CASE REPORT

Concurrent Reactivation of Varicella Zoster Virus and Herpes Simplex Virus with Hepatic Microabscesses after Anifrolumab Treatment in Systemic Lupus Erythematosus Patient - A Case Report.

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Abstract

This report describes a patient with long-standing, refractory systemic lupus erythematosus (SLE) who developed concurrent varicella zoster virus (VZV) and herpes simplex virus (HSV) reactivation following treatment with anifrolumab. Diagnosed with SLE at 18 years of age, she experienced multiple haematological flares and major organ involvement despite prolonged immunosuppressive therapy, including mycophenolate mofetil, cyclophosphamide, and rituximab. Ongoing disease activity led to initiation of intravenous anifrolumab. Six days after the third infusion, she presented with painful vesicular lesions involving the extremities and genital region, systemic inflammatory features, and gastrointestinal symptoms. Investigations confirmed simultaneous VZV and HSV infection, supported by positive serology and Tzanck smear findings, along with hepatic microabscesses on imaging. She was successfully treated with intravenous acyclovir, broad-spectrum antimicrobials, and intravenous immunoglobulin, with complete clinical and radiological resolution. This case highlights the risk of severe and atypical herpesvirus reactivation in heavily immunosuppressed SLE patients receiving anifrolumab and underscores the importance of early recognition and prompt antiviral therapy.

Keywords: *Anifrolumab, herpes simplex, herpes zoster, hepatic microabscess, systemic lupus erythematosus.*

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by immune dysregulation and involvement of multiple organ systems. Despite advances in understanding its pathogenesis, the precise aetiology remains incompletely defined, and the disease continues to be associated with considerable morbidity and mortality [1]. Clinical expression of SLE is heterogeneous, ranging from limited mucocutaneous disease to severe, life-threatening involvement of major organs, including the central nervous system [2].

Anifrolumab is a human monoclonal antibody that targets the type I interferon receptor, thereby inhibiting interferon-mediated signaling pathways implicated in SLE pathogenesis [3]. In 2021, the U.S. Food and Drug Administration approved anifrolumab as an adjunctive therapy to standard treatment for patients with moderate to severe SLE [4]. Clinical trials, including the TULIP studies and their long-term extension, reported an increased incidence of herpes zoster virus (HZV) reactivation, likely related to suppression of the type I interferon pathway, which plays a pivotal role in antiviral immunity [5,6]. Most reported herpes zoster cases were mild to moderate in severity and responded well to antiviral therapy. In contrast, herpes simplex virus (HSV) infections following anifrolumab treatment have been rarely described, with only a single published case of disseminated herpes simplex infection to date [7].

In this report, we describe a unique case of concomitant herpes simplex and herpes zoster infection with hepatic microabscess occurring in a patient with SLE following treatment with anifrolumab.

Case report

The patient was diagnosed with SLE at 18 years of age. Her initial manifestations included a photosensitive rash, leukopenia, low complement levels, autoimmune haemolytic anemia (AIHA), positive antinuclear antibodies (ANA) with a homogeneous pattern, and positive anticardiolipin IgG antibodies. Over the subsequent eight years (2012–2020), she experienced multiple SLE flares, predominantly haematological (AIHA and leukopenia), which were partially controlled with mycophenolate mofetil (MMF). In 2020, she developed lupus cardiomyopathy and was treated with intravenous cyclophosphamide, achieving clinical resolution after a cumulative dose of 3 g. One year later, she experienced a generalized seizure and subsequently received six monthly cycles of intravenous rituximab (1 g on day 1 and 500 mg on day 15), after which no further seizures were reported. Despite this, she continued to have intermittent haematological, mucocutaneous, and musculoskeletal SLE flares, leading to the initiation of intravenous anifrolumab therapy. At the time, her maintenance immunosuppressive regimen included MMF 1 g twice daily, oral prednisolone 10 mg once daily, and hydroxychloroquine 200 mg once daily. She had no prior history of herpes virus infection.

In early 2025, intravenous anifrolumab was commenced at a dose of 300 mg every 28 days. Six days after the third infusion, she developed painful and pruritic vesicular lesions involving the hands, genital region, and lower back, associated with per vaginal whitish discharge and multiple episodes of diarrhoea. On presentation, her vital signs were stable. Physical examination revealed papules and vesicles over the hands, arms, and lower back (Figure 1). Perineal examination demonstrated bilateral labial swelling with crusted lesions.

