Progressive Multifocal Leukoencephalopathy: Recent Advances and a Neuro-Ophthalmological Review

Padmaja Sudhakar, MBBS, David M. Bachman, MD, Alexander S. Mark, MD, Joseph R. Berger, MD, Sachin Kedar, MBBS, MD

Background: Progressive multifocal leukoencephalopathy (PML) is a severe often fatal opportunistic infection of the central nervous system caused by reactivation of a ubiquitous polyoma virus, JC virus. Although typically characterized by multifocal asymmetric subcortical white matter lesions, it may be monofocal and affect the cortical gray matter. Among the broad spectrum of clinical manifestations that occurs with PML, visual complaints are common.

Evidence Acquisition: Combination of representative personally observed cases of PML and comprehensive review of case series of PML from 1958 through 2014.

Results: Neuro-ophthalmic signs and symptoms were reported in approximately 20%–50% of patients with PML and can be the presenting manifestation in half of these. A majority of these presentations occur from damage to cerebral visual pathways resulting in visual field defects, cortical blindness, and other disorders of visual association. Given the decreased frequency of infratentorial and cerebellar involvement, ocular motility disorders are less common.

Conclusions: Visual complaints occur in patients with PML and are often the presenting sign. Awareness of this

Sachin Kedar has received royalty fees for editorial services from Elsevier Inc.

Joseph Berger reports personal fees from Amgen, Astra Zeneca, Bristol Myers Squibb, Eisai, Janssen, Millenium, Parexel, Pfizer, Roche, Takeda, Genentech, Genzyme, Incyte, Inhibikase, Johnson and Johnson, Novartis, American Academy of Neurology, Consortium of MS Centers and grants from Biogen Idec, PML Consortium and Novartis. The other authors report no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the full text and PDF versions of this article on the journal's Web site (www. jneuro-ophthalmology.com).

Address correspondence to Padmaja Sudhakar, MBBS, Department of Neurology, University of Kentucky, 740 S Limestone, Suite L 445, Lexington, KY 40536, E-mail: psu224@uky.edu condition is helpful in avoiding unnecessary delays in the diagnosis of PML and management of the underlying condition. Recent guidelines have established criteria for diagnosis of PML in the high-risk patient population and strategies to mitigate the risk in these populations.

Journal of Neuro-Ophthalmology 2015;35:296–305 doi: 10.1097/WN0.000000000000271 © 2015 by North American Neuro-Ophthalmology Society

rogressive multifocal leukoencephalopathy (PML) was first described by Aström, Mancall, and Richardson in 1958 as a unique demyelinating disorder with characteristic histopathology in 3 patients with lymphoproliferative disorders (1). It is a severe often fatal demyelinating disease that results from lytic infection of oligodendrocytes by the JC virus, a ubiquitous human polyoma virus (2). PML usually occurs in the immunosuppressed patient and results in a devastating neurological illness which is fatal, unless the underlying immunosuppressive cause is identified and treated. Despite the propensity of PML to produce visual symptoms, very few reports have addressed the neuro-ophthalmological features of this disease. The objective of this review is to provide a current understanding of the disease process including the varied neuro-ophthalmic presentations using illustrative cases. For purposes of this report, we reviewed medical literature on Medline and Google Scholar using the terms PML, progressive multifocal leukoencephalopathy and vision, diplopia, pupils, eye movements, and blindness. Where appropriate, we also used data gathered by Bachmann and Mark (coauthors of this article) reviewing 240 cases of PML published up to 1992.

Epidemiology

PML is almost always observed in association with an immunocompromised state, either from an underlying disease or associated treatment; however, in rare instance, it may be seen in the absence of apparent immunological abnormality (3,4). The PML era can be broadly divided

Departments of Neurology (PS), University of Kentucky College of Medicine, Lexington, Kentucky; Departments of Ophthalmology (DMB), and Radiology (ASM), Washington Hospital Center, Washington, District of Columbia; Department of Neurology (JRB), Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; and Department of Neurological Sciences and Ophthalmology (SK), University of Nebraska Medical Center, Omaha, Nebraska.

into 4 epochs: pre-HIV, HIV (pre-HAART), HIV (post-HAART), and modern era. Before HIV epidemic in the early 1980s, PML was rare and seen almost exclusively in patients with lymphoproliferative and myeloproliferative disorders (5–10). After the HIV pandemic, the incidence of PML increased by almost 50-fold making HIV the leading cause of this disease (11–14).

