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JC Virus Granule Cell Neuronopathy in a patient treated with Rituximab

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JC Virus Granule Cell Neuronopathy (JCV GCN) is a disease distinct from Progressive Multifocal Leukoencephalopathy (PML). It is caused by infection with a mutated form of the JC virus, leading to a shift in viral tropism from glia to cerebellar granule cells[1–3]. Here we present the first reported case of JCV GCN associated with rituximab treatment.

Case report

69 year old with history of lymphoma presented with 8 months of progressive cerebellar ataxia.

Eleven years prior to presentation, the patient was diagnosed with non-Hodgkin's lymphoma and was treated with 6 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with good response. He was started on maintenance rituximab, with infusions initially every 6 months, increased to every month because of persistent lymphadenopathy.

Eight months prior to presentation, the patient noted the gradual onset of gait instability. Brain MRI demonstrated no significant white matter changes and a structurally normal cerebellum (Fig. 1a–c). Lumbar puncture showed 12 WBC/mm^3, with 44% lymphocytes, 56% monocytes, elevated protein at 102 mg/dl and glucose, at 68 mg/dl, without malignant cells on cytopathology.

He 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.

Neurological examination at presentation demonstrated normal cognition and moderate ataxic dysarthria. He had visual field defects in the right eye inferior hemifield and left eye lateral hemifield, and an ophthalmologic evaluation showed retinal degeneration. He displayed saccadic ocular pursuits, square wave jerks and both rebound and gaze-evoked nystagmus. He had marked appendicular and truncal dysmetria, worse on the right, with dysdiadochokinesia. He had a wide-based gait with short strides and could not ambulate

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without assistance. Motor and sensory exam and deep tendon reflexes were otherwise normal.

An extensive laboratory workup (including ESR, ceruloplasmin, AFP, TSH, Vitamin E, B12, heavy metal screen, FTA, RF, anti-dsDNA, SPEP, ANA, ANCA, SS-A, SmRNP, RNP, paraneoplastic antibody panel, GAD-65 Ab, anti-thyroglobulin Ab, anti-gliadin, transglutaminase, and endomysial Ab) was normal. CSF analysis showed 3 WBC/mm^3, 1 RBC/mm^3, protein 81 mg/dL, glucose 67 mg/dL. Oligoclonal bands, fungal/acid-fast bacterial cultures, HSV, EBV, and CMV PCRs were negative. However, CSF PCR was positive for JC virus at 109,000 copies per mL, consistent with active infection. After consultation with his oncologist, rituximab infusions were stopped.

Over the ensuing 4 months, the patient continued to decline. His swallowing difficulties and visual field deficits progressed, with increasing weight loss and fatigue. He was readmitted after several episodes of non-responsiveness suspicious for seizure. An EEG and cardiovascular workup were unremarkable. He was empirically started on levetiracetam and these episodes resolved. Brain MRI one year after symptom onset showed progressive cerebellar volume loss with T2 hyperintensity in the dorsal midbrain, pons, and cerebellar peduncles (Fig. 1d–f). Repeat lumbar puncture showed CSF protein of 86 mg/dL, glucose of 56 mg/dL, 1 WBC/mm^3 and 0 RBC/mm^3. Repeat JCV PCR demonstrated 18,000 copies/mL. He passed away 17 months after onset of neurological symptoms. Post mortem examination was not performed.

Viral mutational analysis

JCV from the CSF obtained at presentation demonstrated a new GCN type JCV strain with a 12 bp in frame deletion located in the C terminal of VP1 gene (2496-2507 in Mad1 DNA sequence) which we named JCV_{GCN5} [1]. Using a redesigned ice-COLD PCR method[4, 5], we identified JCV_{GCN5} in 5% of clones, with wild-type JCV as the predominant species, consistent with a pleiotropic infection.

Discussion

Human polyomavirus JC (JCV) is well known for causing PML, a demyelinating disease that occurs in the setting of severe immunosuppression. PML results from lytic infection of glia by JCV, which typically triggers a leukoencephalopathy predominantly in the posterior supratentorial white matter. Rarely, mutations in JCV can trigger a change in tropism, leading to involvement of other cell types. JCV GCN has been previously reported in immunocompromised hosts where the mutated virus is the predominant species[2–4]. In this case, the clinical presentation and presence of both WT JCV and JCV_{GCN5} in the CSF is suggestive of JCV GCN with evolution into the PML spectrum. Consistent with this, repeat MRI imaging revealed more typical white matter PML lesions in addition to cerebellar atrophy (Fig. 1e,f).

