CLINICAL VIGNETTE

A Case of Disseminated Herpes Simplex Virus-2 Complicating Active Systemic Lupus Erythematosus

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Introduction

Viral infections in a patient with systemic lupus erythematosus (SLE) may complicate the approach to management. Viral etiologies are considered by some to be under diagnosed given the lack of clinical recommendations for diagnosing and managing viral infections in SLE patients[1]. Disseminated herpes simplex virus (HSV) infections are rare examples. In immunocompromised patients, including those with SLE, disseminated HSV may result in hepatitis and encephalitis associated with a high mortality rate[2]. Patients with SLE are at an even higher risk for HSV encephalitis given immunosuppression from steroid use and compliment deficiency related to SLE[3]. In this case report, we present a 26-year-old female patient with evidence of an acute SLE flare along with primary HSV-2 hepatitis and encephalitis. Two reports of HSV-1 encephalitis in SLE patients have been reported[1,4] and, to our knowledge, this is the first reported case of HSV-2 encephalitis in the setting of an active SLE flare.

Case Presentation

A 26-year-old female with a 6-year history of SLE (manifested by positive anti-nuclear antibodies, photosensitive malar rash, recurrent oral ulcers, arthritis, hypocomplementemia, and serositis) presented with a one-week history of dysuria, oral ulcers, fevers, and chills. On the day of admission, the patient had a temperature of 39.8° C, along with myalgias, arthralgias, and fatigue. The patient also complained of a headache that was not associated with visual changes or meningismal signs. Neurological signs included intermittent confusion and difficulty forming sentences due to a clouded sensorium. The patient reported that these symptoms were similar to previous flares, other than the high fever and altered mental status. Over the past two months, the patient had her usual regimen of belimumab held and prednisone tapered from 15 to 10 mg per day due to a concurrent HPV infection, raising the suspicion that her current presentation was an SLE flare triggered by lower doses of immunosuppression.

On physical examination at initial presentation, the patient was febrile but with otherwise normal vital signs. Examination revealed a 0.3cm white, painful tongue ulcer with a clean base and multiple 0.2-0.3 cm genital ulcers with similar appearance. While the patient had a history of oral ulcers with her lupus, she denied a history of prior genital ulcers. She reported sexual activity with one male partner with variable condom use. She had a thin, grey, malodorous vaginal discharge. There was mild right upper quadrant tenderness on deep palpation. Neurological exam was significant for intermittent confusion and altered attention. She had no focal neurological signs.

Initial evaluation included a basic metabolic panel, hepatic panel, complete blood count, viral PCR of the genital lesions, anti-double stranded DNA and MRI brain with and without contrast. Initial laboratory analysis revealed only a mild transaminitis (Table 1). MRI of the brain showed no abnormal enhancements or changes in white or gray matter. Wet mount revealed clue cells. Right upper quadrant ultrasound was normal. Viral PCR were not yet resulted. Rheumatology was consulted and concluded this was likely a lupus flare given her fevers, myalgias, arthralgias, and negative brain MRI for encephalitis and increased daily prednisone to 15 mg. The patient continued to have fevers to 39° F, drenching sweats, episodes of confusion, and right upper quadrant tenderness. Four days after presentation, blood cultures and viral PCR of the genital lesions returned positive for HSV-2. Lumbar puncture was then performed and CSF viral PCR was also positive for HSV-2 and the patient was started on parenteral acyclovir. Blood cultures, urine cultures, and CSF cultures were otherwise negative, and workup for

other viral infections – including HIV, Cytomegalovirus, and Epstein-Barr virus – were also negative. Evaluation for other concurrent sexually transmitted infections was positive only for previously diagnosed HPV. CSF fluid was negative for rheumatologic serologies associated with lupus cerebritis, including anti-ribosomal p protein and anti-neuronal antibody. Additionally, anti-double stranded DNA antibody titers were negative. Within 24 hours of starting parenteral acyclovir, the patient became afebrile with resolution of drenching sweats, confusion, and improvement in the oral and genital ulcers. With treatment, her right upper quadrant tenderness also resolved and liver enzymes trended down.

The patient was diagnosed with HSV-2 encephalitis and hepatitis and continued on parenteral acyclovir. After clinical improvement, she was transitioned to high dose oral valganciclovir for 2 weeks followed by life long HSV oral suppression. Following discharge, the patient continued to complain of mild headache, fatigue, and joint pain, which resolved over the following weeks. She had no recurrence of her fevers, altered mental status, or right upper quadrant pain. Her genital lesions also resolved. Her oral prednisone dose was lowered again to 10mg daily with no occurrence of lupus symptoms. She was able to return to her courses as a college student and continued to do well.

