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Letter to the Editor

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Herpes zoster complicated with aseptic meningitis after cardiac transplantation: Report of two cases and review of the literature

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Sir,

Varicella-Zoster Virus (VZV) is a frequent cause of morbidity in solid organ transplant (SOT) recipients, especially after heart transplant (HTx) [1]. Both VZV primoinfection and reactivation can entail visceral involvement [2]. We describe two cases of HTx recipients who developed Herpes Zoster (HZ) with associated meningitis, a condition of unknown prevalence and prognosis in this population.

Patient #1, a 45-year-old man, underwent HTx in September 2018 due to familial transthyretin amyloidosis with advanced heart failure. Maintenance immunosuppressive therapy (IST) was based on tacrolimus, mycophenolate mofetil (MMF) and prednisone. After HTx he suffered progressive cytopenias, making it necessary to down-titrate MMF. The patient had an intermediate risk citomegalovirus (CMV) serostatus (donor +/recipient +), so a preemptive therapy approach was followed in order to avoid further hematologic toxicity.

Five months after HTx the patient was admitted with a 2-day history of fever and vesicular rash suggestive of disseminated HZ affecting right cervical and dorsal regions (Figure 1A-B). He also had cephalea, nausea, photophobia and neck stiffness, but no neurological deficit at examination. Blood tests were unremarkable. Intravenous acyclovir (10 mg/kg/8h) was started and lumbar puncture was performed because of suspected central nervous system (CNS) involvement. Analysis of cerebrospinal fluid (CSF) showed 13 leukocytes/mL with 88% of mononuclear cells, glucose of 49 mg/dL and proteins 108 mg/dL. Qualitative polymerase chain reaction (q-PCR) on a CSF sample was positive for VZV-DNA. Bacterial and fungal cultures were sterile. Cerebral magnetic resonance was normal, so disseminated HZ with associated meningitis was diagnosed and IST down-titrated. He completed a 3-weeks course of antiviral therapy, with complete resolution of cutaneous lesions and meningeal symptoms. No further VZV-reactivations have been observed during follow-up.

Patient #2, a 72-year-old female, underwent HTx in August 2018 due to familial dilated cardiomyopathy with advanced heart failure secondary to a pathogenic variant in RBM20, a gene that encodes RNA-binding motif protein 20, which regulates the splicing of several sarcomeric genes. After HTx she developed multifactorial severe renal dysfunction. At discharge she was receiving MMF, prednisone and tacrolimus. The patient had an intermediate CMV risk profile (donor -/recipient +), so a preemptive therapy strategy was adopted in order to avoid further renal toxicity

Thirteen months after HTx she presented with HZ affecting left D6-D8 dermatomes. She also suffered mild cephalea, in this case without meningeal symptoms. Neurological examination was unremarkable. Laboratory tests showed normal leukocyte count, liver function parameters and C-reactive protein. Lumbar puncture was performed because of persistent cephalea. CSF analysis showed no pleocytosis and normal levels of glucose and proteins, but q-PCR was positive for VZV-DNA. Bacterial and fungal cultures were sterile. Cerebral computed tomography showed a normal cerebral parenchyma without focal lesions. Thus, VVZ subclinical meningitis associated to HZ was diagnosed. She received a 14-day course of intravenous acyclovir adjusted to renal function, with complete resolution of the cutaneous lesions and cephalea. Nowadays she remains asymptomatic and free from further VZV-reactivations.

We describe two cases of HTx recipients with HZ and only mild neurological symptoms who were diagnosed with VZV-meningitis and who had good clinical course under antiviral therapy. VZV is nowadays recognized as one of the most common causes of aseptic meningitis in general population, where it has a better prognosis than meningoencephalitis [3-6]. Nev-

