Varicella zoster virus reactivation and the increased risk of cerebrovascular accidents: the unexpected role dermatologists can play

Francisco Gil[1], Margarida Rato[1], Joana Parente[1], Natália Teixeira[2], Marta Dias[3], Marta Duarte[4]

Affiliations: [1]Dermatology Department, Hospital de Santarém EPE, Santarém, Portugal, [2]Internal Medicine Department, Hospital de Santarém EPE, Santarém, Portugal, [3]Neurology Department, Hospital de Santarém EPE, Santarém, Portugal, [4]Hematology Department, Hospital de Santarém EPE, Santarém, Portugal

Corresponding Author: Francisco Gil, Departamento de Dermatologia, Hospital de Santarém EPE, Avenida Bernardo Santareno, 4º piso, 2005-177 Santarém, Portugal. Email: franciscosgil@gmail.com

Abstract

Varicella zoster virus (VZV) primary infection usually causes varicella and its reactivation may lead to different clinical manifestations depending on the site of viral reactivation and its subsequent tissue spread. There is a growing recognition of the association between VZV reactivation and ensuing cerebrovascular accidents (CVA). The virus can spread to cerebral arteries, causing a wide clinical spectrum related to VZV vasculopathy. Herein we present an 80-year-old man with a previously undiagnosed immunosuppressive condition, admitted with disseminated herpes zoster, who subsequently developed an acute ischemic CVA and showed a substantial neurologic recovery under antiviral therapy.

Keywords: varicella zoster virus reactivation, disseminated herpes zoster, cerebrovascular accident, varicella zoster virus vasculopathy

Introduction

Varicella zoster virus (VZV) is a highly neurotropic double-stranded DNA virus. Varicella zoster virus primary infection usually causes varicella and the virus establishes latency in neuronal cells. Its reactivation from nerve ganglia produces different clinical manifestations, including herpes zoster, visceral involvement, or a variety of neurologic complications depending on the site of viral reactivation and its subsequent dissemination [1]. Recently there has been increasing recognition, both clinical and epidemiological, of the relationship between VZV reactivation and subsequent cerebrovascular accidents (CVA), [2]. We present an elderly man with disseminated herpes zoster and altered mental status who was diagnosed with acute ischemic CVA in the context of a previously undiagnosed immunosuppressive condition.

Case Synopsis

An 80-year-old diabetic and hypertensive man, under good control by his primary care physician, presented to the emergency department with the sudden onset of an eroded and exudative plaque on the left lumbar, iliac, and hypogastric regions. There were also hemorrhagic crusts and scattered eroded papules and vesicles scattered over the trunk and limbs (**Figure 1**), consistent with disseminated herpes zoster. Laboratory tests showed an increased white cell count (20.4×10^9/L) and lymphocytosis (57.1%). The remaining laboratory workup did not show additional relevant abnormalities. The patient was initiated on intravenous acyclovir 10mg per kilogram every 8 hours and *peripheral blood immunophenotyping* was requested. On the second day, the patient exhibited an altered mental status with disorientation and acute left-sided weakness and numbness. A head computerized tomography (CT) revealed a right *temporoparietal hypodense* area and a cerebral CT angiography showed an occlusion of the temporal branch of the M2 segment of the right middle cerebral artery (**Figure 2**), confirming the diagnosis of an acute ischemic CVA. At this point,

