

Case Report

VZV fulminant necrotizing encephalitis with concomitant EBV-related lymphoma and CMV ventriculitis: report of an AIDS case

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A case of AIDS with varicella zoster virus fulminant necrotizing encephalitis associated with cytomegalovirus ependymitis-subependymitis and a periventricular Epstein – Barr virus-related lymphoma is described. The patient had no herpes zoster cutaneous eruptions and died three days after the onset of symptoms. Varicella zoster virus and cytomegalovirus antigens were found by immunohistochemistry in the same area around a necrotic periventricular lesion; a periventricular lymphoma, large B cell type, was also observed. *In situ* hybridization with Epstein – Barr virus-encoded- RNAs probe was positive in about 40% of the neoplastic cells. The association of herpes-related lesions in the same cerebral region should be consistent in AIDS cases with acute neurological symptoms.

Keywords: varicella zoster virus; cytomegalovirus; Epstein – Barr virus; human immunodeficiency virus; encephalitis

Introduction

Varicella zoster virus (VZV) encephalitis has been described occasionally in immunocompetent patients, although it is more frequently reported in the elderly and in immunocompromised subjects (Gray *et al*, 1994). In patients with acquired immunodeficiency syndrome (AIDS), VZV infection of the central nervous system (CNS) accounts for up to 2% of all neurological diseases (Petito *et al*, 1986), irrespective of the presence of cutaneous zoster lesions (Ljungman *et al*, 1986; Silliman *et al*, 1993). The clinical course of the disease is not pathognomonic: rapidly neurological deterioration (Chretien *et al*, 1993; Gray *et al*, 1992) or chronic progressive encephalitis (Gilden *et al*, 1988; Gray *et al*, 1992; Manian *et al*, 1995; Silliman *et al*, 1993) have been described. Some authors (Gray *et al*, 1994; Kleinschmidt-DeMasters *et al*, 1996) reported different clinicopathological patterns of VZV lesions in the CNS of AIDS patients: multifocal leukoencepha-

litis, ventriculitis, meningo-myeloradiculitis, focal myelitis and large/small vessel vasculopathy.

Here, a fatal case of fulminant VZV ventriculoencephalitis in an AIDS patient is described, without any herpes zoster cutaneous lesions. In the same cerebral area as that involved by the VZV lesion, ependymitis and subependymitis due to cytomegalovirus (CMV) and a periventricular lymphoma were also found.

Case report

A 35-year-old male intravenous drug user was found to be HIV-1 seropositive in 1989. In March 1992, during hospitalisation because of headache, computed tomography (CT) revealed a brain lesion of the parietal cortex, treated successfully for toxoplasmosis.

From December 1992 until July 1993, the patient was treated with DDI, 400 mg/die.

In January 1994, he was admitted to L. Sacco Hospital, Milan, because of sudden confusion and fever, that had started three days before. Neurological examination revealed disorientation and behavioural disturbances; no cerebrospinal fluid and serological analyses or brain CT were per-

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formed because of the rapid worsening of his general condition. The patient died four hours after admission. He had no history of herpes zoster cutaneous lesions.

The last serological analysis, performed in July 1993, revealed a CD4 count of 51 cells/ μ l.

Methods

Brain samples were taken from the frontal, temporal, parietal and occipital lobes, the basal ganglia and thalamus, the cerebellum, the brain stem, the spinal cord and from all of the areas with macroscopically evident lesions. Autopsy samples were fixed in 10% buffered-formalin and embedded in paraffin.

Immunohistochemistry (IHC) was performed using the following mono- and polyclonal antibodies: anti-VZV (Biosoft, Histo-Line Laboratories, Milan, Italy), anti-CMV (Dako, S.p.A., Milan, Italy), anti-p24 HIV protein (Dako), anti-herpes simplex virus type 1/2 (HSV 1/2, Dako), anti-CD20 B-cell antigen (L26, Dako), and anti-CD45-RO T-cell antigen (UCHL1, Dako). The reactions were detected by means of the indirect double immunoperoxidase method with 3,3'-diaminobenzidine free base as a chromogen.

