



CASE REPORT

## Progressive multifocal leukoencephalopathy mimicking cerebral vasculitis in systemic granulomatosis

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### KEYWORDS

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**Summary** We describe the case of a 69-year-old man with systemic granulomatosis who presented with left-sided hemiplegia. Initial diagnosis concerning the neurological troubles was cerebral vasculitis. Corticosteroids associated with antituberculosis therapy showed a rapid but transient amelioration followed by neurological aggravation. Two weeks later, JC virus was detected in cerebrospinal fluid by PCR and the diagnosis of progressive multifocal leukoencephalopathy (PML) was made. Treatment with cytarabine and cidofovir was initiated but the patient died three months after the first neurological signs. In the presence of central neurological symptoms occurring during systemic granulomatosis before specific therapy, PML should be evoked.

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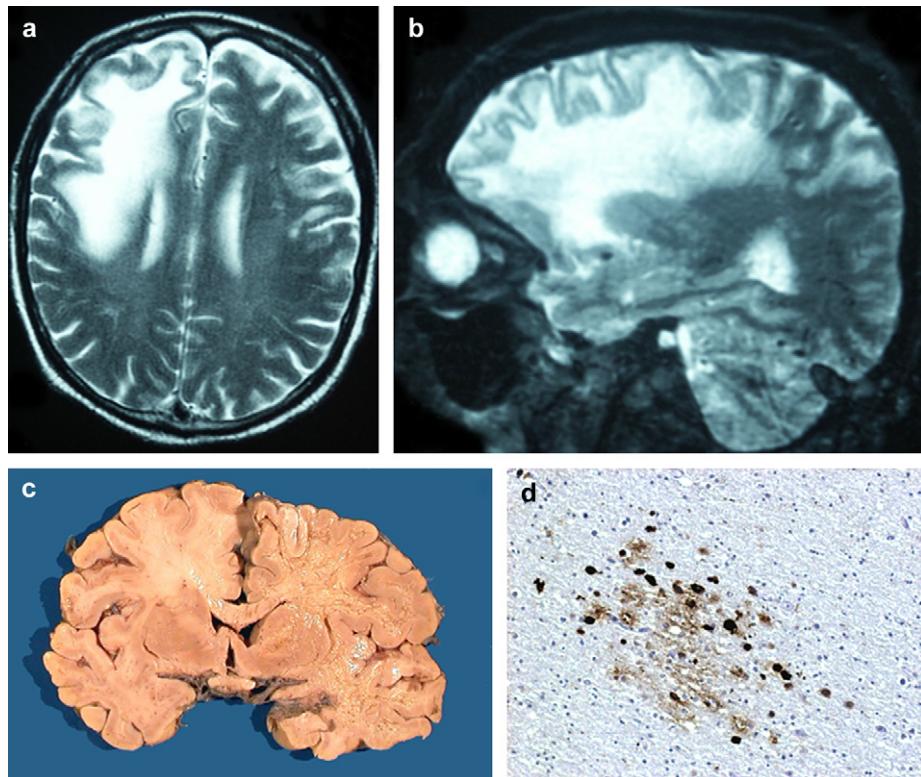
## Introduction

Progressive multifocal leukoencephalopathy (PML) is a progressive demyelinating disorder of the brain's white matter caused by JC virus (JCV), a member of the *Papovavirus* family.<sup>1</sup> PML usually occurs as a late complication of diseases associated with impaired immunity like acquired immunodeficiency syndrome (AIDS) and lymphoproliferative disorders such as Hodgkin's disease and chronic lymphocytic leukaemia.<sup>2</sup> PML is also described in patients with connective tissue disorders, mainly systemic lupus erythematosus, receiving immunosuppressive therapy.<sup>3</sup> We describe a case of PML occurring three months after the diagnosis of systemic granulomatosis, and initially diagnosed as cerebral vasculitis.

## Case report

A 69-year-old man was referred to our hospital for the recent onset of mental deterioration and left-sided hemiplegia. Three months previously, systemic granulomatosis revealed by the deterioration of the general health status and pancytopenia was diagnosed by the demonstration of non-necrotizing granulomas in multiple organ biopsies (gastric, bone marrow, liver and minor gland salivary). Sarcoidosis, tuberculosis and other known causes of granulomatosis were ruled out after an exhaustive biological and histological

