


Development of Systemic Lupus Erythematosus After Infectious Mononucleosis in a 64-Year-Old Woman

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by heterogeneous symptoms that can manifest in any organ, and often presents at a young age. Infectious mononucleosis (IM) is the acute clinical manifestation of Epstein–Barr virus (EBV). It is characterized by low-grade fever, malaise, lymphadenopathy, splenomegaly, and occasionally symmetrical arthralgias. It has been proposed that EBV is a trigger for new-onset SLE, and patients with autoimmune disorders such as SLE are more likely to have recurrent IM infections. The patient, a 64-year old Caucasian female who's only past medical history was hypertension, developed several months–long period of vague symptoms, including fatigue, malaise, nausea, and nonbilious vomiting with oral intake. She presented with symmetrical polyarthritides involving the hands and elbows, with no history of arthritis before this episode. At the 5-month follow-up, she presented with worsening arthritis bilaterally in her elbows and in her right knee. For several decades, there has been a theoretical association between EBV and SLE, with EBV thought to be one of the many possible triggers for development of SLE. Based on the disease course, we theorize that the patient's IM and EBV infection led to development of SLE. A small fraction of SLE cases have been reported in literature to be associated with EBV. This case adds to that literature with EBV triggering development of SLE in a seemingly previously asymptomatic patient.

Keywords

systemic erythematosus lupus, infectious mononucleosis

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by heterogeneous symptoms that can manifest in any organ, and often presents at a young age with an age of onset in over 80% of cases between 16 and 55 years.¹ Although this disease has been associated with specific HLA genes and a multitude of other immune-related genes, monozygotic twin studies have suggested a large environmental influence on development of the disease.² One such environmental factor are viral infections, of which Epstein-Barr virus (EBV) has been proposed to have an association with SLE for several decades, though a strong mechanistic theory for this association has never been elucidated.

Infectious mononucleosis (IM), which is the acute clinical manifestation of EBV, is often characterized by low-grade fever, malaise, lymphadenopathy, splenomegaly, and occasionally symmetrical arthralgias.³ It is a point of contention whether EBV is a trigger for new-onset SLE, or if immune-impaired patients with autoimmune disorders such as SLE are more likely to have recurrent IM infections.⁴ This is because both

diseases can have similar presentations, which again points to a possible association between the 2 disease processes.

Despite the difficulty in separating these 2 scenarios, this case presents a patient who seems to show EBV as a causal agent for the development of SLE. A literature review on PubMed shows 6 reported cases of EBV-triggered SLE since 1998, all of which involved patients who presented within a usual age of onset for SLE. Our case is unique in which our patient had never had symptoms related to SLE before an acute phase of IM followed by onset of SLE-associated symptoms at the age of 64 years, which is also older than patients in prior case reports and outside the usual age of presentation for SLE.

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Case Presentation

The patient, a 64-year-old Caucasian female who's only past medical history was hypertension treated with lisinopril and hydralazine, first developed a several months–long period of vague symptoms including fatigue, malaise, nausea, and nonbilious vomiting with oral intake. She denied any fevers, night-sweats, sore throat, or facial swelling during this time but had a 40 to 50 lbs weight loss since the start of the year. Chest imaging, abdominal imaging, and esophagogastroduodenoscopy were normal. She was treated unsuccessfully with amitriptyline for possible abdominal migraines and symptomatically with ondansetron. Eventually, her nausea resolved, but she began developing symmetrical polyarthralgia that gradually worsened.

She initially presented to rheumatology clinic with symmetrical polyarthritis involving the hands and elbows for 3 to 4 months, with no history of arthritis before this episode. Affected joints were swollen with stiffness lasting more than 1 hour. Pain normally lasted throughout the day, was worse in the morning, and mildly improved with physical activity. The patient had leukopenia with white blood cells at 3800 cells/ μ L (lymphocytes 34.4%, neutrophils 58.1%), and anemia with hemoglobin (hgb) at 10.9 g/dL. C-reactive protein and erythrocyte sedimentation rate were elevated at 6.8 mg/dL and 65 mm/h, respectively. Rheumatoid factor was negative, and autoimmune antibodies were negative for anti-CCP, and ANA was negative. Virologic testing revealed negative hepatitis B antibody and antigen, negative hepatitis C antibodies, negative antistreptolysin O, and positive Parvovirus B19 IgG (immunoglobulin G), but negative IGM. On this initial visit, she met ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) criteria for rheumatoid arthritis and was started on methotrexate.