For *in situ* hybridization (ISH) we used fluorescein-conjugated Epstein-Barr virus (EBV encoded-RNAs, EBER, Dako) PNA probe. This probe is complementary to the two nuclear EBER RNAs encoded by Epstein-Barr virus. The ISH procedure was performed according to the Dako Specification Sheet.

The specificity of the antibodies to VZV, HSV I/II and CMV was tested on paraffin sections from AIDS cases with zoster cutaneous lesions, herpes simplex lesions (esophagous and uterine cervix), primitive cerebral lymphoma (patient with EBV-positive cerebrospinal fluid PCR) and CMV esophagitis proved by culture. No cross reaction was observed.

ISH-EBER specificity was tested using the same controls as those described above. Once again, no cross reaction was observed.

Pathological findings

At macroscopic examination, the brain revealed a large yellowish necrotizing area (5 cm across) with haemorrhagic foci and perilesional oedema, that was located in the right parietal lobe and extended to the right ventricle. The other organs examined had no macroscopical lesions. Light microscopy showed that the necrotic area of the brain contained a large number of cells with Cowdry type A nuclear inclusions in and around the central necrosis. Small and large blood vessels of this area were microscopically normal.

The ependymal lining and the subependymal white matter of the right ventricle contained large cells with nuclear and cytoplasmic inclusions consistent with changes due to CMV infection.

A cerebral non-Hodgkin lymphoma was found in the right periventricular region; the neoplastic elements were surrounded by cells containing Cowdry type A inclusions.

There were no signs of previous toxoplasmic encephalitis nor of any additional neuropathological lesions in the other sections. A small nodule of lymphoma was found in the lower lobe of the right lung, which was cytologically similar to that observed in the brain. Cytomegalic cells were intermingled with the lymphomatous elements. A necrotizing CMV infection of the adrenal glands was also observed.

IHC reaction for VZV antigens showed nuclear and cytoplasmic positivity in both cells with Cowdry type A inclusions, and in small cells, probably of glial origin, without any cytopathic

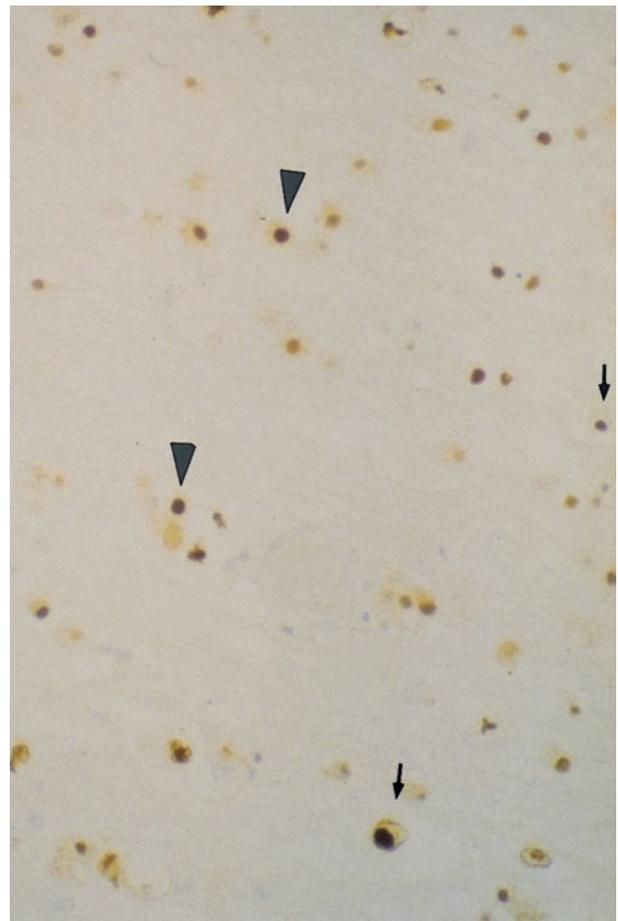


Figure 1 Immunohistochemical positivity to VZV antigens in cells with (arrows) and without (arrowheads) Cowdry type A nuclear inclusions. Immunohistochemistry, mouse anti-VZV monoclonal antibody, haematoxylin counterstain, 200 \times