During this era (HIV pre-HAART), 5% of patients with HIV developed PML with a median survival of 6 months with fewer than 10% survival rate 1 year after symptom onset. With the advent of highly active antiretroviral therapy (HIV post-HAART era), there was a significant decline in the incidence (15). Mortality rates from PML improved from 90% in the 1980-1990 decade to 50% in the first decade of the 21st century (16). A new era of PML dawned in 2005 when PML was reported in association with treatment with natalizumab for Crohn's disease and multiple sclerosis (MS) (17-19). This resulted in a temporary withdrawal of natalizumab, an anti-alpha-4 integrin, from the market in 2005. Of 99,517 patients treated with natalizumab until 2012, there were 212 confirmed cases of natalizumab-associated PML (20). Other than natalizumab and efalizumab, PML has also been reported with various monoclonal antibodies and immune-modifying therapies. Among other immunomodulatory agents that have implicated in predisposing to PML are the anti-TNF-alpha agents, infliximab, adalimumab, and etanercept, ruxolitinib (inhibitor of JAK 1 and 2), and oral agents used in treatment of MS, dimethyl fumarate (Tecfidera) (21,22). Currently, several drugs carry an FDA-mandated black box warning for PML, including natalizumab, rituximab, brentuximab-vedotin, and mycophenolate mofetil.

Pathogenesis

Subclinical infection with JC virus generally occurs within the first decade of life and by adulthood; 50%-80% of the population is seropositive for the virus (23,24). The virus remains latent in the kidney, bone marrow, and lymphoid organs (8). PML is caused by reactivation of the JC virus in the setting of immunosuppression with spread to the CNS leading to oligodendrocyte infection and demyelination. JC virus infection of the brain typically causes a subacute progressive disorder with multifocal asymmetric subcortical white matter involvement from which the disease entity derives its name. Astrocytes and neurons may also be infected but the virus does not complete its entire replicative cycle in the former. Instances of monofocal disease and gray matter involvement of cerebellar granular cells (25,26) and cerebral cortical neurons have been described (27). Isolated lesions of the cerebellum and brainstem are rare [Joseph Berger, MD and 2013 personal observation and Mossakowski and Zelman (28)] and may be higher in the HIV/AIDS population with PML (12) compared with other predisposing causes such as natalizumabassociated PML (29).

Clinical Presentation

Despite a propensity to affect the cerebral hemispheres, any part of the brain may be affected, which produces a variety of neurological manifestations. Behavioral and cognitive abnormalities are seen in one-third to half of all individuals (12,29). Common findings include motor weakness, gait abnormalities, visual field defects, language problems, and incoordination (12,30). Less common findings include headache, sensory loss, seizures and diplopia (12,30). Spinal cord involvement has only been reported in pathologic specimens; myelopathy has not been described clinically (31). There are no descriptions of optic nerve disease or peripheral nervous system involvement by PML. Despite significant overlap in clinical presentation, cognitive problems more often herald natalizumab-related PML, whereas motor weakness is associated with HIV-related PML (29).

Neuro-ophthalmology of PML

Very few studies in literature have systematically described the neuro-ophthalmic features of PML (32,33). Brooks and Walker (30) reviewed 230 published and unpublished cases of PML and reported visual field deficits (34.7%), visual blurring (7.2%), diplopia (1.4%), optic atrophy (1.4%), and cortical blindness (2.9%). Only 45% of these were virologically or pathologically confirmed cases. Berger and Pall (12) reported visual field defects (19%) and diplopia (9%) in their series of 154 HIV-associated patients with PML at presentation. In their review of 240 published cases of PML, Bachman and Mark found 125 patients (52%) with neuro-ophthalmological findings (2-7,11,34-138). Of the 74 patients with AIDS, 40 (54%) had neuroophthalmological findings (See Supplemental Digital Content, Table E1, http://links.lww.com/WNO/A163). Visual disorders can be the presenting features in approximately 20% of patients with both HIV-associated and non-HIV-associated cases of PML (10-12,41,120,139-142). In the following sections, we will describe the pertinent neuro-ophthalmological features using illustrative cases.