Laboratory investigations showed anaemia with a haemoglobin level of 9.6 g/dL (reference interval [RI]: 13–17 g/dL), a normal white blood cell count of 9.9 × 10^9/L (RI: 4–10 × 10^9/L), markedly elevated C-reactive protein of 376 mg/L (RI: <2 mg/L), elevated reticulocyte count of 6.98% (RI: 0.5–2.5%), elevated aspartate aminotransferase 73 U/L (RI:0-35 U/L) and reduced complement C3 level of 0.6 g/L (RI: 0.9–1.8 g/L). Serological testing revealed positive IgM for for both VZV and HSV. A Tzanck smear obtained from vesicular lesions demonstrated multinucleated

giant cells with ground-glass inclusions (Figure 2). Blood, urine, fungal, and stool cultures showed no growth. Urethral smear for *Neisseria gonorrhoeae* was negative, while a high vaginal swab revealed mixed microbial growth. Contrast-enhanced computed tomography of the abdomen demonstrated numerous discrete scattered hypodense lesions in the liver suggestive of microabscess (Figure 1d).

She was treated with intravenous piperacillin–tazobactam (4.5 g four times daily), metronidazole (500 mg three times daily), and fluconazole (400 mg once daily). Intravenous acyclovir (500 mg three times daily) was added for two weeks based on the clinical suspicion of herpes infection, which was subsequently confirmed by serology and Tzanck smear findings. In view of ongoing disease activity and infection, intravenous immunoglobulin was administered at a dose of 400 mg/kg/day (total 17.5 g) for five days, with a repeat course given one month later. The patient showed good clinical improvement and was discharged after a three-week hospital stay. At discharge, she was prescribed oral prednisolone 40 mg once daily, amoxicillin clavulanate 625 mg three times daily, and hydroxychloroquine 200 mg once daily, while MMF was withheld. A repeat liver ultrasound performed one month later demonstrated complete resolution of the hepatic lesions.

Discussion

To our best knowledge, this is the first case reporting both herpes zoster and herpes simplex in a patient who received anifrolumab. This case underscores the potential risk of viral infections in patients receiving anifrolumab. An increased incidence of herpes zoster has been reported, particularly during the first year of therapy, with rates declining over time [6]. Although uncommon, disseminated herpes virus infections have been described, highlighting the importance of appropriate patient counselling and close clinical monitoring [7]. Given that type I interferons play a central role in host antiviral defence, inhibition of this pathway by anifrolumab may have contributed to viral reactivation in this patient [8]. Furthermore, the concurrent use of additional immunosuppressive agents, such as prednisolone and mycophenolate mofetil, as seen in this case, likely increased susceptibility to infection.

In most patients, herpes simplex virus (HSV) infection is diagnosed clinically. However, laboratory confirmation may be required to distinguish active infection from viral reactivation. Polymerase chain reaction (PCR) is currently regarded as the gold standard for the diagnosis of acute HSV infection [9]. Serological testing for HSV-specific IgM and IgG antibodies provides an additional diagnostic approach. IgM antibodies typically appear early following primary infection, whereas IgG antibodies become detectable approximately 21 to 28 days after exposure and usually persist for life [10]. In the present case, the concurrent detection of both IgM and IgG antibodies supports a diagnosis of recent primary HSV infection rather than reactivation, particularly in the absence of a prior history of HSV infection [11].

Simultaneous reactivation of HZV and HSV can occur, particularly in individuals with impaired immune function. The clinical course of HSV infection may arise before the onset of zoster, coincide with it, or develop subsequently. Although both HSV and VZV are DNA viruses with certain shared virological characteristics, they also possess distinct biological and pathogenic properties, which may account for the infrequent occurrence of dual reactivation [12]. In most patients, the two infections can be differentiated based on clinical features alone; however, overlapping presentations may obscure the diagnosis, underscoring the importance of maintaining a high index of suspicion and considering laboratory confirmation to ensure accurate diagnosis and appropriate management.

Disseminated HSV in anifrolumab-treated SLE patients was rarely report and only one case report

was published. Hepatic microabscesses secondary to HSV was noted in few of the publications [13]. Based on the limited case reports, the imaging findings in HSV hepatitis showed multiple hypodense lesions which indicative of hepatitis necrosis similar to our case report [14,15]. Liver biopsy is the gold standard but reserved if another etiology is considered. In our case, pyogenic liver abscess secondary to a bacterial organism was unlikely based on the investigations but was still treated empirically with antibiotics. In disseminated HSV infection, longer time from symptom onset to IV acyclovir initiation was associated with higher mortality [16].