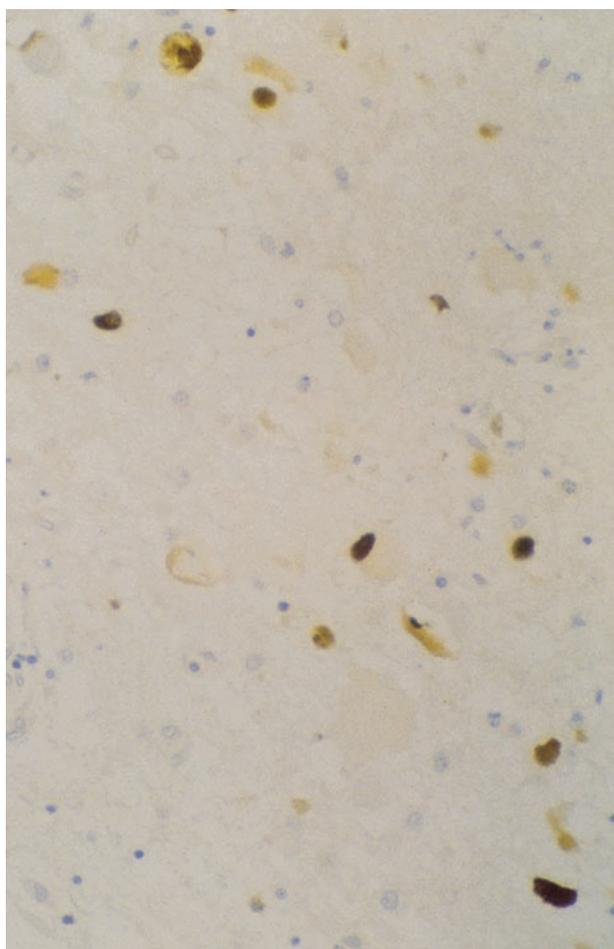


Figure 2 CMV subependymitis: nuclear positivity for CMV antigens in cells with cytopathic changes attributable to the virus. Immunohistochemistry, mouse anti-CMV monoclonal antibody, haematoxylin counterstain, 200 ×

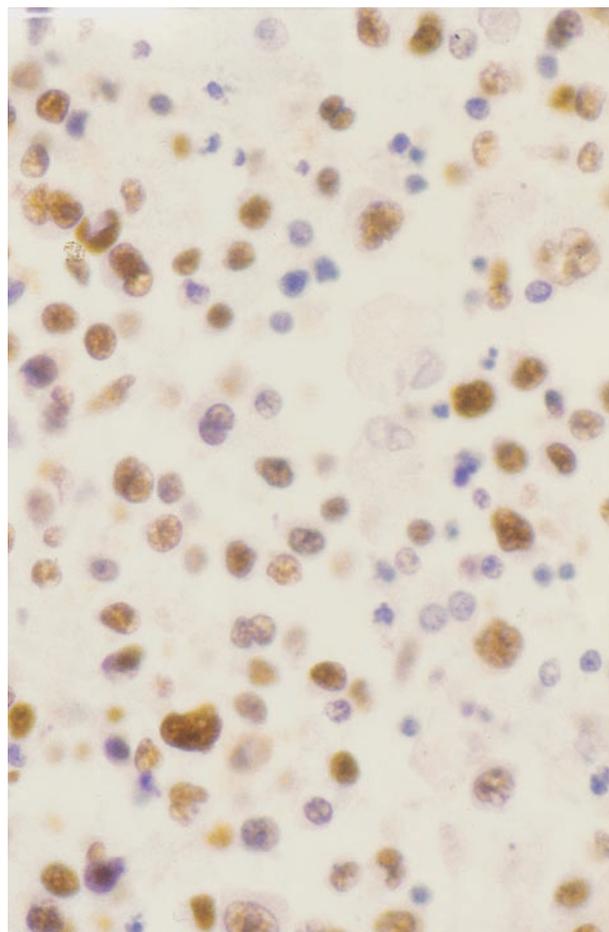


Figure 3 Cerebral lymphoma: nuclear positivity of the neoplastic elements stained by EBER probe. *In situ* hybridization, EBER probe, haematoxylin counterstain, 400 ×

changes (Figure 1). VZV-infected cells were found only within and around the necrotic lesion.