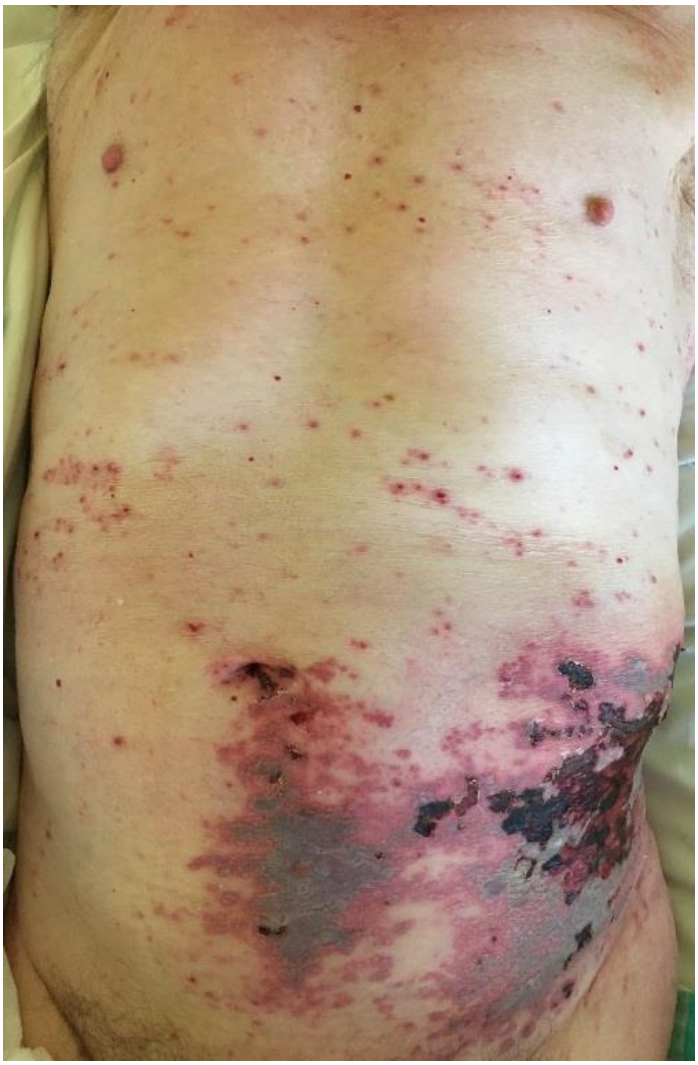

Figure 1. *Eroded and exudative plaque with hemorrhagic crusts in a dermatomal distribution and dispersed eroded papules and vesicles.*

a lumbar puncture was performed, disclosing an increased level of proteins (127.3 mg/dL) and cells (200/mm^3), predominantly mononucleated. Cerebrospinal fluid VZV polymerase chain reaction was positive. Meanwhile, peripheral blood immunophenotyping results became available, identifying an abnormal population of B lymphocytes, consistent with B cell chronic lymphocytic leukemia (CLL). The combination of immunosuppression caused by the CLL allowed VZV reactivation with dissemination and the occurrence of acute ischemic CVA. VZV DNA in the cerebrospinal fluid was consistent with VZV-related vasculopathy. The patient was continued on intravenous acyclovir for a total of 21 days. During the hospital stay there was satisfactory healing of the skin lesions and a significant neurologic recovery, although a residual left hemiparesis remained.

Case Discussion

Disseminated herpes zoster is defined as the involvement of greater than 2 noncontiguous dermatomes or the presence of at least 20 lesions occurring outside the primary affected dermatome [3]. Its relationship with immunosuppression has long been recognized. It occurs more frequently and is a significant cause of morbidity and mortality in the immunocompromised patients, including those with hematological malignancies, who are prone to severe and frequently life-threatening complications. During the hospital admission the patient was diagnosed with CLL, an immunosuppressive condition associated with predisposition to the reactivation of VZV. Occasionally, after reactivation in either immunocompetent or especially, immunocompromised patients, the virus spreads to the spinal cord and brain [4], explaining why these patients are also more prone to neurologic complications. Concomitantly with the reactivation of the VZV causing disseminated herpes zoster, the patient developed an altered mental status and neurological deficits. Head CT imaging was consistent with an acute right temporoparietal CVA, documented by cerebral CT angiography as an occlusion of a branch of the right medial cerebral artery.

Multiple recent epidemiological and clinical studies have revealed an increased risk of CVA after herpes zoster [1,5]. This association is mediated by VZV vasculopathy [6], an inflammatory vasculopathy affecting small and large intracranial cerebral or extracranial arteries, producing inflammation culminating in hemorrhage or ischemia [7]. Varicella zoster virus is the only human virus that has been shown to replicate in arteries [6] and this productive infection leads to the development of a neo-intima composed of smooth muscle cells that may originate from the tunica media, changing the arterial caliber and contractility [8]. The clinical features of VZV vasculopathy have been described as protean [9];

