Unusual presentation of fatal disseminated varicella zoster virus infection in a patient with lupus nephritis: a case report

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Abstract  
**Background:** The risk of life-threatening complications, such as visceral disseminated varicella zoster virus (VZV) infection, is greater in immunosuppressed individuals, such as systemic lupus erythematosus (SLE) patients.  
**Case presentation:** Here, a case is reported of a Caucasian woman diagnosed with lupus nephritis and anti-phospholipid syndrome, who was subjected to mycophenolate mofetil and high-dose steroid remission-induction therapy. Two months later she developed abdominal pain followed by a fatal rapid multi-organ failure. As no typical skin rashes were evident, death was initially attributed to catastrophic anti-phospholipid syndrome. However, autopsy and virological examinations on archival material revealed a disseminated VZV infection.  
**Conclusions:** Overall, this case highlights the importance of having a high clinical suspicion of fatal VZV infections in heavily immunosuppressed SLE patients even when typical signs and symptoms are lacking.  
**Keywords:** Varicella zoster virus, Herpesviruses, Systemic lupus erythematosus, Immunosuppression, Multiple virus reactivations, Latent virus infections, Mycophenolate mofetil, Steroid therapy

Background  
Varicella-zoster virus (VZV), a member of the family of herpesviridae, remains latent in dorsal roots and autonomic ganglia after a primary infection, but it can always reactivate leading to a secondary infection, which is usually characterized by skin rash and acute neuritis. In some cases, more severe complications may occur especially in immunocompromised patients, where multi-organ involvement can develop with manifestations such as encephalitis, aseptic meningitis, pneumonia and hepatitis [1].  
Here, a case is reported of fatal visceral disseminated VZV in a patient affected by systemic lupus erythematosus (SLE) and anti-phospholipid syndrome (APS) treated with mycophenolate mofetil (MMF) and high-dose glucocorticoids.

Case presentation  
A 49-year-old Caucasian woman affected by SLE and APS presented to the Emergency Department complaining of acute onset of abdominal pain. She denied fever, nausea or vomit. Two months earlier, the patient, with no previous medical history, had been hospitalized for deep vein thrombosis. Her vaccination history was as follows: diphtheria, polio, smallpox and tetanus; she had never been vaccinated for chickenpox, measles, mumps or rubella. During that period, she had been diagnosed with both SLE —positive homogeneous antinuclear antibody titer of 1:320 with a homogeneous pattern— and APS —positive lupus anticoagulant—, with multi-organ dysfunction consisting of lupus nephritis with nephrotic
syndrome, lung serositis, hemolytic anemia and arthritis. Consequently, the patient had been treated with MMF (1.5 g qd) and prednisone (50 mg qd) by nephrologists. On hospital admission, vitals were normal except for heart rate at 120 bpm. Physical examination revealed petechiae at thorax and limbs. Complete blood count showed low lymphocyte \(0.50 \times 10^9/L\) and platelet \(58 \times 10^9/L\) counts. Other serum abnormal laboratory data included decreased levels of immunoglobulin (Ig) G \(118 \text{ mg/dL (NR:700–1600)}\) and increased values of aspartate aminotransferase (AST), alanine aminotransferase (ALT) \(22 \times \text{ and } 13 \times \text{ upper limit of normal (ULN), respectively}\) and lactate dehydrogenase (LDH) \(13 \times \text{ ULN}\). Activated partial thromboplastin time \(1.5 \times \text{ ULN}\) and international normalized ratio (INR) \(5.9\) were prolonged, whereas renal function was normal. At peripheral blood smear, a number of echinocytes and \(2–3\) schistocytes/high-power field were detected; platelets were normalized but decreased \(5/\text{high-power field}\).

All these findings led to the suspicion of catastrophic APS (CAPS). Therefore, methylprednisolone (1 g qd) was started, but the patient’s conditions worsened dramatically as blood tests revealed persistent decrease in platelet count \(23 \times 10^9/L\) and substantial increase in INR \(7.75\), LDH \(25x \text{ ULN}\) and D-dimer \(71x \text{ ULN}\), consistent with disseminated intravascular coagulation (DIC). Therefore, platelet transfusions and fresh frozen plasma were administered. Later on, plasmapheresis and immunoglobulin infusion became necessary. The patient began to show signs of multiple organ failure (MOF) such as acute kidney injury, increasing elevation of liver function tests, glycemia and troponin I, appearance of confusion and, finally, respiratory distress that required intubation. During the procedure, pseudo-membranes, white exudates and diffuse petechiae were detected in the pharynx (consistent with a possible infective exudative pharyngitis). Later on, hypotension and acute onset anemia appeared, and the patient eventually died a few hours later.