Case 1

A 63-year-old woman with a history of Sjogren's syndrome and ovarian cancer developed difficulty reading a clock face and began bumping into objects in her left visual field. Her symptoms were initially attributed to "chemobrain"; but 3–4 months later, she developed stuttering, difficulty folding clothes, tying her shoes, and dressing herself, followed a month later by left arm and leg weakness. Neurological examination showed dyscalculia, difficulty following threestep commands, dressing apraxia, dense left homonymous hemianopia, and mild left hemiparesis. Brain magnetic resonance imaging (MRI) obtained 2 months later showed a large T2/fluid-attenuated inversion recovery image (FLAIR) hyperintense signal abnormality affecting the right parietal and occipital lobes with extension across splenium

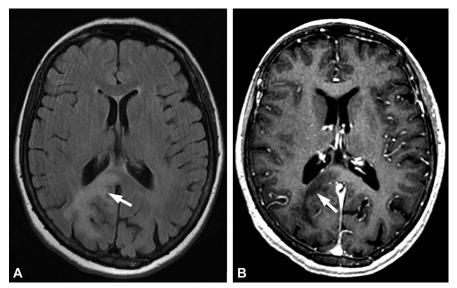


FIG. 1. Case 1. Magnetic resonance imaging of progressive multifocal leukoencephalopathy. On axial fluid-attenuated inversion recovery image image (**A**), there is a hyperintense lesion (*arrow*), which appears hypointense and does not enhance (*arrow*) on postcontrast T1 axial scan (**B**).

of the corpus callosum (Fig. 1). There also was involvement of the right thalamus, posterior limb of internal capsule, and right cerebral peduncle. The lesion was hypointense on T1 imaging, did not enhance with contrast, was subcortical in location, and did not demonstrate mass effect. CSF examination showed JC virus DNA by polymerase chain reaction (PCR technique). She had an absolute CD4 count of 390 cells per microliter and CD4/8 ratio of 0.5.

Homonymous Hemianopia

Homonymous hemianopia (including quadrantanopia) is the most common ophthalmic manifestation of PML from involvement of optic radiations in both AIDS and non-AIDS series, seen in 25% of the 240 cases of PML reviewed by Bachman and Mark through 1992 (See **Supplemental Digital Content**, Table E1, http://links.lww.com/WNO/A163). Other studies have reported higher figures (35%–45%) for homonymous hemianopia in reported cases of PML (30,32). Unilateral and bilateral homonymous hemianopia and quadrantanopia may be the presenting symptom of PML in AIDS (33,142,143). Reversal of both vision and other neurological deficits 8 months after resumption of highly active antiretroviral therapy (HAART) was reported in patients with HIV-associated PML (144,145).

Homonymous hemianopia also has been reported in cases of PML from natalizumab. In a series of 28 patients with natalizumab-associated PML, 5 had homonymous hemianopia and 3 reported diminished vision as a presenting manifestation (29). Homonymous hemianopia in patients with MS on natalizumab should raise suspicion for PML. This has prompted recommendations for visual acuity and visual field testing every 3 months in patients with MS treated with natalizumab for 1 year or longer (146).

Case 2

A 35-year-old man with a history of HIV and non-Hodgkin's lymphoma, in remission for 7 years after treatment, developed dizziness, confusion, and blurred vision. He discontinued HAART 3 years earlier and was lost to follow-up. For the last 3 months, he had difficulty driving and had sideswiped cars on his right side. Neurological examination performed 1 month later was remarkable for cortical blindness, visual agnosia, pure word deafness, and right hemiparesis. MRI brain showed T2/FLAIR hyperintense signal in the left parietal and occipital lobes and splenium of corpus callosum (Fig. 2). There was extension into the left posterior frontal lobe, external capsule, and posterior limb of the internal capsule, thalamus, mid-brain, pons, and contralateral occipital lobe. Most recent CD4 count was 26 cells per microliter, CD4:CD8 ratio was 0.18, and HIV viral load was 74,800 copies per mL. CSF examination confirmed JC virus DNA by PCR technique. Biopsy of the occipital lesion showed features that were consistent with PML (Fig. 3).

