.2 The prevalence of SLE was reported 40/100,000 among Iranian population.3 SLE is a very multifaceted and innovative disease that can have catastrophic impacts on any organ system. A typical SLE patient could present with multiple symptoms from any organ system. Fever, myalgias, fatigue, weight loss, arthralgia and lupus nephritis are the most commonly presented manifestations. Less frequently, patients can also present with neuropsychiatric manifestations, myocardial infarctions, thromboembolic diseases and vasculitis. According to its wide variety of manifestations, SLE is known as the “great mimicker”. There has been reports concerning atypical manifestations such as atypical chest pain and elevated troponin levels concerning for Acute Coronary Syndrome, acute cutaneous LE, bullous LE, and enteritis and cystitis. 4,5

Herein we report 42-year-old women presented with generalized lymphadenopathy and fever in the presence of EBV infection, as initial manifestations of SLE followed by sacroiliitis for the first time.

1. **Case Presentation**
   1. **Case history/Examination**

A 42-year-old woman was admitted to our hospital with myalgia, arthralgia, gait impairment, lower limb paresthesia, and pain in the left hip radiating to the anterior compartment of the thigh for 2 months. The pain would lessen with heat and exacerbated with activity. She also mentioned a two months history of night sweat but no weight loss. No history of aphthous or any similar mucocutaneous lesions was recorded, neither she had eating raw or unpasteurized dairy products. In the physical examination, she had generalized lymphadenopathy involving inguinal, axillary and cervical nodes in both sides. Nodes were soft, mobile, and painful with no skin changes on top. Her past medical history was remarkable for diabetes mellitus, ischemic heart disease and hypothyroidism. The patient was afebrile with stable vital signs.

1. **Methods**
   1. **Differential Diagnosis, investigations and treatment**

Laboratory test results on admission date were as follows: WBC: white blood cell (WBC), 16600/μL (4000-11000) with shift to left (71.2% neutrophil); hemoglobin (Hb), 13 g/dL (12-16); platelets (plts), 16.2 × 104/μL (15-45 × 104); C-reactive protein (CRP), 56.2 mg/dL (positive>9, negative<6); erythrocyte sedimentation rate (ESR), 67; creatinine (Cr), 1 mg/dL (0.6-1.2); blood sugar (BS), 79 mg/dL; lactate dehydrogenase (LDH), 478 U/L; long with normal liver function tests and electrolytes (Table 1).

Sonographic assessments showed several prominent lymph nodes with 15×20 mm, 15×22mm, 19×11 mm, and 17×20mm in paraaortic, porta hepatis, inguinal, and left iliac in addition to mild splenomegaly. Sputum smear analysis was normal. Following, acid fast bacilli was not seen and bronchoscopy evaluation was negative for any pathological finding. At first, infectious causes were ruled out. Tests for brucellosis were all negative as well as Hepatitis B antibody (HBs Ab); coronavirus disease of 2019 (Covid-19) real time polymerase chain reaction (RT-PCR); Human Immunodeficiency Virus antibody (HIV Ab); Cytomegalovirus immunoglobulin G (CMV IgG), 47.8 (positive>=22); CMV IgM, 0.31 (positive>=0.9); Epstein Bar Virus Viral Capsid Antigen IgG (EBV-VCA), 0.4 (positive>=1); and EBV IgM, 4 (positive>1.1) (Table 2).

These findings led to the possible diagnosis of lymphoma. Peripheral blood smear showed hypereosinophilia. Whole body bone scan was negative for any bone metastasis. Excision of inguinal lymph nodes showed reactive lymph node with follicular hyperplasia and absence of malignancy or granuloma. Laboratory test results were as follows: ESR, 102 mm/h; CRP, 18.4; cancer antigen (CA)-125, 32.5 U/mL (=<35); CA 19-9, 34.10 U/mL (<40); Alpha-fetoprotein (AFP), 0.5 ng/mL (0.2-8.5); carcinoembryonic antigen (CEA), 1.20 ng/mL (0.3-5). Bone marrow aspiration reported absence of malignancy. Lymphoma excluded, thus, in the third place; rheumatologic diseases were considered. No alopecia, rash, oral ulcers, photosensitivity, neurological disorder, or bladder irritation was noted. In the second physical examination, we found general inflammatory polyarthritis of small joints of hand, shoulder, and elbow. Magnetic resonance imaging (MRI) of lumbosacral joint revealed slight disc bulging at L4-L5 and L5-S1 joints. Hip MRI showed was normal and sacroiliac imaging highlighted mild sacroiliitis with left dominance without subchondral erosion. Laboratory test results were as follows fluorescent antinuclear antibody (FANA) (indirect immunofluorescence test) 1:100 (normal<1: 100) cytoplasmic and nucleoplasm granular; a total hemolytic complement (CH50), 92 % (41.2-95); complement 3 (C3), 68 mg/dL (90-160); C4, 5.9 mg/dL (10-40); anti-double stranded DNA antibody (anti-ds DNA), 46.21 IU/mL (positive>18); Anti-cyclic citrullinated peptide antibody (anti-CCP Ab), 17.5 (positive>18); Rheumatoid Factor (RF), negative; Sjögren’s-syndrome-related antigen A (anti-SSA), 6.77 RU/ml (positive>18); anti-SSB, 9.43 RU/ml (positive>18) (Table 2).

