

Pontocerebellar Progressive Multifocal Leukoencephalopathy. Radiological, Clinical, Histological and Immunohistochemical Findings in a Hematological Patient

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Abstract

Objective: To describe the radiological, histological and immunohistochemical findings in a case of Progressive Multifocal Leukoencephalopathy (PML) affecting the cerebellar peduncles in a patient with chronic lymphocytic leukemia. **Patient and Methods:** Magnetic Resonance Imaging (MRI), histological picture (H.E., Kluver-Barrera) and immunohistochemical picture (GFAP, neurofilaments, CD68, JC virus) were obtained. **Results:** 1) Magnetic resonance imaging: Asymmetric and progressive lesions on middle cerebellar peduncles, that were hyperintense in T2/FLAIR, extended towards the pons, had no mass effect and were unmodified after intravenous contrast. 2) Histology: Marked reactive gliosis with cytopathic changes suggesting viral infection, plus demyelination areas with axonal preservation. 3) Immunohistochemistry: Marked positivity for viral (polyoma and JC virus) markers in glial cells showing cytopathic changes. **Conclusions:** The importance of histological and immunohistochemical diagnosis in everyday assistance; of the collaboration between clinicians, radiologists and pathologists; and the validity of post-mortem studies as a key element for research and clinical quality assessment must be stressed.

Keywords

Progressive Multifocal Leukoencephalopathy, JC Virus, Immunohistochemistry

1. Introduction

The unstoppable and impressive advances in antineoplastic and immunomodulatory therapies entail contradictory consequences. On the one side, the spectacular improvements in survival and quality of life for cancer patients. On the other side, the appearance of new, often severe, adverse events impairs their performance. One of such adverse effects is the opportunistic infections linked to immunosuppression. This kind of infections often poses a diagnostic and therapeutic challenge to the physicians caring immunodeficient patients.

To illustrate these problems, we present a case report of an opportunistic viral infection typically related to immunosuppression.

2. Case Report

An 85-year-old woman diagnosed of chronic lymphocytic leukemia developed progressive limb ataxia, drowsiness, dysarthria and dysphagia while in combination treatment with ibrutinib, rituximab and venetoclax. Cerebrospinal fluid analysis was unremarkable. Magnetic resonance imaging showed rapidly growing asymmetric lesions on both middle cerebellar peduncles. These lesions were hyperintense in T2/FLAIR, markedly hypointense in T1 and showed peripheral hyperintensity in diffusion-weighted imaging (**Figure 1**).

The patient clinical status deteriorated rapidly, and she died in coma.

Necropsy revealed a slight encephalic atrophy with moderate to severe cerebral atheromatosis. Middle cerebellar peduncles were swollen. An exhaustive sampling was obtained for microscopy.

Histologic study revealed the presence of pallid areas where a marked reactive gliosis, rich in histiocytary elements, was observed (**Figure 2**). In these areas Kluver-Barrera staining revealed an intense myelin loss with axonal preservation (**Figure 3**). Abnormal glial cells with cytopathic alterations were strongly positive for immunohistochemical JC virus markers (**Figure 4**).

Based in these findings, the definitive final diagnosis was Progressive Multifocal Leukoencephalopathy.

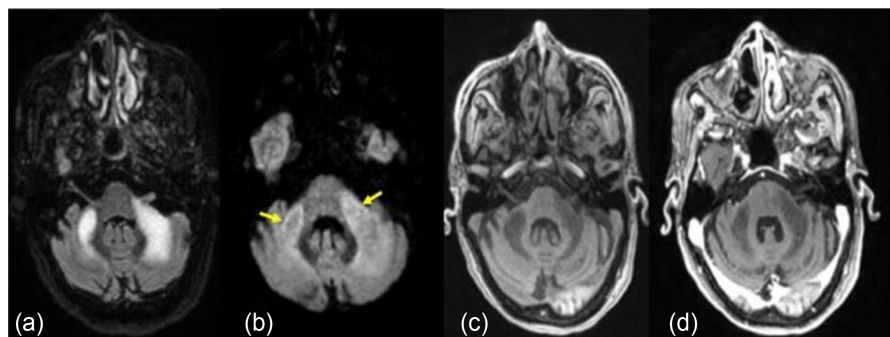


Figure 1. PML (MRI). (a) Asymmetric hyperintense lesions on both middle cerebellar peduncles (T2/Flair). (b) Hyperintensity (arrows) on the periphery of lesions (diffusion-weighted imaging). (c) Hypointense lesions (T1 without contrast). (d) Absence of enhancement or compressive signs after iv contrast (T1 with contrast).

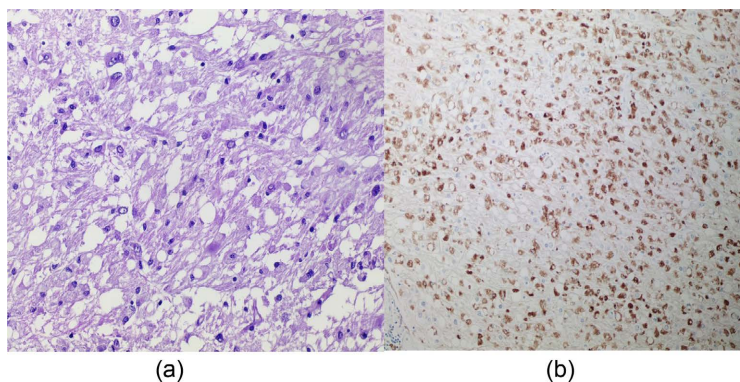


Figure 2. PML. (a) Reactive gliosis areas with tumid appearance (H.E. 200×). (b) Reactive gliosis areas rich in histiocytes (CD68 immunohistochemistry 100×).

