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Unusual Case of Progressive Multifocal Leukoencephalopathy in a Patient With Sjögren Syndrome

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Unusual Case of Progressive Multifocal Leukoencephalopathy in a Patient With Sjögren Syndrome

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Abstract: Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease caused by reactivation of John Cunningham virus affecting typically subcortical and periventricular white matter of immunocompromised hosts (human immunodeficiency virus infection, hematologic malignancies). Cerebral hemispheric white matter is most commonly affected by lytic infections, leading to progressive damage to oligodendrocytes in the central nervous system. Neuroimaging usually highlights scattered foci of white matter hypodensity not attributable to contrast enhancement or mass effect. In contrast, we present an unusual case of PML predominantly affecting cervical spinal cord and brainstem in an immunocompetent host. This is a rare subset of PML case that can occur in association with connective tissue disorders (Sjögren Syndrome in this case), systemic lupus erythematosus being the most common. Progressive multifocal leukoencephalopathy should be considered in the differential diagnosis of spinal cord or brainstem lesions, particularly in the patients with connective tissue disorders.

Key Words: progressive multifocal leukoencephalopathy, Sjögren syndrome, John Cunningham virus, oligodendrocytes, connective tissue disorders

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CASE PRESENTATION

A 65-year-old woman with known history of Sjogren syndrome presented to the emergency department at Henry Ford Hospital, Detroit, MI, with a broken ankle secondary to a 4-month-old fall. She also reported a 4-week history of vertigo, hemiparesis, and right-sided weakness. Her medical history was pertinent for cryptogenic cirrhosis, ascites, obstructive sleep apnea on continuous airway positive pressure, and hypothyroidism on Synthroid.

On examination, she appeared ill, pale, minimally responsive, falling back to sleep quickly after waking. She was obtunded, oriented to person and date, but not to place. She was minimally verbally responsive. Her speech was slurred with monosyllabic responses. Her pupils were equal and reactive to light with full extraocular movements. She appeared to have a right facial droop with no cough and gag reflex. There was absent and reduced muscle tone in the right extremities and left upper extremity, respectively. Sensation to light touch and pain was intact but the patient was dysmetric with bilateral Babinski sign. There were diminished breath sounds in bilateral lung bases.

Laboratory test showed high ammonia levels (47 μmol/L), with abnormal liver enzyme (aspartate transaminase, 56 IU/L), elevated blood urea nitrogen at 37 mg/dL, and normal serum creatinine levels at 1.16 mg/dL.

Cerebrospinal analysis was suggestive of a traumatic tap (red blood cell count, 89,559; white blood cell count, 104×10^9/L with 84% neutrophils; glucose, 71 mmol/L; protein, 183 g/dL with negative cultures and no malignant cells on cytology). Hepatitis C antibody screen was negative. Immunoglobin G antibodies to Sjögren syndrome–related antigen A and anti–Sjögren syndrome-related antigen B were positive. Thyroglobulin antibodies and antinuclear antibodies were elevated. Autoimmune serological tests for other antibodies, including antineutrophil cytoplasmic antibodies, DNA, Scl-70, perinuclear antineutrophil cytoplasmic antibodies, rheumatoid factor, and Smith antigen, were negative.

Initial computed tomography of the head without contrast showed no intracranial abnormality. Multiplanar multisequence magnetic resonance imaging (MRI) of the brain without contrast showed no acute process. Magnetic resonance imaging of the spine without contrast showed T2 signal abnormality involving the medulla extending into the upper cervical cord to C2 to C3 level with C3 medullary lesions (Fig. 1). Differentials, including low-grade neoplasm, such as astrocytoma, chronic demyelinating disease and infection, were considered. Follow-up imaging 3 days later remained unchanged. Patient continued to clinically deteriorate. She was managed for sepsis, pancytopenia, ventilator dependency, and progressive hepatic decompensation. Eight days later, she died.

At autopsy, gross examination of the brain revealed unremarkable cerebral hemispheres, midbrain, basal ganglia, cerebellum, pons, medulla and spinal cord. Histological examination revealed confluent, extensive multifocal white matter lesions in the medulla. The cervical spinal cord, pons, mid brain, cerebellum, and basal ganglia were affected to a lesser degree. These lesions were characterized by pallor, edema, perivascular lymphocytic cuffing, microglial nodules, influx of activated microglial, and numerous oligodendroglial nuclei with ground glass inclusions (Figs. 2, 3, and 4). The inclusions were immunoreactive with simian virus-40 (SV-40) (Figs. 5, 6), highlighted by P53 and MIB-1 immunostains. Other areas showed moderate hypoxic ischemic changes in the neocortex and hippocampus. These findings supported a diagnosis of progressive multifocal leukoencephalopathy (PML) with moderate hypoxic ischemic changes (Figs. 7–14).