At 1 month follow-up, she reported minimal improvement in her arthritis. Over the next month, she had developed painless oral ulcers, worsening gastritis, and her leukopenia worsened to 2000 cells/ μ L. As a result, methotrexate was discontinued, and additional workup was ordered to evaluate her new symptoms. ANA was positive at 1:1280 in a homogeneous pattern. Anti-cardiolipin IgM was positive at 104 MPL, IgG was negative. Anti-Smith, anti-DsDNA, anti-centromere, anti-Scl-70, anti-RNP, anti-histone, anti-SS-A, and anti-SS-B antibodies were negative. Virologic studies showed positive EBV viral capsid antigen (VCA) IgG, IgM, and EBV nuclear antigen (EBNA) IgG, suggesting a recent acute IM infection. In light of this, the patient was thought to possibly have viral arthritis and was started on nonsteroidal anti-inflammatory drugs.

At 5-month follow-up, she presented with worsening arthritis, including tenderness and synovitis in the proximal interphalangeal joints bilaterally, as well as tenderness bilaterally in her elbows and in her right knee. Repeat blood work at this follow-up was again negative for anti-DsDNA antibody. Despite stopping methotrexate the prior month, she

continued to have leukopenia, anemia, and oral ulcers. She met both Systemic Lupus International Collaborating Clinics and ACR diagnostic criteria for SLE, and she was treated with hydroxychloroquine, azathioprine, and a short course of methylprednisolone.

The patient could not tolerate azathioprine due to nausea and vomiting, and it was discontinued. On hydroxychloroquine therapy, the patient had significantly improved arthritis, oral ulcers had resolved, and her leukopenia and anemia had recovered to a white blood cell count of 6000 cells/ μ L and hemoglobin of 12.9 g/dL.

Discussion

For several decades, there has been a proposed association between EBV and SLE, with EBV thought to be one of many possible triggers for development of SLE. One theory suggests that in those with a genetic predisposition for SLE, increased EBV activity causes heightened cellular degradation. This leads to larger quantities of cellular waste, and exposure of these cellular products to the immune system leads to creation of auto-antibodies.⁵ Alternatively, molecular mimicry between specific anti-EBV antibodies and auto-immune antibodies can cause Connective Tissue Disease, particularly EBV nuclear antigen-1 mimicking anti-Smith or anti-SS-A antibodies.⁶ There has thus far been no cohesive or unify theory to validate this association.

Despite these proposed mechanisms for EBV-triggered SLE, the opposite is also true that SLE enables EBV activation, and people with SLE are more susceptible to recurrent bouts of IM. Serologic studies in young patients with SLE show that upward of 99% are seropositive for EBV, compared with 70% of the general population.⁷ In these EBV seropositive patients, those with SLE tend to have higher viral loads of EBV, with their peripheral blood mononuclear cells carrying as many as 40 times the EBV load that healthy patients have.⁸ This spills over to the adaptive immune system, as SLE patients have 10 times the frequency of EBV-infected peripheral B-cells as their healthy counterparts.⁹ These higher viral loads contribute to greater EBV disease activity in SLE patients, and SLE patients tend to have higher rates of prior IM when compared with the general population, with an odds ratio of 2.08 for positive anti-VCA IgG serology.¹⁰ Again, there seems to be an association between EBV and SLE, though whether this is due to an overall autoimmune reaction versus specific causality is again uncertain.

