

## CASE REPORTS

# MENINGITIS DUE TO VARICELLA-ZOSTER VIRUS REACTIVATION WITHOUT RASH IN AN IMMUNOCOMPETENT ADOLESCENT

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### ABSTRACT

Varicella-zoster virus is a neurotropic virus that after the primary infection, usually manifested as chickenpox, may reactivate with infection of the central nervous system. When no skin lesions are present, a high clinical suspicion is required to reach the diagnosis. We report a case of an adolescent boy with varicella-zoster virus reactivation with meningitis in the absence of a zoster rash.

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Meningitis, Herpes Zoster, Chickenpox, Vaccines, Exanthema.

### Case Report

A 15-year-old boy was admitted to the emergency room with a nine-day history of persistent frontal headache. The headaches responded poorly to analgesia but had no other alarming features. Two days prior to admission, he complained of nausea, vomiting and hypersensitivity to light and loud noises. He had no fever, rash, or additional symptoms.

His past medical history was unremarkable except for an uncomplicated varicella infection at 9 months of age. There were no severe or prolonged infections, nor he presented poor response to antibiotic therapy in the past. He had a harmonic height-weight progression. The family history was also irrelevant.

On a complete clinical background, there was no history of recent infection or immunization. He had not travelled abroad recently, nor had he been in contact with sick people. The patient had been vaccinated according to the Portuguese vaccination calendar and had not received varicella- or zoster-vaccines.

The physical examination at admission had no distinctive findings. He was alert, oriented and had an appropriate speech. There was no nuchal rigidity, gait abnormalities or other neurological findings. There was also no visible rash.

Laboratory tests showed a white blood cell (WBC) count of 5,900/ $\mu$ L (neutrophils: 56.4%, lymphocytes: 33.5%). Serum biochemical parameters of kidney

and liver function were normal, as was the C-reactive-protein level. The patient was observed by an ophthalmologist, who could not exclude the presence of papilledema. A brain CT-scan was carried out and showed no evidence of central nervous system abnormalities. The cerebrospinal fluid (CSF) was clear, with normal opening pressure (18 cmH<sub>2</sub>O), a cell count of 355/ $\mu$ L WBC (with predominance of lymphocytes), increased protein concentration (239 mg/dL) and glucose level of 58 mg/dL (with CSF-to-serum glucose ratio of 0.5). The CSF was sent for gram-stain, culture, and polymerase chain reaction (PCR) for neurotropic viruses and bacteria. An electroencephalogram (EEG) was also performed, with no evidence of slow waves or paroxysmal activity.

The patient was started on intravenous ceftriaxone and admitted to the paediatric infectious diseases and immunodeficiency's unit. A contrast-enhanced brain-MRI was later conducted and revealed abnormal leptomeningeal enhancement consistent with an active inflammatory process. On the second day of hospitalization, CSF PCR-analysis for neurotropic viruses revealed a positive result for VZV-DNA and, therefore, intravenous acyclovir was added to therapy. The CSF-gram stain and -cultures did not demonstrate bacterial growth, hence ceftriaxone was stopped.

After two days of acyclovir, the headache and vomiting resolved completely. The patient never developed fever or rash. He completed six days of intravenous acyclovir followed by eight days of oral valacyclovir. On his follow-up visit, one month after discharge, he remained asymptomatic and in good health condition.

### Discussion

Varicella-zoster virus (VZV) is a neurotropic virus that

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belongs to the *Alphaherpesvirinae* group, and causes infection exclusively in humans.<sup>1,2</sup> VZV primary infection (chickenpox) normally occurs in preschool or school-aged children.<sup>1</sup> After the primary infection, the virus remains latent in cranial nerves, dorsal roots, and autonomic ganglia, and it may reactivate years after the primary infection as zoster.<sup>1,3</sup> Both chickenpox and zoster may have neurologic complications, mainly in immunocompromised or older patients.<sup>1,3,4</sup>

Reactivation is linked to a decline in cell-mediated immunity, and so, associated with immunocompromised or older individuals, being exceedingly rare in paediatric immunocompetent patients.<sup>1,5</sup> Pediatric reactivation cases seem to occur mainly when VZV-infection was acquired in the first year of life.<sup>5</sup> Investigations have suggested that children under one year may have immature or incomplete cellular immunity during the primary infection, failing to maintain virus latency later in life.<sup>5</sup>

The most usual form of reactivation is Herpes-Zoster (HZ) that manifests clinically by a vesicular rash following a dermatome.<sup>1</sup> However, neurologic complications, such as meningitis or encephalitis, are also possible.<sup>1,3</sup> Their frequency is considerably lower, but there is a strong possibility that these diagnosis might have been underestimated for years due to the paucity of microbiological exams with high diagnostic yield for viruses.<sup>1,6</sup> The widespread availability of PCR exams in recent years, might help us understand the increasing numbers of this diagnosis.<sup>6</sup>

Meningitis in children has also been reported in association with live attenuated varicella-zoster vaccine.<sup>7</sup> Two recent case reviews described 14 cases of varicella vaccine meningitis: only three were in immunocompromised patients and all were preceded by herpes zoster; eight cases occurred in children only once-immunized, and six in twice-immunized.<sup>7,8</sup> Even though there is a dramatic reduction of chickenpox in countries with a well-established varicella vaccination program, questions still arise on its role on late reactivations and CNS complications.<sup>7</sup>

The case described above is an example of a VZV-reactivation in a paediatric immunocompetent patient, involving the CNS, after a primary infection at young age (9-months-old). This case has the remarkable feature that VZV-reactivation occurred without skin manifestations, a phenomenon only reported in a few cases in literature.<sup>4</sup> Although VZV is a well-known cause of aseptic meningitis, its clinical presentation is usually linked to a zosteriform rash.<sup>6</sup> Without the usual skin lesions, a high clinical suspicion is required to reach the diagnosis. In these cases, the diagnosis is only possible with the identification of VZV-DNA in the CSF.<sup>1,2,4</sup>

In our case, the CSF results were in conformity with what was previously described in aseptic meningitis, except for significant increased protein levels.<sup>1,3</sup> MRI results supported the presence of an inflammatory leptomenigeal process. Encephalitic involvement was excluded based on a normal pattern in EEG and the absence of more serious neurological manifestations.

A recent review accounts only for 15 described cases of VZV-meningitis or -encephalitis without skin

manifestations in paediatric age.<sup>3</sup> Similarly to our case, these patients' inflammatory markers were within reference ranges and CSF analyses revealed marked lymphocytic pleocytosis and highly elevated CSF protein.<sup>3</sup>

Our patient had a fast and favourable response to the treatment with complete resolution of symptoms and no complications. After 11 days of symptoms, the improvement was noticeable only after starting acyclovir. VZV-meningitis is usually a benign disorder in immunocompetent hosts. However, there is one study in children with CNS VZV-infection reporting neurologic sequelae in almost a quarter of the patients (23%).<sup>3,4</sup> Therefore, the treatment with antiviral agents is still controversial, with the optimal treatment dose and duration still ill-defined.<sup>2,3,6</sup> Nevertheless, evidence seems to demonstrate that for an optimal clinical outcome, the treatment (if used) should be initiated as soon as possible.<sup>6</sup>

This case emphasizes the importance of considering VZV in the differential diagnosis of acute meningitis in the immunocompetent paediatric patient, even in the absence of the characteristic rash. PCR tests that detect nucleic acids from multiple agents are an important tool for diagnosis and their widespread use may reveal a higher incidence of zoster meningitis.

#### Compliance with Ethical Standards

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Conflict of Interest: None

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