In sum, new onset or worsening cerebellar ataxia in patients being treated with rituximab or natalizumab warrants early assessment for JCV infection[6, 7].

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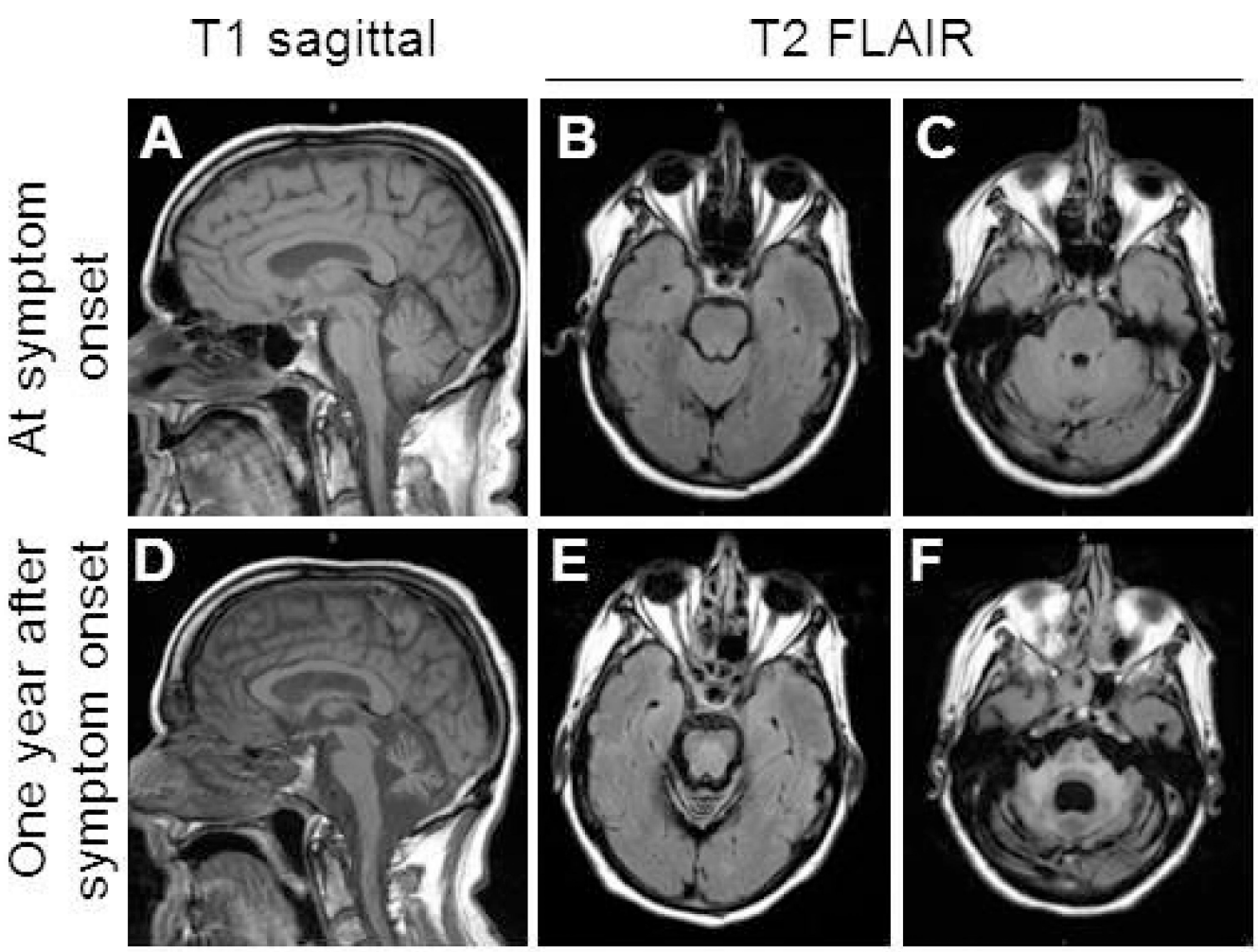

Figure 1. Brain magnetic resonance imaging (MRI) shows progressive cerebellar atrophy and white matter tract changes

At symptom onset (A–C), no significant cerebellar or white matter abnormalities were seen. However, one year after symptom onset, there was significant cerebellar atrophy (D–F), as well as abnormal signal involving the cerebellar peduncles (F) and the white matter tracts of the dorsal midbrain (E) and pons (F). The supratentorial white matter remained relatively spared.