Progressive multifocal leukoencephalopathy in a patient with alcoholic cirrhosis

**Leucoencéphalopathie multifocale progressive chez un patient ayant une cirrhose alcoolique**

Progressive multifocal leukoencephalopathy is a severe demyelinating disease of the central nervous system caused by JC virus, a DNA virus from the polyomavirus family, resulting in demyelination and significant neurological disorders. It occurs in immunodeficient patients affected by any process, which decreases cellular immunity. The diagnosis can be made with cranial magnetic resonance imaging (MRI) and by detection of JC viral DNA in cerebrospinal fluid with polymerase chain reaction (PCR). The prognosis is usually poor. We report the first published case of progressive multifocal leukoencephalopathy in a patient with cirrhosis.

**Case report**

A 51-year-old man was admitted to our unit in October 2008 because of progressive right-sided weakness, dysarthria and gait instability. This patient had been followed for alcoholic cirrhosis for 8 years. His medical history included three hospitalizations for tense ascites in the past year. The most recent episode in September 2008 was triggered by spontaneous bacterial peritonitis. He was not on waiting list for liver transplantation at admission because he was still actively consuming alcohol. Corticosteroids were not administered in the absence of proven severe acute alcoholic hepatitis. The patient had never been diagnosed with hepatic encephalopathy. He belonged to Child C class.

The patient’s current medications associated norfloxacin and spironolactone. Alcohol had been discontinued since the last hospitalization 5 weeks before. There was no illegal drug use and the patient had not travelled recently. Clinical examination showed dysarthria related to a central right-sided facial droop and right hemiparesia.

Cranial computed tomography (CT)-scan was performed and showed a hypointense lesion in the left subcortical frontal white matter, extending from the left centrum semioual to the left external capsula. No mass effect was observed. Cranial MRI confirmed the presence of a single lesion, which was hypointense on diffusion-weighted images, hyperintense on T2-weighted images and hypointense on T1-weighted images, with no contrast enhancement after gadolinium administration (Fig. 1). This lesion was strictly limited to the white matter suggesting an old cerebral infarct, a brain tumor or a demyelinating disease.

Blood test results were as follows: haemoglobin 10 g/dL, platelet count 45 000/mm³, and lymphocyte count 456/mm³. Child-Pugh score was C13 with a prothrombin index at 37%, serum albumin at 26 g/L and serum bilirubin at 133 μmol/L. There was no renal failure or inflammation. Liver tests included: gamma glutamyltransferase 71 IU/L (N < 60), aspartate aminotransferase 90 IU/L (N < 24), alanine aminotransferase 42 IU/L (N < 45), alkaline phosphatases 146 IU/L (N < 240).

In the next few weeks, the patient’s deficit fluctuated considerably. Several electroencephalograms were performed during that period but did not confirm either seizure or metabolic encephalopathy. One week later, the right side motor deficit and aphasia worsened. A second cranial MRI study showed that the left frontal lesion had the same magnetic properties but had grown extending through the splenium of the corpus callosum to the right side parietal white matter (Fig. 2). Spectrometry showed an increase in choline to creatinine ratio, a decrease in the N-acetyl-aspartate peak and a lactate doublet. Perfusion sequences suggested an increase in neangiogenesis. Lumbar puncture yielded clear, colorless cerebrospinal fluid with a normal cell count. The glucose level was normal and total protein levels were 0.56 g/L (N: 0.18–0.53). PCR analysis showed the JC virus in the cerebrospinal fluid. Blood sample analysis confirmed lymphopenia with only 132 CD4+ (N: 330–1200) and 100 CD8+ (N: 230–900) lymphocytes. Antibodies against HIV, hepatitis B virus and hepatitis C virus were all negative. Chest and abdominal CT-scan did not show any tumors or abnormal lymph nodes excluding any underlying solid tumour or lymphoma. Based on these results progressive multifocal leucoencephalopathy was diagnosed linked to immunosuppression secondary to alcoholic cirrhosis. The patient died 70 days later.

**Discussion**

Progressive multifocal leucoencephalopathy is a severe demyelinating disease of the central nervous system caused by reactivation of the polyomavirus JC, which affects immunosuppressed individuals. Asymptomatic seroconver-
sion to the JC virus usually occurs in childhood. Eighty to 90 percent of healthy adults are seropositive for JCV [1]. The virus usually remains silent in the kidney cells or the lymph organs. When the cellular immune response is deficient, it can be reactivated, spreading to the central nervous system by a hematogenous route and inducing lytic infection of oligodendrocytes [2]. This disease was quite uncommon before 1984. In the early 1980s, the epidemiology of progressive multifocal leukoencephalopathy changed as AIDS became a major source of cellular immunosuppression.