Autopsy findings of other organs were consistent with bilateral pleural effusion secondary to acute bronchopneumonia, ascites secondary to hepatic cirrhotic, splenomegaly, and cardiomegaly.

DISCUSSION

Progressive multifocal leukoencephalopathy is an opportunistic demyelinating disease of the central nervous system caused by reactivation of the DNA viruses of the polyoma group.[1] It is caused by 1 of 2 polyomavirus, John Cunningham (JC) virus, named after the first patient whose brain the virus was first isolated from.[2] Strains of the JC virus has been isolated in nearly all of the documented PML cases with rare cases linked to the nonhuman primate viruses, such as simian vacuolating virus 40.[3] The disease predominantly affects immunocompromised hosts, including people with leukemia, human immunodeficiency virus-1 infection, lymphomas, and renal transplant.[4]

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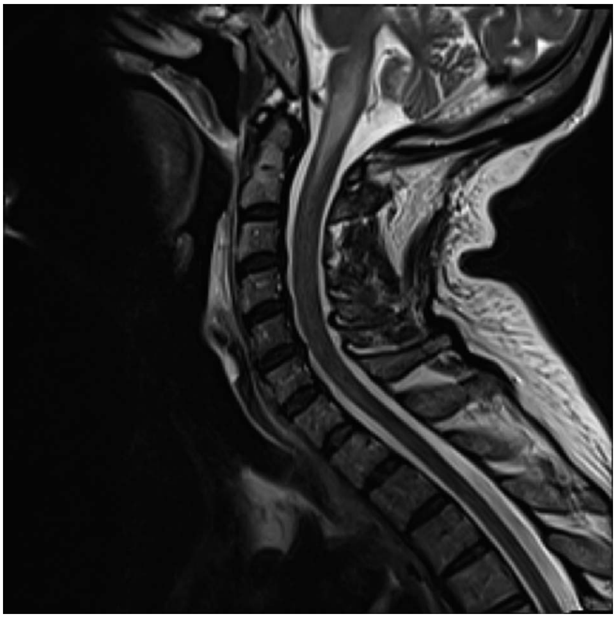

FIGURE 1. MRI of the spine without contrast. Arrow shows T2 abnormality involving the medulla extending into the upper cervical.

Since the isolation of JC virus from the human brain of a patient with PML in the 1970s, JC virus seropositivity has been demonstrated in approximately 33% to 90% of people, depending on the study and geographical location.[5,6] Although a large number of the population are infected with the virus, people remain asymptomatic until they develop defective long-standing cell-mediated immunity.[7] Reports have been made in patients with chronic meningoencephalitis in a young patient[8] with chronic clinical course[9] and in an immunocompetent patient with sepsis.[10]

The disease was initially recognized as a paraneoplastic condition in patients with hematological malignancies.[11,12] Inciting factors to the development of PML are the possibility of transformation of a large proportion of lymphocytes which become unable to participate in immune responses and therapy-induced immunodeficiency.

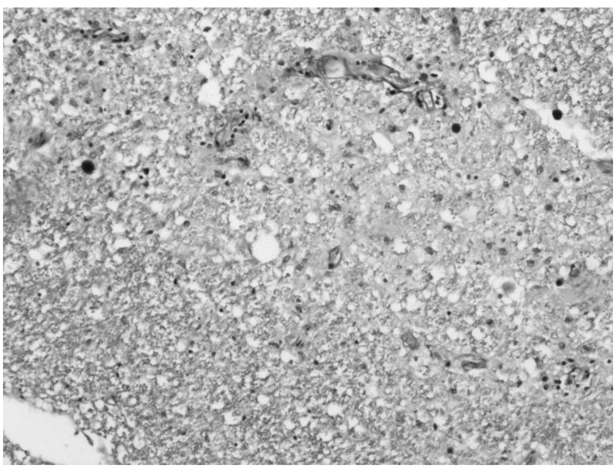

FIGURE 2. Myelin immunostain, luxol fast blue/periodic acid-Schiff ×100 showing patchy myelin loss in the white matter of the medulla.

