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CASE REPORT

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Sentinel HSV Infection Revealing Systemic Lupus Erythematosus and Antiphospholipid Syndrome in a Chronically Ill Adolescent Female: A Case Report

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ABSTRACT

Childhood-onset systemic lupus erythematosus (cSLE) is a severe autoimmune disorder with diverse multisystem manifestations; neuropsychiatric involvement is an uncommon initial feature. Herpes simplex virus (HSV) encephalitis, although rare, is a potentially life-threatening infection that primarily affects immunocompromised individuals, including those with SLE. Cases where HSV encephalitis precedes SLE diagnosis are exceedingly rare.

We present a 14-year-old Filipino female with autoimmune thyroiditis who developed acute behavioral changes after a mild febrile illness. Cranial MRI revealed an acute right frontotemporoparietal infarct; laboratory workup showed bicytopenia and nephrotic-range proteinuria. Positive HSV-1 IgG supported a diagnosis of HSV encephalitis, and empiric acyclovir was initiated. Strongly positive antinuclear antibodies met the entry criterion of the 2019 European League Against Rheumatism / American College of Rheumatology (EULAR/ACR) criteria, with the mucocutaneous, hematologic, and renal domains fulfilled.

Her course was complicated by severe hypertension, Class III lupus nephritis, and persistent lupus anticoagulant positivity with cerebral infarction, confirming secondary antiphospholipid antibody syndrome.

This case illustrates the layered pathology of infection, inflammation, and thrombosis, where an infectious trigger unmasked an autoimmune process and vascular complications. The interplay between HSV neurotropism and immune dysregulation may have predisposed her to neuroinflammation and systemic autoimmunity. Early multidisciplinary intervention was pivotal to recovery. Further studies are needed to clarify viral-autoimmune interactions in pediatric SLE.

Keywords: Herpes Simplex Virus (HSV) Encephalitis, systemic lupus erythematosus, antiphospholipid syndrome (APS), immune dysregulation, neuroinflammation

INTRODUCTION

Childhood-onset systemic lupus erythematosus (cSLE) is a severe, multisystem autoimmune disorder caused by loss of immune tolerance and production of autoantibodies, most commonly antinuclear antibodies (ANA). It presents with varied manifestations involving constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, and renal systems. While rash, arthritis, cytopenias, or nephritis are common, neuropsychiatric features such as seizures, stroke, or leukoencephalopathy are rare initial presentations.[1,2]

Herpes simplex virus (HSV) is the most common cause of sporadic viral encephalitis worldwide, responsible for up to 70% of identified viral cases. In children beyond the neonatal period, HSV-1 predominates and is a major cause of severe encephalitis with high mortality and risk of long-term neurological sequelae despite treatment.[3]

Patients with established SLE have increased susceptibility to HSV due to intrinsic immune dysregulation and immunosuppressive therapy. The incidence of HSV encephalitis in pediatric SLE is unclear, and it is exceptionally rare for it to precede SLE diagnosis. Literature review revealed no documented pediatric cases where HSV encephalitis was the initial event.[4]

We report a rare case of an adolescent female in whom HSV encephalitis unmasked cSLE and antiphospholipid syndrome (APS), highlighting the need to consider autoimmunity in severe pediatric CNS infections.

CASE

A previously well 14-year-old female presented with acute behavioral changes (confusion, irritability) after a week of low-grade fever and mild respiratory symptoms. She reported easy fatigability and pallor. There was no history of seizures, trauma, or substance use. Her history included autoimmune polyendocrinopathy (alopecia areata, subclinical hypothyroidism) diagnosed five months earlier, and she was on levothyroxine. Family history was notable for SLE in a maternal aunt.

On admission, she was conscious but intermittently irritable, without meningeal signs or focal deficits. MRI (Figure 1A) showed acute infarction in the right frontotemporoparietal lobes with faint meningeal enhancement; MRA revealed incomplete obstruction at the right M1/M2 junction.[5] Lumbar puncture was deferred. Complete blood count showed persistent bicytopenia (Table 1). Infectious screening (dengue, malaria, respiratory pathogens) was negative.