Conclusion

This case highlights the occurrence of concurrent VZV and HSV reactivation in a patient with refractory systemic lupus erythematosus receiving multiple immunosuppressive therapies, including anifrolumab. The temporal association with anifrolumab initiation raises awareness of severe and atypical herpesvirus infections in highly immunosuppressed patients. Clinicians should maintain a high index of suspicion for viral reactivation when new vesicular lesions or systemic inflammatory features develop, as early recognition and prompt antiviral therapy are essential to prevent morbidity.

Conflict of interest

No conflicts of interest.

Funding

None.

Ethical consideration

Informed written consent was obtained from the patient before the publication of this case report as well as accompanying images.

Authors' Contribution

PSO, WCY and CGK conceived the report and were responsible for the clinical management of the patient. KYC analysed the laboratory data and the histopathology report. PSO critically revised the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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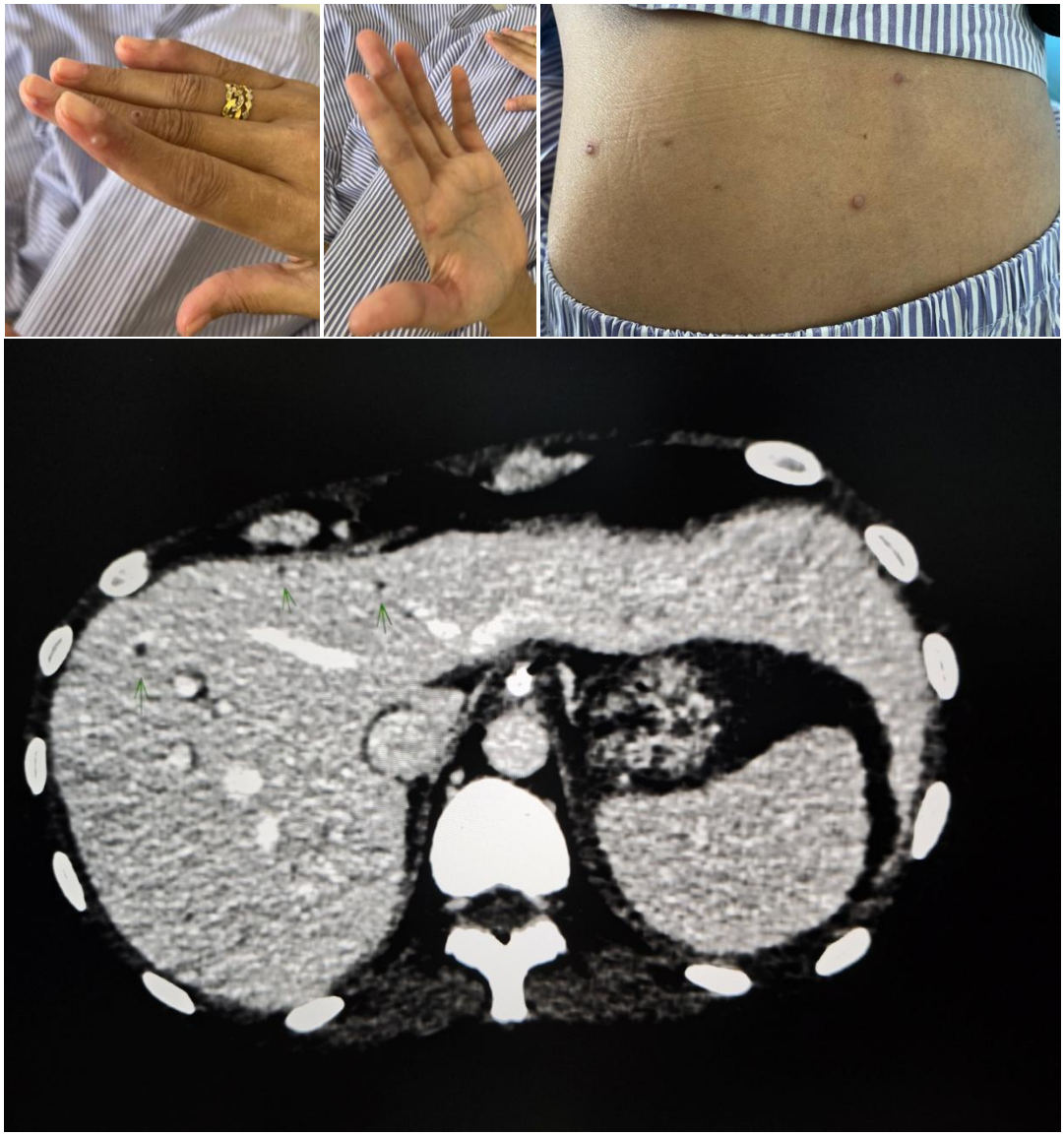