Immunostaining for CMV was positive in the enlarged cells with typical cytological changes attributable to the viral infection (Figure 2). Immunostaining for HSV 1/2 and for HIV antigens was negative. IHC showed that the pulmonary and cerebral foci of the lymphoma were positive for B-cell markers; ISH with EBER probe was positive in about 40% of the neoplastic pulmonary and cerebral lymphoma cells (Figure 3).

Discussion

This report describes the fatal case of an AIDS patient with no herpes zoster cutaneous eruptions but with a clinical history of acute encephalitis and cerebral lesions due to three concomitant direct or related herpetic infections: necrotizing ventriculo-encephalitis due to VZV, endymenitis and sub-

ependymitis due to CMV and periventricular EBV-correlated lymphoma.

VZV infections of the CNS have been not infrequently described in AIDS patients: literature data reported both cases of acute encephalitis (Chretien *et al*, 1993; Gray *et al*, 1992), with an average duration of symptoms of 30 days, and cases with a chronic progression of neurological disease (Gilden *et al*, 1988; Gray *et al*, 1992, 1994; Manian *et al*, 1995; Silliman *et al*, 1993) lasting more than three months. Some authors (Gray *et al*, 1994; Kleinschmidt-DeMasters *et al*, 1996; Schmidbauer *et al*, 1996) have identified different pathological patterns that may be related to the different routes of viral diffusion.

The difficulty of recognising VZV encephalitis appears to be related to the variability of its clinical presentation and the absence of cutaneous eruptions before or during the course of the neurological disease (Gray *et al*, 1992; Kenyon *et al*, 1996; Manian *et al*, 1995; Morgello *et al*, 1988; Silliman *et al*, 1993), as in our case.

In our patient, VZV encephalitis was associated with CMV ependymitis and subependymitis, and periventricular EBV-related lymphoma. The concomitant presence of herpetic-related brain lesions has been previously described but most of the reports regarded HSV type 1 or 2 encephalitis associated with other herpesviruses.

Vital *et al* (1995) has described the presence of HSV type 1 necrotizing encephalitis, CMV ventriculoencephalitis and EBV-positive cerebral lymphoma in one AIDS patient. Chretien *et al* (1996) reviewed the literature cases of HSV encephalitis and observed that most of them were associated with CMV lesions. The authors presented the case of a patient with HSV type 1 encephalitis and concomitant CMV ventriculitis, who also had a possible VZV-related cerebral infarct.

VZV encephalitis has been found to be associated with lymphoma in three patients, two of whom also had concomitant CMV infection (Gray *et al*, 1992; Morgello *et al*, 1988; Petito *et al*, 1986). In the first case (Gray *et al*, 1992), multiple foci of VZV necrotizing encephalitis involved vast areas of the brain and a lymphoma was observed in the left cerebral hemisphere; in the second (Morgello *et al*, 1988), VZV encephalitis was localized to the

cerebral cortex and putamen, whereas a perivascular lymphoma was observed in the cerebral and cerebellar hemispheres and the CMV infection presented as radiculomyelitis; in the third (Petito *et al*, 1986), the VZV and CMV infection respectively presented as bulbar and micronodular encephalitis in the cortex and basal nuclei, and a lymphoma was observed in the parieto-occipital region.

Gray *et al* (1994) observed also one case of VZV focal myelitis in an AIDS patient with CMV encephalitis. However, in none of these cases the authors demonstrated the presence of EBV in the lymphomatous cells by IHC or ISH and, finally, the multiple cerebral lesions appeared to be located in different areas of the CNS. In our case, VZV, CMV and EBV-related lesions were found in the same cerebral region, suggesting that the acute neurological symptoms could be caused by their association.

Conclusion

The possibility of multiple focal lesions due to concomitant direct or related herpetic infections should be considered in AIDS patients with neurological symptoms.

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