Eighty percent of progressive multifocal leukoencephalopathy patients have AIDS. In a series of 58 progressive multifocal leukoencephalopathy HIV negative cases, 55% had hematological malignancies, 15% had chronic inflammatory diseases, 9% had sarcoidosis, 7% were transplant recipients, 7% had other conditions and 7% had no detectable predisposing illness [3]. In HIV negative patients, the prognosis is currently less than 4 months but several cases of prolonged survival have been reported. Until now, several cases of progressive multifocal leukoencephalopathy were reported after solid organ transplantation including five after liver transplantation [4] but to our knowledge, this is the first case of confirmed progressive multifocal leukoencephalopathy with no other cause of immunosuppression than cirrhosis.

Although progressive multifocal leukoencephalopathy is probably rare in cirrhosis it might be underestimated. Non-invasive PCR could be useful in patients with cirrhosis and neurological deficits for the diagnosis of progressive multifocal leukoencephalopathy and to exclude other neurological disorders. The incidence of progressive multifocal leukoencephalopathy in patients with cirrhosis needs to be assessed. In the present case, the main causes of immunosuppression were excluded: HIV, immunosuppressive agents, solid tumours, chronic inflammatory diseases and haematological malignancies. Cirrhosis is a leading cause of immunosuppression and infections are common in these patients.
Lymphopenia is associated with hypersplenism observed in cirrhotic patients. The increased susceptibility to infection in cirrhotic patients is associated with impaired monocyte function, a bactericidal and opsonic activity deficit, depressed phagocytic activity in the reticuloendothelial system, defective chemotaxis and cytokine dysfunction. Furthermore, alcohol even without cirrhosis reduces the functional marrow granulocyte reserve, suggesting that there is a depressed granulopoietic activity.

The presentation of progressive multifocal leukoencephalopathy is usually multifocal with sub-acute neurologic deficits including weakness (hemiparesis or monoparesis), confusion, appendricular or gait ataxia, and visual symptoms (hemianopsia or diplopia). However clinical manifestations vary depending on the distribution of the demyelinating lesions. Another peculiarity of this case is the monofocal presentation. Cases with a single lesion could be mistaken for a stroke or a tumour. Repeating cranial MRI and performing spectroscopy can help exclude these other diagnoses. The characteristics of MRI results in our patient’s lesion are quite typical, although progressive multifocal leukoencephalopathy lesions are usually multiple and asymmetric. Progressive multifocal leukoencephalopathy lesions are hypointense on T1 sequences and hyperintense on T2 sequences. There is no mass effect and no contrast enhancement. The demyelinating process affects the subcortical white matter and U fibers. In the past, the gold standard for the diagnosis of progressive multifocal leukoencephalopathy was brain biopsy. Due to the risk of fatal complications (2.9%) and morbidity (8.4%) with the procedure, detection of JC virus DNA in the cerebrospinal fluid by PCR has now replaced brain biopsy for the diagnosis of progressive multifocal leukoencephalopathy. PCR analysis has a sensitivity of 72 to 93% and specificity of 92 to 100% for the diagnosis of progressive multifocal leukoencephalopathy [5].

Although several drugs have been tested for progressive multifocal leukoencephalopathy there is no approved treatment for this disease. The cytosine arabinoside (cytarabine: two doses at 5 mg/kg) may be effective in decreasing JC virus replication in vitro and resulted in stabilization of seven out of 19 HIV negative patients with progressive multifocal leukoencephalopathy [6]. Nevertheless, whenever possible cell immunity should be restored. Thus, highly active antiretroviral therapy improved survival in HIV patients with progressive multifocal leukoencephalopathy. Therapy should be stopped or reduced in patients being treated by immunosuppressive therapy. Cytosine arabinoside was not administered to our patient with severe pancytopenia since this drug is toxic to bone marrow.

In conclusion, the diagnosis of progressive multifocal leukoencephalopathy should be considered in patients with cirrhosis who experience sub-acute, focal neurologic deficits and with MRI results showing demyelinating lesions. Funding: There are no financial disclosure.

Conflict of interest statement

No conflict of interest.

References


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Available online 23 May 2010

Positive PET-CT scan in hepatocellular adenoma with concomitant benign liver tumors

Fixation d’un adénome hépatocellulaire au TEP-scanner associée à d’autres tumeurs bénignes du foie

Introduction

Positive positron emission tomography (PET)-computed tomography (CT) in the diagnosis of hepatocellular adenoma without neoplastic transformation has never been described. Moreover, there is only one report of the association of hemangioma, focal nodular hyperplasia and hepatocellular adenoma in the literature [1].

We present a new case of three hemangiomas concomitant with two hepatocellular adenomas and focal nodular