Figure 1 (a) Vesicles on the distal right index finger typical of an early phase of a herpetic whitlow. (b)Erythema multiforme due to the herpes simplex on the left palm. (c) Multiple vesicle lesions affecting the lumbar region(d) Contrast-enhanced computed tomography of the abdomen demonstrated numerous discrete scattered hypodense lesions (arrow) in the liver suggestive of microabscess.

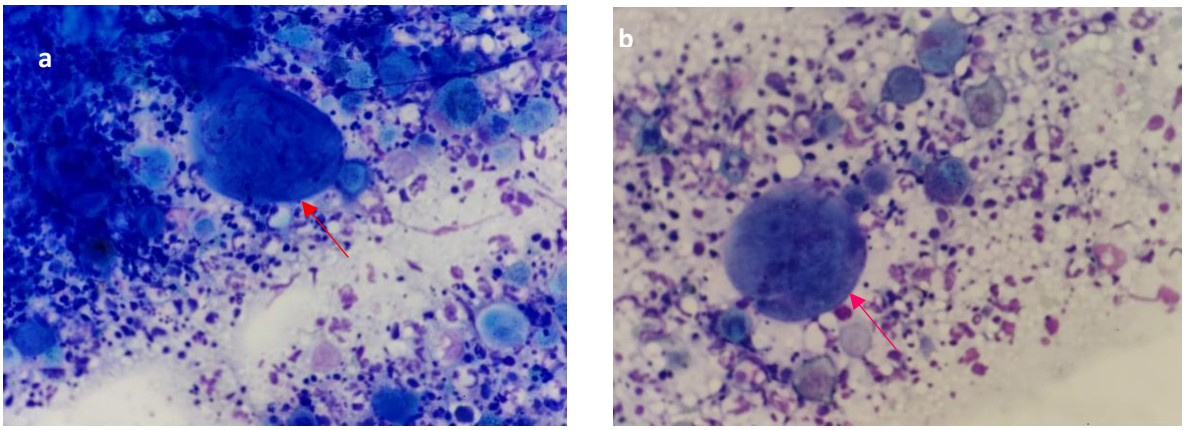

Figure 2 (a,b) Multinucleated giant cell (arrow) with ground glass nuclei and intranuclear inclusion. Background shows some acantholytic cells, mixed inflammatory cells, and cell debris.

Table 1. Clinical timeline of the patient's disease course and management

Date/ Period	**Event**
Age 18 (approx. 2012)	Diagnosed with SLE; presented with photosensitive rash, leukopenia, low complement, AIHA, positive ANA, positive anticardiolipin IgG
2012–2020	Multiple haematological flares partially controlled with MMF
2020	Developed lupus cardiomyopathy; treated with IV cyclophosphamide (cumulative 3 g) – clinical resolution achieved
2021	Generalized seizure; received 6 monthly cycles of IV rituximab (1 g day 1, 500 mg day 15) – no further seizures
Early 2025	Maintenance therapy: MMF 1 g bid, prednisolone 10 mg daily, hydroxychloroquine 200 mg daily; anifrolumab 300 mg IV every 28 days started
Day 6 after 3rd anifrolumab infusion	Presented with painful vesicular lesions on hands, genital region, lower back, vaginal discharge, diarrhoea
On presentation (day 0)	Vital signs stable; lab: Hb 9.6 g/dL, CRP 376 mg/L, AST 73 U/L, C3 low; VZV and HSV IgM positive; Tzanck smear: multinucleated giant cells; CT abdomen: hepatic microabscesses
Hospital day 0–14	Treated with IV acyclovir, piperacillin–tazobactam, metronidazole, and fluconazole
Hospital day 5–9	IV immunoglobulin 400 mg/kg/day for 5 days
Hospital day 21	Discharged on prednisolone 40 mg daily, amoxicillin–clavulanate, hydroxychloroquine; MMF withheld
One-month post-discharge	Repeat liver ultrasound: complete resolution of hepatic lesions

Footnote: AIHA: autoimmune haemolytic anaemia; ANA: antinuclear antibodies; MMF: mycophenolate mofetil

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