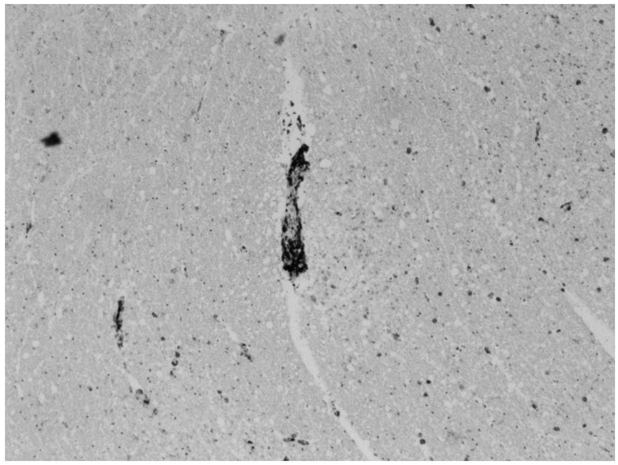

FIGURE 3. CD45 immunostain ×40 highlighting perivascular lymphocytes.

Patient with autoimmune conditions, such as systemic lupus erythematosus, sarcoidosis, rheumatoid arthritis, and connective tissue disease, such as Sjogren disease independent of immunotherapy could develop PML due to disease associated lymphopenia. In 1998, Smith et al[13] described a syndrome characterized by T-lymphocytes less than 300/μL or a CD4+ cell count of less than 20% of the total T cells on 2 occasions, in the absence of any defined immunodeficiency of therapy leading to low CD 4+ T-cell levels. By this definition, Kirtava et al[14] reported that 5.2% of Sjorgren syndrome have CD4+ T-lymphocytopenia. In 2008, Power et al[12] reported a rare case of PML in a patient with CD4+ T-lymphocytopenia and Sjogren syndrome. The pathophysiology could be attributed to leukocyte sequestration in enlarged spleen arising from portal hypertension from hepatic cirrhosis leading to patients developing leucopenia. In addition, hypogammoglobinemia sequel to liver cirrhosis contributes to decreased immunity. Transient failure of cellular immunity as seen in renal failure, liver cirrhosis, pregnancy, hepatitis C infection, malnutrition, and neurodegenerative disorder and idiopathic CD4+-associated lymphopenia increases the risk of opportunistic infections and PML.[15] This association of PML with hepatic cirrhosis was documented by Gheuens et al[15] who observed the disease as an underlying condition in seven patients that developed

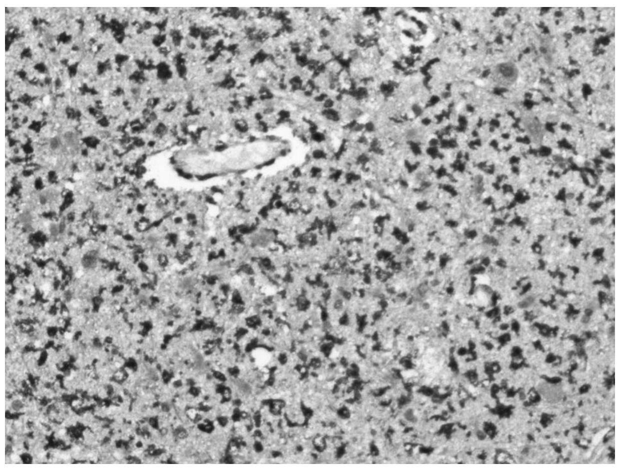

FIGURE 4. CD 163 ×100 immunohistochemistry stain highlighting perivascular monocyte/macrophage.

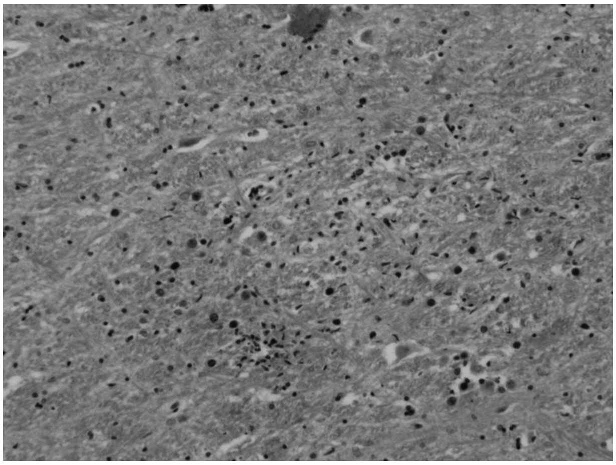

FIGURE 5. Hematoxylin and eosin stain ×40 highlighting JC virus inclusions within oligodendroglial nuclei.