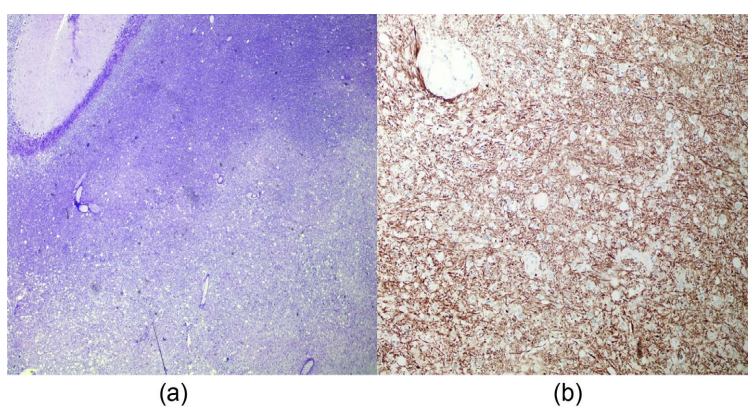


Figure 3. PML. (a) Conspicuous pallor in demyelination areas (Kluver-Barrera 20×). (b) Axonal integrity in demyelination areas (Neurofilament immunohistochemistry 100×).

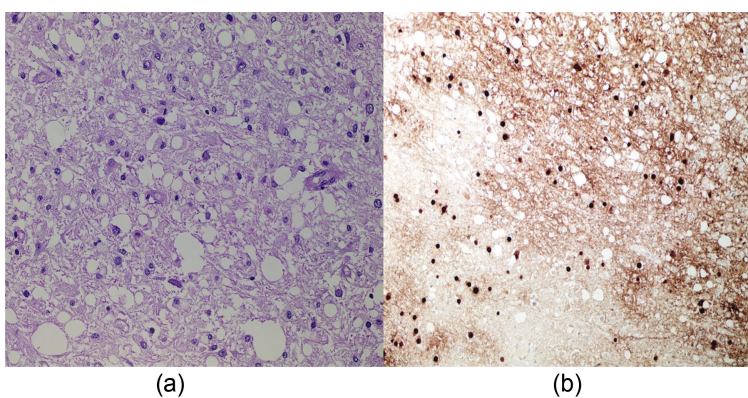


Figure 4. PML. (a) Reactive gliosis area with cytopathic changes suggestive of viral infection (H.E. 400×). (b) Intense positivity for JC virus in cytopathic glial cells (JC virus immunohistochemistry Virus 100×).

3. Discussion

Polyomaviridae are a family of viruses with unenveloped icosahedral shaped capsid and a double-stranded DNA genome [1].

These mostly nonpathogenic viruses have been isolated and identified in many different tissues from immunocompetent people [2] [3] [4].

However, in immunodeficient patients some polyoma viruses turn to be pathogenic giving rise to severe infectious or neoplastic disorders. BK virus, for example, is related to tubulointerstitial nephropathy and hemorrhagic cystitis in renal or bone marrow transplant recipients [5] [6], MC virus, on the other hand, is related to Merkel cell neuroendocrine carcinoma.

As for JC virus, it causes multifocal progressive leukoencephalopathy, as illustrated by our case [7] [8]. Nominated with the initials of the patient from which it was isolated, it was described in 1971 [9]. In the same way that other polyoma viruses, it was soon realized that a high percentage of healthy people harbored it with no apparent harm. Most of them acquire the infection through respiratory transmission before adolescence [10]. Being an opportunistic pathogen, it affects immunodepressed patients. Although initially most cases attained hematological patients, nowadays the most common underlying disease is AIDS [11]. JC virus provokes two types of neurological disorders:

- Granule cell neuronopathy, a rare disorder caused by JC viral variants with tropism towards cerebellar granule cells, giving rise to a marked cerebellar atrophy [12].
- PML, in which viral tropism is towards oligodendrocytes [13]. As indicated by its name, lesions are progressive, multifocal, and restricted to white matter. In the setting of demyelination, cytopathic changes in glial cells suggest viral etiology, an etiological suspicion that can be confirmed by immunohistochemical techniques [14] [15].

Noteworthy in our case is that damage was limited to the pontocerebellar area, sparing the typical localization of PML lesions in subcortical areas (more than 90% of cases), mostly in frontoparietal white matter [16]. When PML involves posterior fossa structures, usually subcortical affectation is also present [17], so that isolated infratentorial localization is very infrequent [18]. However, the MR image in our case fits to those reported by other authors [19].

Another point of interest in our case is the negativity of JC viral DNA PCR in cerebrospinal fluid. False negative results have been described in the setting of immune reconstitution inflammatory syndrome in AIDS patients with PML initiating antiretroviral treatment. It has been recently stressed that PCR negativity does not exclude a diagnosis of PML in biopsy proven cases [20] [21].

As to the histological and immunohistochemical picture, it provides definitive differential diagnostic clues. Astrocytomas are excluded because of the presence of reactive glial cells with cytopathic changes and of numerous histiocytes. Subacute cerebellar degeneration, a paraneoplastic disorder, is discarded by the integrity of Purkinje neurons [22]. The absence of Negri bodies excludes rabies [23]. The clinical picture rules out other demyelination disorders such as multiple sclerosis, Alexander disease (a rare autosomal dominant leukodystrophy with prominent Rosenthal fibers) [24] or spongiform encephalopathies which

show neuropil spongiform degeneration and prionic plaques [25].

4. Conclusions

To conclude, we wish to stress three facts:

- The importance of histological and immunohistochemical diagnosis in everyday assistance.
- The importance of the collaboration between clinicians, radiologists, and pathologists for an adequate care.
- The importance and validity of postmortem studies as a key element for research and clinical quality assessment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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