Discussion

Viral syndromes have been shown to mimic the primary presentation of SLE and lupus flares, however there are few reports due to disseminated HSV-2[1,3-7]. Our patient had prior history of lupus on chronic oral prednisone with multiple flares characterized by fevers, headaches, oral ulcers, arthralgias and myalgias, and abdominal pain. During this presentation she had some similar symptoms, however with higher fevers, new genital ulcers, and new confusion. Therefore, while her corticosteroids were slightly increased to treat any SLE-related symptoms, multiple microbiobial cultures and serologies were also sent to investigate other etiologies. After no response to SLE directed therapy, further evaluation revealed disseminated HSV-2 with positive PCR in the blood and CSF as well as evidence of mild hepatitis. The patient had complete resolution of symptoms upon treatment with parenteral acyclovir.

In a compilation of case studies demonstrating viral infections influencing the presentations of primary SLE or lupus flares, only 9 out of 88 cases were due to an HSV infection[1]. Of those cases due to HSV infection, none presented as mimicking a lupus flare; however, systemic infection was found in 4 cases. In this review, other viruses reported to mimic SLE were cytomegalovirus and parvovirus B19, viruses commonly implicated as possible primary etiologies of developing SLE. Other infrequent viruses mimicking primary SLE or a lupus flare included Epstein-Barr virus, varicella-zoster virus, hepatitis A virus, norovirus, measles virus, and mumps virus[1]. While there are many papers evaluating the role of cytomegalovirus, parvovirus B19, and Epstein-Barr virus as etiologies for developing SLE[5], there are few reviews evaluating viral illnesses complicating the diagnosis of SLE or a lupus flare.

Of particular interest was our patient's positive HSV-2 PCR in CSF with neuropsychiatric symptoms including altered mental status and delirium. HSV-2 encephalitis in patients with SLE is not commonly reported. One case reported HSV-1 encephalitis and necrotic retinitis in a patient with comorbid SLE on continuous oral mycophenolate mofetil and methylprednisolone[4]. Neuropsychiatric symptoms occur in 10-80% of patients diagnosed with SLE and often present as cognitive dysfunction, similar to our patient, however these symptoms are most often associated with lupus cerebritis rather than encephalitis[4].

A literature review of cases reporting HSV infections in SLE yielded several reports of organ-specific infections[1,3,4,8-10]. HSV infections in patients with lupus tended to involve the eye and liver, and were all rare complications of HSV. These infections were severe and, particularly in the case of HSV hepatitis, potentially fatal. In a review of HSV-2 hepatitis treated with parenteral acyclovir, the mortality rate was 33% (5 out of 15), however these cases were not limited to patients with comorbid SLE[8]. In a review of 52 adults with HSV hepatitis, 44 of the 52 had underlying conditions causing varying degrees of immunocompromise[11]. The most prevalent conditions included renal transplantation, use of steroids (other than those used for renal transplantation), pregnancy, and cancer. There was one case of HSV hepatitis secondary to steroid use for treatment of SLE. Degree of transaminitis was predictive of outcome with higher elevations portending a worse prognosis[8]. In our case, the patient had mild transaminitis with resolution after treatment with parenteral acyclovir.

HSV viremia may be associated with primary genital infection even in immunocompetent hosts, however the clinical significance is unclear[6]. Patients with

primary HSV genital infections often present with systemic symptoms including fever, photophobia, constitutional symptoms, and headache; however cognitive dysfunction has not been reported associated with primary genital infections[6]. In a review of immunocompetent hosts with primary HSV genital infections, 24% (40 out of 164) were found to have positive HSV-2 DNA PCR of the blood[6]. None of these subjects progressed to more advanced systemic infections such as hepatitis or encephalitis.

Our patient presented with a primary HSV genital infection and viremia with symptoms and laboratory analysis suggesting HSV-2 encephalitis and hepatitis. While these organ-specific HSV infections in previous reports have all been severe, our patient had a mild clinical course with complete response on parenteral acyclovir. HSV viremia is not uncommon in primary HSV genital infections and our patient was immunocompromised leaving her at risk for organ-specific involvement secondary to viremia. The prognosis of organ-specific involvement in primary genital HSV viremia in an immunocompromised host has not been reported, however it likely has the potential to be severe. The severity of disease would likely be worsened with incorrectly diagnosed with a lupus flare and treated with higher doses of immunosuppressant agents. Particularly in patients who have comorbid SLE that may present very similarly to organ-specific HSV infections, it is critical to evaluate for disseminated viral infections in patients presenting with suspected primary SLE or lupus flares. It is also significant to highlight the importance of safe sexual practices given the increased risk of infection amongst immunosuppressed patients.

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Appendix:

Table 1

	HD 1	HD 2	HD 3**	HD 4	HD 5	HD 6
AST	138	172	199	156	77	23
ALT	122	139	158	169	129	57
Alkaline Phosphatase	76	79	76	81	88	88
Total Bilirubin	0.6	0.5	0.4	0.4	0.4	0.5
Creatinine	0.7	0.6	0.6	0.6	0.6	0.7

*HD-Hospital Day; AST- Aspartate Amino-transferase; ALT- Alanine Aminotransferase
** Acyclovir administration beginning on hospital day 3