In the case of our patient, there are phases of progression that suggests IM as the trigger for her SLE. Through her life up to presentation, she endorsed neither signs nor symptoms associated with SLE, before having a period of malaise, fatigue, nausea, and vomiting corresponding to possible IM. This was suggested by serologic studies positive for IgM and IgG directed against the Epstein-Barr VCA, which corresponds to a sensitivity of 97% and a specificity of 94% for IM.¹¹ For our patient, the positive anti-VCA IgM suggests

she had an acute infection within the prior 3 months, which correlates with her symptoms.¹² Our patient also tested positive for anti-EBNA IgG, which usually begins to appear after resolution of symptoms and is present for life.¹³ First-time IM where the patient has had no prior exposure to EBV is confirmed with a positive anti-VCA IgG and IgM along with a negative anti-EBNA IgG. For our patient, who is positive for anti-VCA and anti-EBNA antibodies, we are unable to establish whether her acute infection was the first instance of EBV exposure, or a reactivation of latent EBV.

Her initial symptoms of malaise, fatigue, nausea, and vomiting resolved. Then, over the course of the next 5 months, she developed symmetrical polyarthritis characterized by tenderness and synovitis. She was originally thought to have rheumatoid arthritis because she met ACR/EULAR criteria, with 1 point from elevated erythrocyte sedimentation rate/C-reactive protein, 5 points from involvement of greater than 10 small joints, and 1 point for persistence of symptoms greater than 6 weeks, totaling to 7 points.¹⁴ She was started on methotrexate. However, her symptoms did not abate while on therapy, and evolved with painless oral ulcers and worsening leukopenia. Methotrexate was discontinued, further workup was done, returning with a now positive 1:1280 ANA, and low C4. These laboratory findings, combined with her characteristic arthritis and oral ulcers, qualifies as the 4 criteria for diagnosis of SLE based on both ACR, and Systemic Lupus International Collaborating Clinics classification criteria.^{15,16}

Based on the disease course, it is suggestive that the patient's IM and EBV infection led to development of SLE. Importantly, she had none of the symptoms that qualified her for SLE prior to her episode of IM, and gradually developed them after an asymptomatic period; this is unusual given her age, 64 years, is outside the usual period of onset for SLE. Additionally, her IM symptoms were different than her SLE symptoms, with arthritis only appearing after resolution of IM. This fact is particularly important because it separates her IM and onset of SLE, eliminating the possibility that she had manifested SLE shortly before-hand, leading to reactivation of latent EBV. Though there are no evidence-based causality between EBV and SLE, we believe that this case represents a rare subset of SLE patients whose disease was, at least in part, brought on due to EBV infection. The chronology and well as virology and immunologic titers and markers suggest that and EBV infection occurred then subsequently SLE developed, without any other obvious triggers for SLE prior or during EBV infection.

Although the sequence of events suggests IM was the catalyst for her SLE, her diagnosis occurred while she was taking 2 drugs associated with drug-induced lupus: hydralazine and lisinopril. Of patients taking hydralazine, as many as 10% develop clinical signs of systemic lupus, and 95% of these patients test positive for anti-histone antibodies.^{17,18} Lisinopril and other angiotensin-converting

enzyme inhibitors very rarely cause drug-induced lupus. When they do, most often they are associated with anti-SS-A antibodies rather than anti-histone antibodies, both of which were negative in our patient, and when it does manifest, lisinopril is mostly associated with subacute cutaneous lupus, which our patient never developed.^{19,20}

However, our patient stopped taking both hydralazine and lisinopril during the course of evaluation, shortly after presenting to rheumatology clinic, hydralazine was stopped by her cardiologist because of orthostatic hypotension, and lisinopril was stopped after an episode of angioedema. Despite discontinuing both hydralazine and lisinopril, the patient continued to be symptomatic for months afterwards until beginning hydroxychloroquine therapy, while in the case of most drug-induced lupus, there is normally improvement or resolution of symptoms within weeks of stopping the offending agent.²¹

In general, a small fraction of SLE cases have been reported in literature to be associated with EBV. This case offers evidence of EBV triggering development of SLE in a patient who had previously displayed no signs nor symptoms of autoimmune disease before developing IM verified by serologic testing. Her IM symptoms resolved and she developed new-onset SLE symptoms afterward, showing a chronologic sequence of IM leading to SLE, which is further supported by the distinct presentation of both disease processes. Of course, the exact pathogenesis of SLE has not been elucidated, and association of EBV causing SLE stands as a very small fraction of a wide variety of possible etiologies.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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