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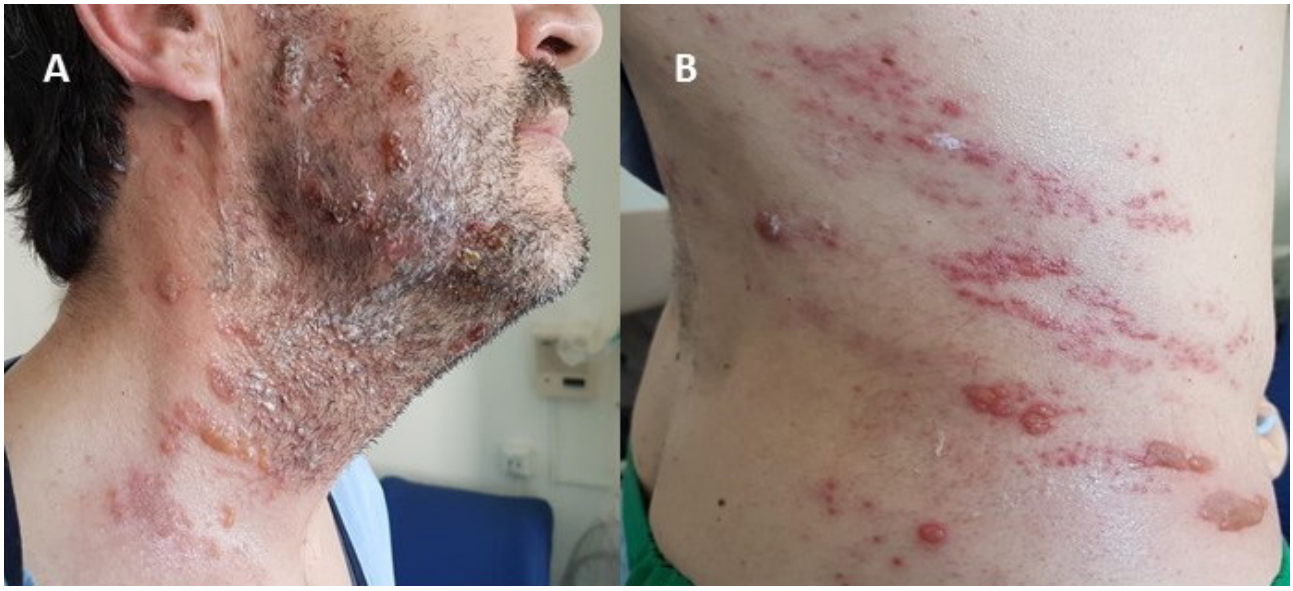

Figure 1 | **Physical examination findings of Patient #1. Disseminated HZ affecting C2-C3 (A) and D10-D12 (B) dermatomes.**

ertheless, it is risky to assume such good outcomes in SOT recipients with meningitis, since immunocompromised patients are underrepresented in general population series and studies focused in SOT recipients are lacking. A case series of VZV-CNS infection after SOT, by Kang et al, described 12 meningoencephalitis cases with poor prognosis: 33% of patients died due to the infection, 17% experienced a limited recovery with neurological sequelae and only 50% achieved full recovery [7]. Nevertheless, encephalitis was early ruled out in our patients based on the absence of neurological deficits, diminished level of consciousness or abnormalities in brain imaging techniques.

Regarding the spectrum of VZV-CNS involvement, it is noteworthy the absence of meningeal symptoms and inflammatory parameters in CSF in Patient #2 despite the presence of VZV-DNA. Pleocytosis and/or VZV-DNA in CSF have been reported in up to 61% of immunocompetent patients with HZ and no neurological symptoms but cephalea, suggesting a high prevalence of subclinical meningitis. In this population, CSF abnormalities were not associated to a worse prognosis [8]. However, the prevalence and outcomes of subclinical meningitis in immunocompromised patients with HZ have not been established yet, so it could be an under-recognized condition.

In summary, as prevalence and prognosis of VZV-meningitis in SOT recipients with disseminated HZ remains unclear, it might be reasonable to have a low threshold to perform lumbar puncture in this clinical scenario. Early initiation of intravenous antiviral treatment should also be considered until CNS involvement has been ruled out. Rapid diagnostic tools such as meningitis multiplex PCR test in CSF could be very helpful in this scenario.

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None to declare.

CONFLICT OF INTEREST

The authors declare no conflicts of interest

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