HSV encephalitis was highly suspected. Intravenous acyclovir was consequently started. The HSV Antibody Panel showed a positive HSV-1 IgG result (Table 2).[6] EEG showed focal dysfunction in the right frontotemporal region. On the second hospital day, she developed left central facial palsy. Multisystem presentation (hematologic, neurologic, infectious, autoimmune predisposition) raised suspicion for an autoimmune process, prompting workup. ANA was strongly positive. The 24-hour urine protein was 6.2 g/day. Physical exam revealed a faint malar rash. Using the 2019 European League Against Rheumatism /American College of Rheumatology (EULAR/ACR) SLE criteria (Table 3), she met the diagnostic threshold with thrombocytopenia, malar rash, and proteinuria.[7,8]

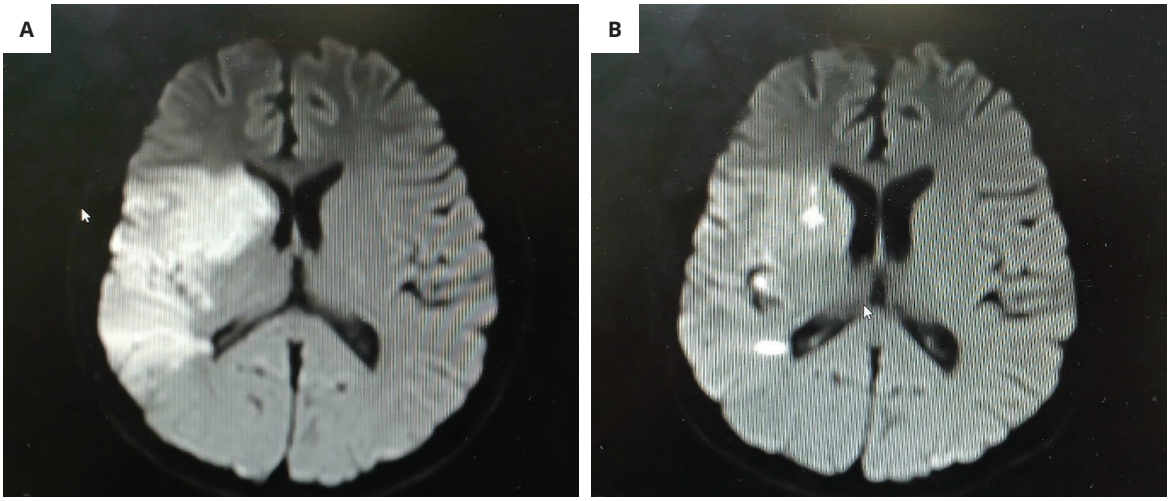


Figure 1. **(A)** Cranial MRI done on Day 1. **(B)** Cranial MRI done on Day 17.

Table 1. Serial Complete Blood Count done during admission

CBC Parameters	Day 1	Day 3	Day 5	Day 6	Day 9 (Before MPPT*)	Day 12 (1 Day Post-MPPT*)	Day 18
WBC (x10³/uL)	6.7	7.9	7.8	4.0	3.4	10.3	9.2
Differential Count (%)							
Neutrophils	68	82	75	55	74	77	68
Lymphocytes	22	13	18	34	24	17	24
Monocytes	9	5	5	8	2	6	8
Eosinophils	1	0	1	2	0	0	0
Basophils	0	0	0	1	0	0	0
Hemoglobin (g/dL)	8.9	8.3	8.8	8.4	9.4	9.9	9.8
Hematocrit (%)	26.8	24.8	26.3	25.3	27.8	30.1	39.4
RBC indices							
MCV (Fl)	83.2	82.9	83	82.7	81.5	83.1	83.8
MCH (pg)	27.6	27.8	27.8	27.5	27.6	27.3	27.9
MCHC (g/dL)	33.2	33.5	33.5	33.2	33.8	32.9	33.3
RDW (%)	11.9	12.1	12.2	12.3	11.9	12.8	14.5
Platelet (x10³/uL)	84	82	70	82	54	72	151

**MPPT – Methylprednisolone Pulse Therapy*

Table 2. Serum Herpes Simplex Virus (HSV) Antibody Panel Test

Test	Result (U/ml)	Cutoff	Interpretation
HSV-1 IgM	7.80	<20	Negative
HSV-2 IgM	4.10	<20	Negative
HSV-1 IgG	>200	>25	**Positive**
HSV-2 IgG	3.0	<20	Negative

Table 3. 2019 EULAR/ACR Criteria domains met on initial admission

Domains	Findings/Score
Entry Criteria	Positive ANA titer (13.7; Normal Value: 0-1.2)
Hematologic	Thrombocytopenia (4)
Mucocutaneous	Acute Cutaneous Lupus (6)
Renal	Proteinuria >0.5g.24 hr (4)
Total	14 (Threshold: >10)

Nephrology service was consulted, and methylprednisolone pulses (days 9–11) were given for presumed lupus nephritis.[9] She developed hypertensive urgency (BP 180/120 mmHg) one day post-methylprednisolone pulse therapy, requiring pediatric intensive care unit transfer and nicardipine infusion, later transitioned to oral enalapril, losartan, and amlodipine.