assessment. At admission, physical examination showed normal consciousness and left-sided hemiplegia with left facial paralysis. Blood tests showed pancytopenia, hepatic cholestasis and cytosis. The CD4 cell count was low (34/mm<sup>3</sup>) with severe T lymphopenia. Immune responses evaluated before therapy, by lymphoproliferation assays, showed normal responses to mitogens and no reactivity against microbial antigens. HIV serology and plasma HIV viral load were negative. CT-scan of the brain revealed a hypodense lesion of the right frontotemporal lobe, without edema, mass effect or contrast enhancement. These findings were confirmed by cerebral-MRI (Fig. 1a). The brain angio-MRI was normal. First results of the cerebrospinal fluid (CSF) analysis – including bacteriological, virological (detection of cytomegalovirus, varicella-zoster virus, herpes simplex virus 1 and 2 by PCR), parasitological, mycological analysis, cytology, angiotensin-converting enzyme level, protein electrophoresis, detection of *Mycobacterium tuberculosis* and *Tropheryma whipplei* by PCR – were normal. Corticosteroids and antituberculosis therapy were initiated for a suspicion of cerebral vasculitis. There was a transient improvement followed by neurological deterioration. Two weeks later, JCV was detected in CSF by PCR. PCR amplification was performed using specific primers which amplified a 171-bp region in JCV large T-Ag. The sequences for sense and antisense primers were 5'-GTG CCA ACC TAT GGA ACA GA-3' and 5'-AGT CTT TAG GGT CTT CTA CC-3', respectively. The amplified sequences were identified by hybridization



**Figure 1** (a) Initial cerebral-MRI: T2-weighted sequences hypersignal and non-enhancing T1-weighted sequences hyposignal of right frontotemporal lobe, without edema or mass effect. (b) Cerebral-MRI after clinical deterioration: extension of the right frontotemporal lesion towards right parietal lobe and callosus body. (c) Autopsy, macroscopic examination of the brain: extensible lesions of the white matter of the right hemispher. (d) Autopsy, microscopic examination: lesions of PML, immunohistochemical analysis with marking anti-papovavirus of the cores of oligodendrocytes within the lesion and in periphery.

with a specific probe: 5'- TGATGAAAACACAGGATCCC-3'. The threshold value of the technique was 1 copy/reaction. Treatment with cytarabine, given intravenously and intrathecally, and cidofovir was initiated. Corticosteroids were tapered down. Motor deficiency rapidly extended together with vigilance disorders. A new MRI showed a bilateral extension of the lesions (Fig. 1b). The patient died three months after the appearance of neurological signs. An autopsy was performed. The macroscopic and microscopic examinations were consistent with the diagnosis of PML (Fig. 1c,d). Post-mortem examination of all the organs did not show features of granulomas after three months of anti-tuberculosis and corticosteroids therapy.

## Discussion

In patients with connective tissue disorders, PML is mainly described in those receiving immunosuppressive therapy for systemic lupus erythematosus,<sup>3</sup> rheumatoid arthritis,<sup>4</sup> Wegener's granulomatosis<sup>5</sup> or inflammatory myositis.<sup>6</sup> There are less reports on PML associated with systemic granulomatosis, mainly sarcoidosis, also treated with steroids or immunosuppressant agents.<sup>7</sup> According to this case report, PML should also be considered in such patients with neurological signs even if they do not receive immunosuppressive treatment.

In our patient, the diagnosis of systemic granulomatosis relied on the presence of non-necrotizing granulomas in multiple organ biopsies. The differential diagnosis between sarcoidosis, tuberculosis and other known causes of granulomatosis is a difficult challenge but no results oriented towards any cause of granulomatosis. Pancytopenia was probably related to granulomatosis, regarding the presence of granulomas on bone marrow biopsy. T cell lymphopenia could be due either to granulomatosis or to an idiopathic CD4+ T lymphopenia supporting the development of granulomatosis.

Central nervous system (CNS) involvement is a common and severe specific complication of connective tissue diseases, for which immunosuppressant agents are initially recommended. However, as illustrated in our case, neurological infection such as PML may be related to immunodeficiency other than that induced by immunosuppressive therapy or AIDS.

Distinguish PML from CNS involvement of connective tissue diseases according to clinical, biological including CSF analysis and radiological data is often difficult. Moreover, corticosteroids may induce a transient improvement.<sup>8</sup> However, this does not rule out the infectious hypothesis. On cerebral-MRI, PML typically appears as bilateral and asymmetric confluent subcortical white matter lesions, in the periventricular area close to the white–grey matter

junction. From a radiological point of view, the differential diagnoses include acute disseminated encephalomyelitis, all cerebrovascular events including vasculitis, and brain tumor. In our case, the detection of JCV in CSF together with the results of the macroscopic and microscopic examinations of the brain confirmed the diagnosis of PML. The absence of contrast enhancement and vascular lesions on brain angio-MRI argue against the association of PML with cerebral granulomatosis or vasculitis as the cause of the neurological symptoms. In addition, the post-mortem brain examination did not reveal any granulomas or signs of vasculitis that could cause the neurological deterioration.

No efficient treatment of PML except restoration of immunity has been found yet. However, cytarabine, cidofovir and interferon-alpha have been used with an inconstant efficiency.<sup>9</sup> The clinical course is most often marked by progressive and fatal deterioration.

In conclusion, practitioners must be aware that CNS involvement occurring during systemic granulomatosis but before the initiation of specific therapy may be related to PML. Early diagnosis of PML is the key point. Even if its treatment is rarely efficient, clinical improvement may be hoped in case of rapid initiation of specific therapy or interruption of immunosuppressant agents.

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