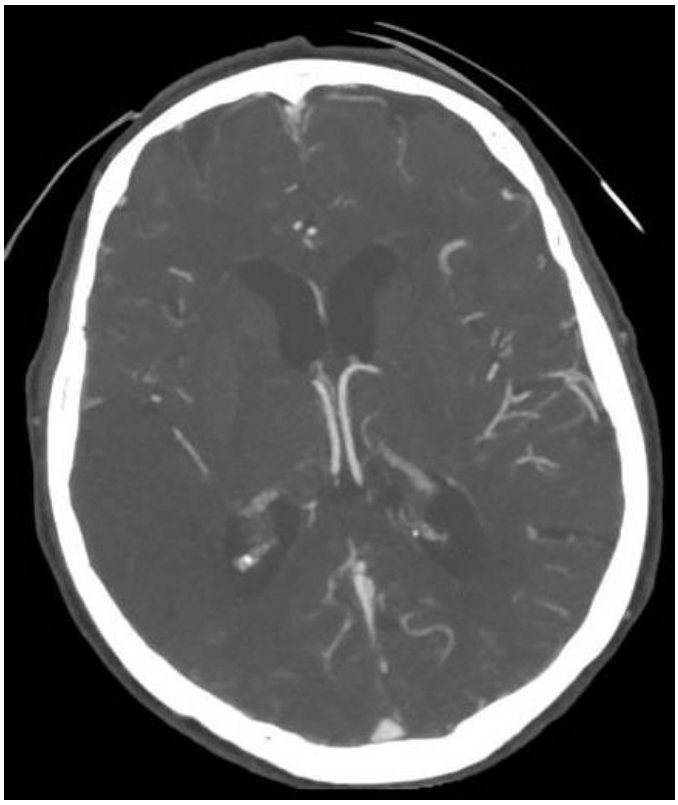

Figure 2. *Cerebral CT angiography showing an occlusion of the temporal branch of the M2 segment of the right middle cerebral artery.*

the condition displays a broad clinical spectrum including ischemic and hemorrhagic insults, transient ischemic attacks, and cerebral and subarachnoid hemorrhage [10]. The clinical diagnosis of VZV vasculopathy is verified by the detection of VZV DNA, anti-VZV IgG or anti-VZV IgM antibody in cerebrospinal fluid, or the presence of anti-VZV IgM antibody in serum [6]. The optimal treatment of VZV vasculopathy is unknown [5]. However, antiviral therapy, should be given as initial therapy to all immunocompromised patients. It has been demonstrated that patients who receive antiviral therapy have a lower incidence of CVA than untreated patients, indicating the value of antiviral treatment in these circumstances [11].

Conclusion

With the current report we intend to promote the recognition that CVA is a possible complication of the reactivation of VZV and emphasize the potential morbidity and mortality that can occur, especially in immunosuppressed patients. The recognition of the coexistence of altered mental status and/or focal neurological deficits and herpes zoster lesions is crucial. Varicella zoster virus vasculopathy should be especially considered in the setting of disseminated herpes zoster, immunosuppressed patients, and involvement of cranial and/or cervical dermatomes. An improvement in the prognosis requires prompt, aggressive treatment with intravenous antivirals to help prevent long-term sequelae and decrease mortality. It is important for dermatologists to be aware of this clinical association.

References

1. Powell D, Patel S, Franco-Paredes C. Varicella-Zoster Virus Vasculopathy: The Growing Association Between Herpes Zoster and Strokes. *Am J Med Sci.* 2015;350(3):243–245. [PMID: 25211583].
2. Kang JH, Ho JD, Chen YH, Lin HC. Increased risk of stroke after a herpes zoster attack: a population-based follow-up study. *Stroke*. 2009;40:3443–3448. [PMID: 19815828].
3. Ellis DL, Barsell A, Riahi RR and Stumpf B. Varicella zoster virus encephalitis in a patient with disseminated herpes zoster: report and review of the literature. *Dermatol Online J.* 2015;21(3). [PMID: 25780972].
4. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicela zoster virus. *N Engl J Med.* 2000;342:635–45. [PMID: 10699164].
5. Shah J, Poonawala H, Keay SK, Serulle Y, Steven A, Gandhi D, Cole JW. Varicella-Zoster Virus Vasculopathy: A Case Report Demonstrating Vasculitis using Black-Blood MRI. *J Neurol Neurophsiol.* 2015;6(6):1000342. [PMID: 27065314].
6. Nagel MA, Gilden D. Developments in varicella zoster virus vasculopathy. *Curr Neurol Neurosci Rep.* 2016;16:12. [PMID: 26750127].
7. Nagel MA, Gilden D. The challenging patient with varicella-zoster virus disease. *Neurol Clin Pract.* 2013;3:109–17. [PMID: 23914320].
8. Nagel MA, Traktinskiy I, Stenmark KR, Frid MG, Choe A, Gilden D. Varicella-zoster virus vasculopathy: immune characteristics of virus-infected arteries. *Neurology.* 2013;80:62–68. [PMID: 23243076].
9. Gilden DH, Mahalingam R, Cohrs RJ, Kleinschmidt-DeMasters BK, Forghani B. The protean manifestations of varicella-zoster virus vasculopathy. *J Neurovirol.* 2002;8(Suppl 2):75–79. [PMID: 12491155].
10. Nagel MA. Varicella zoster virus vasculopathy: Clinical features and pathogenesis. *J Neurovirol.* 2014;20(2):157-163. [PMID: 23918503].
11. Langan SM, Minassian C, Smeeth L, Thomas SL. Risk of stroke following herpes zoster: a self-controlled case-series study. *Clin Infect Dis*. 2014;58:1497–1503. [PMID: 24700656].