By day 17, repeat MRI (Figure 1B) showed infarct evolution with new inflammatory lesions consistent with CNS lupus rather than active HSV. She was neurologically improved, alert, oriented, ambulatory, with resolved facial palsy. Acyclovir was completed; she was discharged on prednisone, mycophenolate mofetil, calcium, and vitamin D.

Outpatient workup for APS was positive on two dilute Russell's Viper Venom Time (dRVVT) tests 12 weeks apart, confirming secondary APS.[10,11] Aspirin was initially started, then transitioned to warfarin upon confirmation of APS. Renal biopsy showed Class III lupus nephritis. Maintenance immunosuppression with mycophenolate mofetil and tapering prednisone was continued; antihypertensives were withdrawn as BP normalized. On last follow-up, she remained neurologically intact with resolved proteinuria and hematuria, stable renal function, and no hypertension.

DISCUSSION

Systemic lupus erythematosus is a chronic autoimmune disease caused by loss of immune tolerance to self-antigens, leading to autoantibody production and pathogenic immune complex formation. These deposits in tissues trigger inflammation and result in multisystem involvement. SLE predominantly affects females of reproductive age, with pediatric cases accounting for 15–20% of patients. Childhood-onset SLE often presents with more severe and atypical features than adult-onset disease.[1]

Infections are a major cause of morbidity and mortality in SLE, driven by disease activity, immunosuppressive therapy, cytopenias, and nephrotic syndrome–related protein loss, all contributing to secondary immunodeficiency.[2] Our patient exhibited early immunocompromised features, which are bicytopenia, proteinuria, and autoimmune thyroiditis, predisposing her to opportunistic infections.

Herpes Simplex Virus encephalitis (HSE), the most common cause of sporadic fatal viral encephalitis worldwide, has an incidence of 1 per 250,000–500,000 annually.[3,4] It typically manifests with fever, altered mental status, and seizures. MRI classically shows asymmetric limbic involvement, especially in the medial temporal lobes, insular cortex,

and inferolateral frontal lobes.[5] Diagnosis relies on HSV DNA detection in cerebrospinal fluid by polymerase chain reaction (PCR).[6]

In this case, lumbar puncture was contraindicated due to extensive infarction and risk of herniation. Serologic testing showed positive HSV-1 IgG, suggesting prior exposure or reactivation.[7] While not diagnostic for acute HSE, pre-existing antibodies are present in up to two-thirds of cases, and only ~10% report recurrent mucocutaneous lesions.[8] Empirical acyclovir was started promptly, in line with guidelines recommending 10 mg/kg IV every 8 hours for 14–21 days in adolescents and adults.[6] Early therapy likely aided neurologic recovery.

Acute neuropsychiatric symptoms (encephalopathy and behavioral change) were attributed to HSE due to a viral prodrome, positive HSV-1 IgG, and improvement with acyclovir. This fits HSE as the primary early neurologic process.

