Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease that occurs in the setting of severe immunosuppression and results from lytic infection of the glia by the JC polyomavirus (JCV). In rare cases, mutations in JCV can trigger a change in tropism, leading to involvement of other cell types.

**Report of a Case**

An older man presented with an 8-month history of progressive cerebellar ataxia. Eleven years before presentation, the patient was diagnosed as having non-Hodgkin lymphoma and treated with 6 cycles of the CHOP (cyclophosphamide, doxorubicin hydrochloride [hydroxydaunorubicin], vincristine sulfate [Oncovin], and prednisone) regimen, with a good response. He started maintenance therapy consisting of rituximab with infusions initially every 6 months. Five years before presentation, the frequency of rituximab infusions was increased to every month because of persistently lymphadenopathy.

Eight months before presentation, the patient noted the gradual onset of gait instability. Magnetic resonance imaging of the brain demonstrated early vermician atrophy in the cerebellum but no significant white matter changes (Figure, A–C). A lumbar puncture 2 months after symptom onset showed a white blood cell count of 12/mm³ with 44% lymphocytes and 56% monocytes, an elevated protein level at 102 mg/dL, and a glucose level within the reference range at 68 mg/dL, without malignant cells on cytopathologic analysis.

Four months before presentation, he gradually developed slurred, slowed speech without word-finding difficulties. His gait worsened, requiring use of a walker. His hand coordination worsened to the point that he could no longer write legibly. He occasionally would choke and cough when drinking.

At presentation, the neurological examination demonstrated normal cognition and moderate ataxic dysarthria. The patient displayed saccadic ocular pursuits, square wave jerks, and rebound and gaze-evoked nystagmus. He had marked titubation when sitting upright and appendicular dysmetria, worse on the right side, with dysdiadochokinesia. He had a wide-based gait with short strides and could not ambulate without assistance. He had visual field defects in the inferior hemifield of the right eye and lateral hemifield of the left eye, and results of an ophthalmologic evaluation revealed retinal degeneration. Results of motor and sensory examinations and deep tendon reflexes were otherwise normal.

Results of an extensive laboratory workup (including erythrocyte sedimentation rate; levels of ceruloplasmin, α-fetoprotein, thyrotropin, vitamins E and B₁₂, fluorescent treponemal antibody, rheumatoid factor, anti-double-stranded DNA, antinuclear antibody, antineutrophil cytoplasmic antibody, Sjögren syndrome A antibody, ribonuclear protein antibody, Smith/ribonuclear protein antibody, glutamic acid decarboxylase antibody [65 kDa], antithyroglobulin antibody, antigliadin, transglutaminase, and endomyal; antibody; heavy metal screening; serum protein electrophoresis; and paraneoplastic antibody panel) were within the reference range. Analysis of cerebrospinal fluid (CSF) showed a white blood cell count...
of 3/mm³, red blood cell count of 1/mm³, protein level of 81 mg/dL, and glucose level of 67 mg/dL. Results of screening for oligoclonal bands, fungal and acid-fast bacterial cultures, and polymerase chain reaction (PCR) for herpes simplex virus, Epstein-Barr virus, and cytomegalovirus were negative. However, the CSF PCR findings were positive for JCV at 109000 copies/mL, consistent with active infection. After consultation with the patient’s oncologist, rituximab infusions were stopped.

During the ensuing 4 months, the patient continued to decline. His swallowing difficulties and visual field deficits worsened, and he became nonambulatory. He developed progressive weight loss and fatigue.

He was readmitted 1 year after symptom onset because of several episodes of nonresponsiveness suggestive of seizure. Results of an electroencephalogram and cardiovascular workup were unremarkable. He started empirical therapy with levetiracetam, and these episodes resolved. A second magnetic resonance image of the brain showed progressive cerebellar volumelosst with T2-weighted hyperintensity in the dorsomidbrain, pons, and cerebellar peduncles (Figure, D-F). A second lumbar puncture showed a white blood cell count of 1/mm³, red blood cell count of 0/mm³, protein level of 86 mg/dL, and glucose level of 56 mg/dL. Subsequent CSF PCR for JCV demonstrated 18000 copies/mL. This patient died 17 months after the onset of neurological symptoms. A postmortem examination was not performed.

The JCV from the CSF sample obtained at presentation demonstrated a new granule cell neuronopathy (GCN)-type JCV strain with a 12-base pair in-frame deletion located in the C-terminal of the VP1 gene (RefSeq NC_001699) (2496-2507 in the Mad1 DNA sequence), which we named JCVGCN5. This deletion is different from deletions previously described in other cases of JCV GCN but is localized in the same area of the VP1 gene. Using a redesigned PCR method with coamplification at a lower denaturation temperature,2,3 we identified JCV GCN5 in 5% of clones, with wild-type JCV as the predominant species, consistent with a pleiotropic infection.

Discussion

Human JCV is well known for causing PML, a demyelinating disease that occurs in the setting of severe immunosuppression. Progressive multifocal leukoencephalopathy results from lytic infection of glia by JCV, which typically triggers a leukoencephalopathy predominantly in the posterior supratentorial white matter. In rare cases, mutations in JCV can trigger a change in tropism, leading to involvement of other cell types. This patient had a novel deletion in the same area of the VP1 gene as other cases of JCV GCN identified to date.1 This area is responsible for linking the 72 pentamers of the VP1 protein that form the viral capsid and is not directly exposed to the virion surface.4 Therefore, these mutations are not likely to cause a direct change in receptor binding but rather cause events after entry that may favor replication and assembly in granule cell neurons.1

The JCV GCN entity has been previously reported in immunocompromised hosts in whom the mutated virus is the predominant species.2-6 In the case we describe, the clinical presentation and presence of wild-type JCV and JCV GCN in the CSF is suggestive of JCV GCN with evolution into the PML spectrum. This patient likely had a coinfection with both strains of the virus before rituximab therapy, and the mutated form was responsible for the JCV GCN phenotype. Subsequently, the
development of more classic PML findings likely represented the emergence of the wild-type virus as the dominant feature driving the disease. Consistent with this possibility, repeated magnetic resonance imaging revealed more typical white matter PML lesions in addition to cerebellar atrophy (Figure, E and F). New-onset or worsening cerebellar ataxia in patients receiving rituximab or natalizumab therapy warrants early assessment for JCV infection.7-9

REFERENCES