At autopsy, diffuse skin petechiae were present. No significant small vessel occlusions could be observed. Pharyngeal mucosa showed ulcerative lesions associated with cytopathic effects of the squamous epithelium (including acantholysis, intranuclear inclusions and cytoplasmic vacuolization), which were suggestive of viral infection (Fig. 1). The liver parenchyma contained areas of coagulative and hemorrhagic necrosis, and hepatocyte nuclei had a diffuse ground-glass appearance, suspicious for viral inclusions. Moreover, occasional multinucleated hepatocytes were observed (Fig. 2). No other significant alterations were present. Being the morphological picture at pharyngeal and liver level consistent with herpesvirus (HV) infection \([2]\), immunohistochemistry was performed with locally available antibodies \[i.e.\ \text{herpes simplex virus 1 (HSV-1) and 2 (HSV-2) and cytomegalovirus (CMV)}\], but it resulted negative both in liver and in pharynx.

In light of these findings and after a multidisciplinary discussion of the case, it was opted to perform virological tests taking in due account the interpretative limitations related to hypogammaglobulinemia and quantitative real-time polymerase-chain reaction assays (PCR; ELITe MGB Kits, ELITech, France) for HV on the plasma samples that had been harvested on the day of death. The most relevant data was a strong VZV positivity \(19,600,000 \text{ copies/mL}\) in the absence of concomitant immune activation \[\text{IgM index } = 0.3 \text{ (cut-off } > 1); \text{ IgG } < 10 \text{ mIU/mL (cut-off } > 150)\]. Furthermore, it was found positivity for CMV \[\text{serological pattern of reactivation with DNA at } 3240 \text{ IU/ml}\], Epstein–Barr virus (EBV) \[\text{serological pattern of reactivation with detectable DNA below the lower limit of quantitation (LLQ)}\].
256 IU/mL] and human herpesvirus 6 (HHV-6) [DNA below the LLQ of 350 IU/mL], whereas samples were negative for HSV-1 and HSV-2 DNA (Fig. 3).

**Discussion and conclusions**

VZV infection may develop as a primary infection or reactivation, the latter one being usually characterized by skin rash and acute neuritis. Nevertheless, immunocompromised patients may display more severe and atypical manifestations, such as encephalitis, aseptic meningitis, pneumonia and hepatitis, along with disseminated visceral and cutaneous involvement [1]. These manifestations frequently represent a diagnostic challenge, as the clinical picture might be insidious, leading to a difficulty in the administration of a prompt and appropriate treatment [3]. Therefore, it appears mandatory to take into account unusual signs and symptoms, especially since these subjects are at higher risk for the rare, but severe,
disseminated VZV infection. Amongst immunosuppressed subjects, SLE patients have been demonstrated to have a particularly high incidence of VZV infection [4, 5]. However, the determinants of this positive association have so far remained unclear, even though a lack of cellular and/or humoral immunity, such as lymphopenia, may be playing a major role [6–8]. Another explanation may be that the use of immunosuppressant drugs is itself a risk factor for VZV. Indeed, the use of combination therapies consisting of MMF and high-dose glucocorticoids has been shown to increase VZV susceptibility [9]. This aspect is particularly relevant to our case. Nevertheless, it is noteworthy that, to be the best of our knowledge, large studies examining the incidence of infections in patients with rheumatic illness treated with MMF are still lacking, so that generalizations can not yet be made. Taking into account these limitations, only a few studies suggest an increased incidence of infectious diseases in such patients [10, 11], as MMF is generally considered a safe drug compared to other immunosuppressive treatments, such as cyclophosphamide [12]. So, even if a MMF role in facilitating viral infections is strongly suspected, a regular monitoring of the presence of VZV in rheumatic patients treated with MMF is not yet recommended.