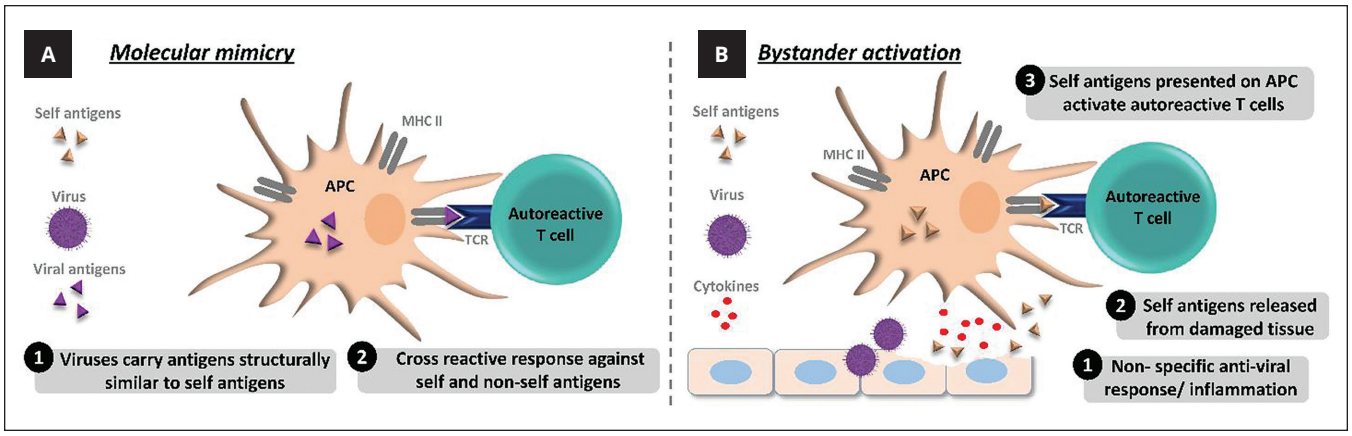
As the course progressed, evolving multisystemic abnormalities (persistent bicytopenia, nephrotic-range proteinuria, malar rash, and autoimmune predisposition) prompted an autoimmune workup. The patient met the 2019 EULAR/ACR SLE classification criteria, with positive ANA (entry criterion) and points for thrombocytopenia, mucocutaneous involvement, and renal disease (total 14, threshold ≥10).[7,8] Neuroimaging evidence of cerebral infarction was attributed to a vasculitis complication of SLE. Following stabilization, persistent proteinuria led to methylprednisolone pulse therapy for suspected lupus nephritis, with clinical improvement. Patient developed secondary hypertension attributed to lupus nephritis, successfully controlled with oral antihypertensives. Renal biopsy confirmed Class III (focal proliferative) lupus nephritis, guiding maintenance with prednisone and mycophenolate mofetil. Proteinuria and hematuria are resolved, allowing steroid taper. While cyclophosphamide is a traditional choice, mycophenolate is now favored for proliferative lupus nephritis, particularly for outpatient management.[9,12]

The patient had a prior history of autoimmune thyroiditis. In the literature review by Ferrari et al.,[13] multiple studies demonstrated a high incidence of thyroid disorders among female individuals with SLE versus healthy cohorts, particularly autoimmune thyroiditis.[13] Autoantibodies present were mainly thyroid autoantibodies, thyroglobulin autoantibodies (TgAb), and anti-thyroid peroxidase autoantibodies (anti-TPO). Furthermore, the literature review suggests that periodic thyroid function follow-up should be done for SLE patients at high risk and appropriate therapeutic interventions implemented as indicated.[13]

The cerebral infarct prompted evaluation for secondary APS. Up to 40% of SLE patients have antiphospholipid antibodies, though not all meet clinical criteria.[10,11] Diagnosis requires at least one clinical event (e.g., vascular thrombosis) and one laboratory criterion (persistent lupus anticoagulant, anti-cardiolipin, or anti-β2 glycoprotein I antibodies) confirmed ≥12 weeks apart.[12] Our patient met these with cerebral infarction and persistent lupus anticoagulant positivity (increased dRVVT), confirming secondary APS. Long-term anticoagulation was initiated with aspirin, then warfarin (target INR 2.0–3.0) upon confirmation of diagnosis per current recommendations.[12]