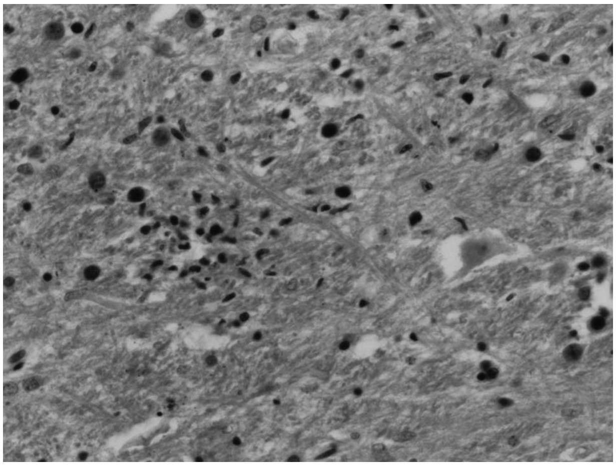

FIGURE 6. Hematoxylin and eosin stain ×200 highlighting JC virus inclusions within oligodendroglial nuclei.

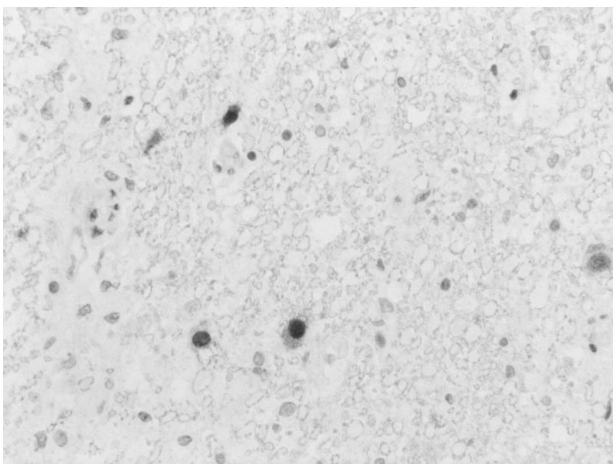

FIGURE 7. Simian virus immunochemistry stain ×200 highlighting JC virus inclusions within oligodendroglial nuclei.

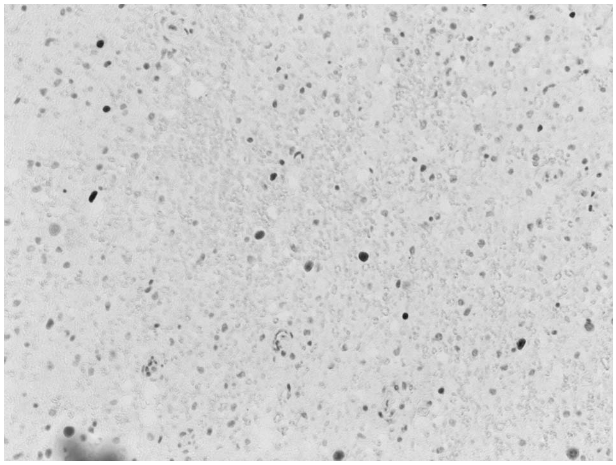

FIGURE 8. P53 immunohistochemistry stain ×100 highlighting JC virus inclusions within oligodendroglial nuclei.

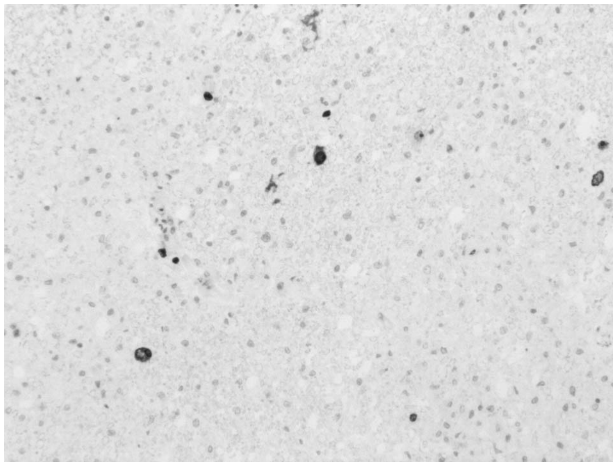

FIGURE 9. MIB1 immunohistochemistry stain ×100 positive in JC virus inclusions in oligodendroglial nuclei.