One of the most recent contributions from the Literature on this topic comes from Habuka et al. who recently described a dramatic case of disseminated VZV infection in a patient with lupus nephritis treated with the aforementioned combination regimen, not only highlighting in a patient with lupus nephritis treated with the afore-

mentioned combination regimen, but also suggesting a possible connection between Asian and experiencing worse outcomes [13]. Although these elements make that case similar to ours, here it is shown an unprecedented case in a Caucasian subject. Moreover, our patient presented with a rarely found combination of disseminated VZV infection and MOF. Another peculiarity of our case is that the patient did not show any signs or symptoms suggestive of VZV infection, when this latter is usually accompanied by cuta-

neous manifestations, which help make a correct diagnosis. The only complaint reported by the patient was in fact abdominal pain. This symptom is generally considered un-

common and it has always been reported as being con-

comitant with or, at least, preceding skin manifestations [14]; it is generally considered to occur due to direct viral infection of the enteric nervous system, from at least two different pathways: viremia, in which circulating T cells carry VZV, and axonal transport from dorsal root ganglia [14, 15]. Coming back to our patient, it is possible that she did not have the time to manifest typical skin signs. Not surprisingly, the initial diagnosis failed to recognize viral infection. The differential diagnosis was in fact between acute DIC and CAPS. However, since a clear confirmation of small vessel occlusion was lacking at autopsy, the final cause of death was attributed to MOF secondary to severe sepsis, the latter one being likely also the cause of the se-

vere progressive thrombocytopenia.

Another distinctive feature of this case is that, while autopsy revealed signs of viral infection almost exclu-

sively in the pharynx and liver, blood PCR assays on archival material showed an extremely high viral VZV load. Unfortunately, it is not known how much time went by from the first infection/reactivation to sample collection. In any case, considering that the virological tests were performed 3 weeks later, it is tempting to speculate that there should have been an even higher viral load at the collection time. Thus, VZV serology seems to indicate a recent first infection to which the patient was not able to react, probably due to a severe immunosuppression state, as suggested by hypogamma-

globulinemia and lymphopenia (although, at least for the latter one, viral infection cannot be excluded as a con-

tributory cause).

In this patient, the microbiological pattern was further complicated by the occurrence of multiple HV infections concomitant with VZV. These coreactivations are usually associated with poorer outcomes [16, 17]. Among the most commonly reactivated HV, CMV and EBV and, to a lesser extent, also HSV-1, HHV-6 and VZV have been reported [18, 19]. Alternatively, reactivated HV can directly transactivate other latent viruses. As an example, it is known that HHV-6A can reactivate EBV through a BamHI Z fragment leftward open reading frame (BZFL)-

1-dependent mechanism, or through the activation of the Zebra promoter by a cyclic AMP-responsive element [20, 21]. Thus, it is apparent that being able to differenti-

ate between clinically significant and latent viral burden is of the utmost importance when dealing with immuno-
suppressed patients. In this regard, quantitative PCR as-

says can provide valuable help. In our patient, although the CMV viral load was not as high as that of VZV, it reached threshold values usually recommended for the initiation of preemptive therapy. In contrast, EBV and HHV-6 viremias were below the LLQ, so it was not pos-

sible to determine whether they corresponded to true la-
tent virus reactivations, as it was suggested by the concomitant serological responses.

In conclusion, our investigation calls for increased awareness about the unpredictable complications caused by reactivations of specific latent infections under strong immunosuppression: prompt clinical diagnosis might be challenging, so early viral detection is highly recom-

mended [3]. This is because a high index of suspicion on the part of the clinician to monitor for the presence of VZV in MMF-treated patients could result in appropriate timely treatment with acyclovir and better patient outcomes.
Abbreviations
VZV: Varicella-zoster virus; HV: Herpesvirus; SLE: Systemic lupus erythematosus; APS: Anti-phospholipid syndrome; MMF: Mycophenolate mofetil; Ig: Immunoglobulin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ULN: Upper limit of normal; LDH: Lactate dehydrogenase; INR: International normalized ratio; CAPS: Catastrophic anti-phospholipid syndrome; DIC: Disseminated intravascular coagulation; MOF: Multiple organ failure; HSV-1: Herpes simplex virus 1; HSV-2: Herpes simplex virus 2; CMV: Cytomegalovirus; PCR: Polymerase-chain reaction; EBV: Epstein–Barr virus; LLQ: Lower limit of quantitation (LLQ); HHV-6: Human herpesvirus 6; BZF2: BAFH1 Z fragment leftward open reading frame

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Authors’ contributions
VV, AC, and CS2 analyzed and interpreted the patient data comprehensively. CS2, SF and MQ managed the patient. ML and CS1 performed and interpreted the histological examinations. PR performed and interpreted seroepidemiological and molecular biology analyses. VV and CS2 drafted the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated during the survey of this case are included in this published article. The medical file and the histological archive of the patient are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent to publish the case was obtained from the next of kin of the patient (concerning his relative personal or clinical details along with any images to be published in this study).

Competing interests
The authors declare that they have no competing interests.

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