A central discussion point is the immunologic mechanisms by which HSV infection may unmask or stimulate autoimmunity. The Herpesviridae family, which includes HSV-1 and HSV-2, possesses neurotropic and immunomodulatory properties that enable lifelong latency, periodic reactivation, and chronic immune stimulation.[14,15] HSV infects neurons, astrocytes, and oligodendrocytes via the trigeminal and olfactory nerves, bypassing the blood–brain barrier and inducing Golgi stress, which disrupts endothelial tight junctions and promotes neuroinflammation. These processes expose sequestered self-antigens, facilitating bystander activation (Figure 2B) of autoreactive B and T cells. HSV glycoproteins C and E can also modulate host immunity by binding complement components and the Fc region of IgG, thereby impairing viral clearance and sustaining antigenic stimulation. Concurrently, activation of innate immunity through Toll-like receptors (TLR2, TLR3, and TLR9) and the cGAS–STING pathway triggers excessive type I interferon (IFN-1) and NF-κB–mediated cytokine release (e.g., IL-1, IL-6, TNF, and CXCL10), contributing to the IFN signature characteristic of SLE.[16] Molecular mimicry (Figure 2A) further contributes to autoimmunity, as viral peptides resembling nuclear and phospholipid antigens may induce cross-reactive antibodies targeting dsDNA, Sm, Ro/La, and β2-glycoprotein I, linking SLE and APS pathogenesis. Chronic HSV latency and reactivation cause sustained low-grade immune activation, oxidative stress, and endothelial injury, predisposing genetically susceptible individuals to immune dysregulation, autoantibody formation, and thrombotic and inflammatory complications.[17]

Population-based findings further support this viral–autoimmune link. Vista et al. found that Filipino SLE patients had significantly higher HSV-1 and HSV-2 seroprevalence and antibody titers than healthy controls, suggesting more frequent past exposure or viral reactivation. This observation supports the hypothesis that herpes viruses may contribute to immune dysregulation in SLE.[18] However, further studies are warranted to establish HSV-induced mechanisms of autoimmunity.



Adapted with permission from Smatti et al.[16] Modifications: Image cropped from original figure to only include mechanisms A and B.

Figure 2. Mechanisms of virus-induced autoimmunity **(A)** Molecular mimicry model: (1) Viruses carry epitopes structurally similar to self-epitopes; (2) Presentation of viral epitopes by antigen-presenting cells (APCs) activates autoreactive T cells that bind to both self and non-self-antigens and induce tissue damage. **(B)** Bystander activation model: (1) Non-specific and overreactive antiviral immune responses lead to the liberation of self-antigens and release of inflammatory cytokines from the damaged tissue. (2) Self-antigen is taken up and presented by APCs. (3) Autoreactive T cells are activated by APCs, leading to tissue destruction.

In this case, the presence of high HSV-1 IgG titers may indicate prior neurotropic viral activity that triggered or unmasked systemic autoimmunity. The development of SLE with secondary APS in the patient can be immunologically explained by HSV-induced activation of type I interferon pathways, endothelial injury, and molecular mimicry between viral and self-antigens. These mechanisms likely promoted loss of self-tolerance, persistent B-cell activation, and production of pathogenic autoantibodies against nuclear and phospholipid targets. The resulting immune complex formation and vascular inflammation provide a unifying explanation for both neuropsychiatric, thrombotic, and inflammatory manifestations observed in this patient. Further research is needed to clarify the role of HSV neurotropism in SLE pathogenesis and neuropsychiatric complications, particularly in high-risk populations.

This case illustrates the interplay between infectious triggers and autoimmune activation in pediatric SLE. Neurologic symptoms, initially from HSE, were compounded by infarction from SLE with secondary APS, representing a layered pathology of infection, inflammation, and thrombosis. Early multidisciplinary care was critical. The presence of HSV-1 IgG supports the possibility of viral–autoimmune interaction in disease expression.

CONCLUSION

Systemic lupus erythematosus is a complex autoimmune disorder characterized by multisystem involvement and an increased susceptibility to infections, including herpes simplex virus encephalitis. Although HSV infection is uncommon in pediatric SLE, its occurrence is associated with significant morbidity and mortality, necessitating prompt recognition through comprehensive clinical, serologic, and neuroimaging evaluation. Early and concurrent management targeting both the infectious agent and underlying autoimmune pathology is essential to optimize clinical outcomes.

This case underscores the intricate interplay between infectious triggers and autoimmune activation, whereby HSV encephalitis may serve as an initial manifestation unmasking pediatric-onset SLE complicated by secondary antiphospholipid syndrome. The importance of integrated, multidisciplinary approaches to diagnosis and treatment cannot be overemphasized, given the overlapping pathophysiological mechanisms and potential for vascular complications.

Given the rarity of HSV encephalitis preceding SLE diagnosis, further investigations are warranted to elucidate the mechanistic links between neurotropic viral infections and autoimmune dysregulation in genetically susceptible pediatric patients. Enhanced understanding of these associations will inform evidence-based strategies for early identification and management of such complex presentations.

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Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors fulfilled ICMJE authorship criteria.

Author Disclosure
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