1. **Results**
   1. **Outcome and Follow-up**

The patient fulfilled European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) 2019 criteria for SLE with 16 points (FANA=1:100, inflammatory polyarthritis (6 points), as well as low C3 and C4 (4 points), and increased anti-ds DNA (6 points)).6 Intravenous administration of methylprednisolone (1000 mg/day) was started immediately and continued for three days. Finally, after twelve days she was discharged with prednisolone 30 mg/day (0.5 mg/kg.Day) and hydroxychloroquine 400 mg/day. After two weeks of follow-up, all lymphadenopathy and symptoms were diminished.

Regarding her poor compliance, she did not check for her follow-up sessions, hesitated taking medications and a year later, she was expired due to severe neuropsychiatric SLE with fever and cerebritis in another hospital.

1. **Case Discussion**

Lymphadenopathy constitutes a vast majority of etiologies including infections (bacterial, brucellosis, tuberculosis; viral, HIV, EBV, herpes simplex virus, CMV, hepatitis B), cancer (lymphoma, leukemia), Sarcoidosis, Lupus erythematosus, amyloidosis, Rheumatoid arthritis, and etc. To outline the cause of lymphadenopathy, history, physical examination, and laboratory tests are obtained.

Although the exact gene-environment interactions remain vague, SLE includes multiple immunologic components such as hyperactivation of B cells, T cells, and monocytes resulting in the production of countless antibodies, autoantibodies, and cytokines.7 The clinical presentation and evolution of SLE consider an extensive variety. The 2019 EULAR/ACR released the most recent classification criteria for SLE.6 The criteria have two separate parts; clinical and immunological features. Clinical involvements consider constitutional, hematological, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, and renal system and immunological criteria include the presence of ANA, antiphospholipid antibodies, complement proteins and SLE-specific antibodies like anti-ds DNA, anti-Smith, and anti-histone DNA.8 To meet the criteria, the patient must represent at least one clinical criterion, positive ANA along with more than 10 points.

Lupus Lymphadenopathy has been reported in 5-7% in the newly-diagnosed patients.9-11 It has been found that SLE patients first presented with lymphadenopathy more probably show constitutional symptoms such as fever, fatigue, and weight loss, hepatomegaly and splenomegaly, and additionally, decreased complements along with increased anti-dsDNA indicating that lymphadenopathy is a sign of disease activity.12 In the patient currently reported, the diagnosis of SLE was followed by ruling out lymphoma, infections and other causes of lymphadenopathy. Our patient met the criteria with 16 points, presenting with generalized lymphadenopathy as the first manifestation. Interestingly, EBV VCA IgM results of the 42-year-old patient was positive representing acute EBV infection. To date there has been multiple studies approving the association of SLE flare and EBV infection similar to our patient.13,14 Additionally, she had symptoms, signs, and MRI report of mild sacroiliitis which is scarcely reported in SLE patients.14 Recently, a study represented higher titer of CRP as a potential risk factor of sacroiliac involvements in lupus patients.15 We suggest that other risk factors such as EBV reactivation, presence of different lupus specific antibodies should also be evaluated to predict possibility of sacroiliitis as well as rare first manifestations.

1. **Conclusion**

Lymphadenopathy is considered one of rare onset-manifestations. There have been previous case reports of lupus lymphadenopathy, however, the correlation between these nonfrequent presentations and viral reactivations remain vague. Future investigations should be performed to clarify possible risk factors of rare-involvements of SLE in order to prevent late diagnosis. More importantly, physicians should consider SLE as one of the prior differential diagnoses of lymphadenopathy for which proper history, physical and laboratory examination, and lymph node biopsy is needed.

**Declarations**

**Consent**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal

**Data Availability Statement**

All data generated or analyzed during this study are included in this published article.

**Conflict of Interests Statement**

The authors declare no competing interests.