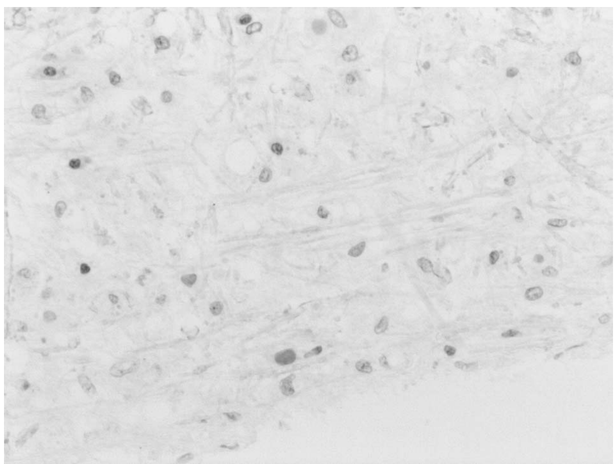

FIGURE 10. Oligodendroglial inclusions show no reactivity to cytomegalovirus immunohistochemistry stain ×200.

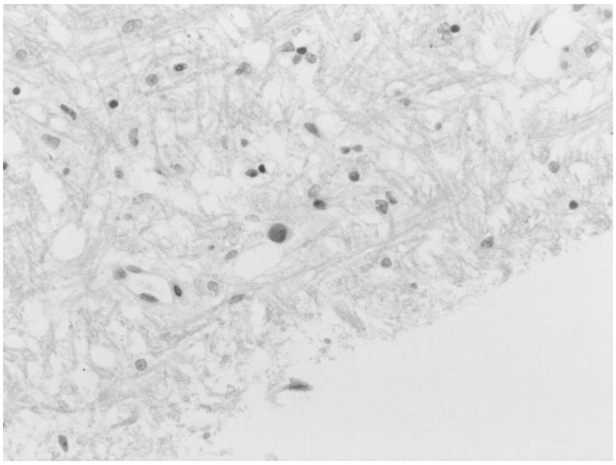

FIGURE 11. Oligodendroglial inclusions show no reactivity to herpes simplex virus 1 immunohistochemistry stain ×200.

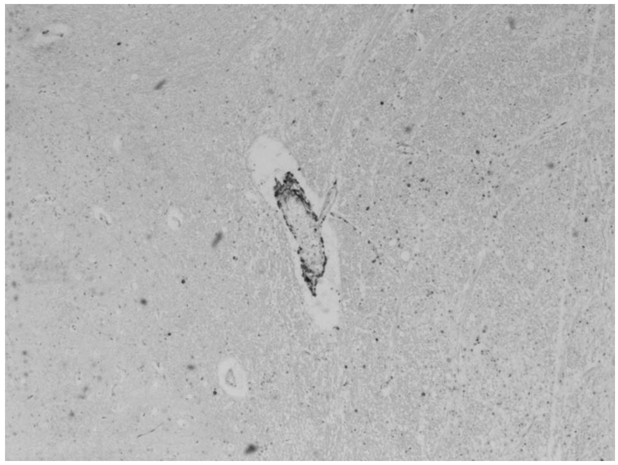

FIGURE 13. CD3 immunostain ×40 showing predominant perivascular T lymphocytic cuffing in comparison to B lymphocytes in Figure 14.

PML in her study. It is our assumption that our patient's chronic lymphopenia might have developed from her underlying connective tissue disease, worsened by cryptogenic hepatic cirrhosis.

Other connective tissue disorders in conjunction with immunotherapy has been associated with PML. In 2005, Clifford et al[16] reported three cases of PML in multiple sclerosis (MS) patients treated with natalizumab. Subsequently, more reports have been made implicating another immunomodulator fingolimod,[17] used in the treatment of MS patients as well as dimethyl fumarate used in to treat psoriasis and MS patients.[18] Other immunomodulatory agents, such as rituximab, glucocorticoids, methotrexate, cyclophosphamide, chlorambucil, and azathioprine, have been associated with PML.

Clinical presentation of PML varies in severity from asymptomatic to lethal.[19] Patients with PML typically present with subacutely evolving clinical features suggestive of a multifocal process. These include motor deficits, cognitive decline, sensory deficits, visual loss, gait disturbances, aphasia, hemianopia, and difficulties with coordination. Other symptoms include seizures, which may result from virus-induced demyelination and inflammation of the cerebral cortex. Similar to our case with a rapid clinical course, Kastrup et al[20] reported a case of PML of the brainstem in an immunocompetent patient, however, with a possible JC and BK polyoma virus coinfection.