**Authors' contributions**

1. Kimia Jazi: Writing – review and editing, approve for publication
2. Zahra Faraji: Writing – original draft
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4. Alireza Shahhamzeh: Writing – review and editing, approve for publication
5. Reihane Tabaraii: Writing – original draft
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**Tables**

**TABLE 1**  Initial laboratory tests of the patient results

|  |  |  |
| --- | --- | --- |
| Test, Unit | Result | Reference Range |
| WBC, µL | 16600 | 4000-11000 |
| RBC, ×106 µL | 4.33 | 4.2-6.3 |
| Hb, g/dL | 13 | 12-16 |
| Platelet, µL | 162 000 | 150000-450000 |
| MCV, fL | 86.1 | 80-100 |
| Neutrophil, % | 71.2% | -- |
| CRP, mg/dL | 56.2 | negative: <6, positive: >9 |
| ESR 1h, mm/hr | 67 | -- |
| BS, mg/dL | 79 | 70-120 |
| Urea, mg/dL | 34 | 10-50 |
| Creatinine, mg/dL | 1 | 0.6-1.2 |
| AST, U/L | 21 | Up to 35 |
| ALT, U/L | 16 | Up to 45 |
| ALP, U/L | 109 | 98-279 |
| LDH, U/L | 622 | 225-500 |
| CPK Total, U/L | 19 | -- |
| Aldolase, U/L | 26.5 | <7.6 |
| Uric Acid, mg/dL | 3.1 | Male 3.4-7, Female 2.4-5.7 |
| Na, mmol/L | 141 | 135-148 |
| K, mmol/L | 4.3 | 3.5-5.3 |

*WBC; white blood cell, Hb; hemoglobin, RBC; red blood cell, MCV; mean corpuscular volume, CRP; c-reactive protein, ESR; erythrocyte sedimentation rate, BS; blood sugar, AST; aspartate aminotransferase, ALT; alanine transaminase, ALP; alkaline phosphatase, LDH; lactate dehydrogenase, CPK; creatinine phosphokinase, Na; sodium, K; potassium*

|  |  |  |
| --- | --- | --- |
| Test, Unit | Result | Reference Range |
| 2-ME | negative | -- |
| Indirect Coombs | negative | -- |
| Wright Agglutination Test | negative | -- |
| COVID-19 RT-PCR | negative | -- |
| HBs Ab | negative | -- |
| HIV Ab | negative | -- |
| CMV IgG | 47.8 | positive>=22 |
| CMV IgM | 0.31 | positive>=0.9 |
| EBV-VCA IgG | 0.4 | positive>=1 |
| EBV-VCA IgM | 4 | positive>1.1 |
| CA-125, U/mL | 32.5 | Negative=<35 |
| CA 19-9, U/mL | 34.10 | Negative<40 |
| AFP, ng/mL | 0.5 | 0.2-8.5 |
| CEA, ng/mL | 1.20 | 0.3-5 |
| FANA | 1:100 | positive reaction at 1:100 or more |
| Anti-ds DNA AB, IU/mL | 46.21 | positive>18 |
| C3, mg/dL | 68 | 90-160 |
| C4, mg/dL | 5.9 | 10-40 |
| CH50, % | 92 | 41.2-95 |
| Anti B2-GLP1 antibody (IgG) | 5 | positive: >20 |
| Anti B2-GLP1 antibody (IgM) | 4 | positive: >20 |
| ACA IgG | 9 | positive: >=12 |
| ACA IgM | 1.9 | positive: >=12 |
| LA antibody (dRVVT) | 33 | direct :25- 45 |
| LA antibody (aPTT) | 29 | after mixing: 25-45 |
| Anti-CCP AB | 17.5 | positive>18 |
| RF | negative | -- |
| anti-SSA, RU/ml |  | positive>18 |
| anti-SSB, RU/ml |  | positive>18 |

**TABLE 2** Specific immunologic tests of the patient

*2ME; 2-Mercaptoethanol, HBs Ab; Hepatitis B antibody, HIV Ab; Human Immunodeficiency Virus antibody, CMV IgG and IgM; Cytomegalovirus immunoglobulin G and M, EBV-VCA; Epstein Bar Virus Viral Capsid Antigen, CA; Cancer Antigen, AFP; Alpha-fetoprotein, CEA; carcinoembryonic antigen, FANA; fluorescent antinuclear antibody, Anti-ds DNA AB; anti-double stranded DNA antibody, C3 and C4; complement 3 and 4, CH50; a total hemolytic complement,* *Anti B2-GLP1 antibody;anti-b2glycoprotein antibody, ACA; anti-cardiolipin antibody, LA antibody; lupus anticoagulant, dRVVT; Diluted Russell Viper Venom Time, aPPT; activated partial prothrombin time, anti-CCP Ab; Anti-cyclic citrullinated peptide antibody, RF; Rheumatoid Factor, anti-SSA and B,* Sjögren's-syndrome-related antigen A and B