Neuroimaging usually highlights the scattered foci of white matter hypodensity not attributable to contrast enhancement or mass effect. This is in contrast to our finding on MRI brain, which only demonstrated some abnormality in the medulla and spinal cord. The absence of typical neuroimaging finding could be attributed to the fact that imaging might have been taken during the early course of the rapidly progressive PML. In addition, since our patient's brain tissue stained positive to SV-40, there is a possibility that the meningoencephalitis experienced by our patient might have been caused by this virus, which typically affects the cerebral gray matter without demyelination.[21]

Although the cerebral hemispheric white matter is most commonly affected by lytic infection, leading to progressive damage to oligodendrocytes in the central nervous system, any level of the central neuraxis may be involved with rare involvement of the cerebellum and spinal cord. In contrast, our index patient had scattered lesions involving the cervical spinal cord and cerebellum.

Our histological findings of edema, perivascular lymphocytic cuffing, microglial nodules, influx of activated microglial,

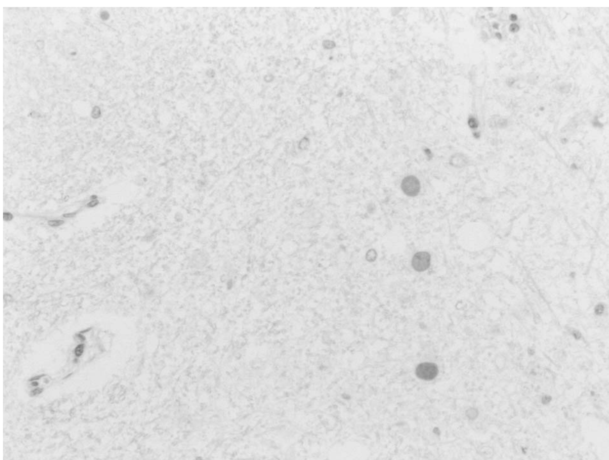

FIGURE 12. Oligodendroglial inclusions show no reactivity to herpes simplex virus 2 immunohistochemistry stain ×200.

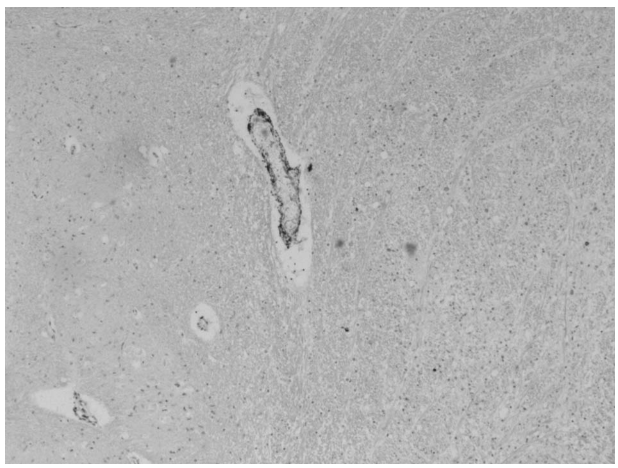

FIGURE 14. CD20 immunostain ×40 showing few perivascular B lymphocytic cuffing in comparison to T lymphocytes in Figure 13.

and numerous oligodendroglial nuclei with ground glass inclusions found on autopsy were consistent with documented findings for PML. To the best of our knowledge, only 2 SV-40 cases have been isolated from brains of patients with PML.[22] Although inoculation of the SV-40 virus in monkeys has produced similar histologic findings consistent with PML in humans, meningoencephalitis related to SV-40 may very well be a distinct disease entity.

Our study has some limitations. Because PML was not considered in the patient's differential, CD4+ T-lymphocyte count, human immunodeficiency virus, JC virus antibody serology were not obtained. No molecular detection by polymerase chain reaction, the recognized sensitive and specific method for detecting human polyomaviruses in clinical samples was performed. The possibility of a virus other than SV-40, but related to SV-40 family or group of viruses cannot be ruled out. Neuroimaging findings and immunohistochemistry positivity to SV-40 is suggestive of the possibility of isolating a virus related to SV-40 in our patient, had this investigation been performed antemortem.

SUMMARY

In this report, we described an unusual presentation of PML occurring in a 65-year-old woman with Sjogren syndrome in which oligodendroglial cells harbored SV-40–positive inclusions. This case highlights that although PML has been documented in immunocompromised patients, it has rarely been associated with Sjögren syndrome. Awareness of this entity is crucial for pathologists, as well as physicians, to consider as a differential diagnosis of white matter lesions, irrespective of the sites of neuraxial involvement.

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