Abnormalities of Visual Association

A large spectrum of disorders of visual association has been observed with PML including visual neglect (12), visual hallucinations (147), prosopagnosia, and impaired spatial perception (12,139). Balint syndrome (148–151) has been reported in patients with PML. These patients frequently complain of visual distortion, difficulty reading, "fragmented" environment, difficulty driving, and other visuospatial abnormalities. In those instances in which Balint syndrome has been attributed to HIV encephalopathy, it is far more likely to have been caused by unrecognized coexisting PML (152,153). Bachman and Mark have seen 2 patients with optic aphasia in

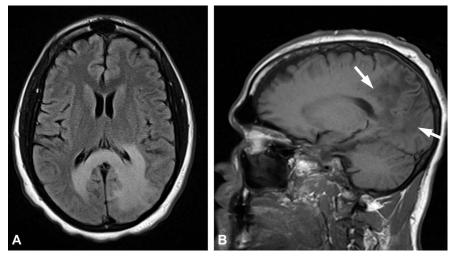


FIG. 2. Case 2. Magnetic resonance imaging of progressive multifocal leukoencephalopathy. **A**. On axial fluid-attenuated inversion recovery image scan, there is a hyperintense lesion with extension through the splenium of the corpus callosum. **B**. The postcontrast T1 sagittal image shows the affected area (*enclosed between the arrows*) to be hypointense without evidence of enhancement.

association with alexia and homonymous hemianopia. Both had involvement of the dominant parietal lobe and corpus callosum producing the "disconnection syndrome." These patients had presented with difficulty reading and naming letters on the Snellen chart despite 20/20 visual acuity.

Cortical blindness in PML results from bilateral involvement of the retrogeniculate visual pathways, typically the optic radiations or the primary visual cortex and may be seen in 6%–8% patients (30,41). These cases may start with visual blurring and progress to visual field loss and cortical blindness, as unchecked PML progresses to bilateral occipital involvement often accompanied by neurological deficits such as prosopagnosia and alexia with agraphia (139). Unless there is a high degree of suspicion, presentation of PML as visual loss may be mistakenly attributed to ophthalmic causes such as cataract or postoperative inflammation after eye surgery leading to unnecessary procedures and diagnostic delay (154,155).

Case 3

A 34-year-old homosexual man with a 12-year history of AIDS and no previous opportunistic infection reported a 2-week history of right face and arm paresthesia, numbness, and weakness. One week before presentation, he developed blurred vision and binocular vertical diplopia. He had discontinued HAART 1 year ago due to intolerance to medications. On examination, he had right hemiparesis, right central facial palsy, and left hypertropia (consistent with skew deviation). Visual acuity, visual fields, pupillary reflexes, and retinal examination were normal. Brain MRI showed a T2 hyperintense lesion in the left pons extending to the left cerebral peduncle (Fig. 4). There also was involvement of the centrum semiovale bilaterally. Lumbar puncture demonstrated 5 white blood cells per mL, 1093 red blood cells per mL (traumatic tap), protein of 86 mg/dL (normal: 15-60 mg/ dL), glucose of 58 mg/dL (normal: 15-45 mg/dL), and 120

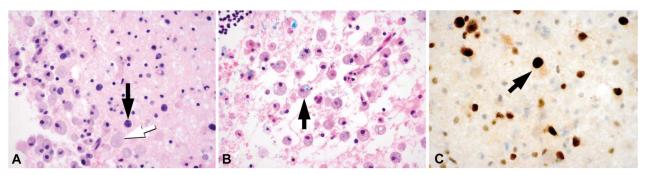


FIG. 3. Case 2. Histopathology of the left parieto-occipital lesion. **A**. There is infiltration with macrophages, scattered bizarre astrocytes (*black arrow*), and oligodendrocytes with "glassy" nuclei (*white arrow*) (hematoxylin & eosin, ×400). **B**. There is loss of myelination with ingestion of myelin by macrophages (*arrow*) (Luxol fast blue, ×400). **C**. JC viral particles are present in atypical astrocytes and oligodendrocytes (*arrows*) (SV40T immunostain, ×600). Courtesy of Craig Horbinski, MD, PhD, University of Kentucky, Lexington, KY.

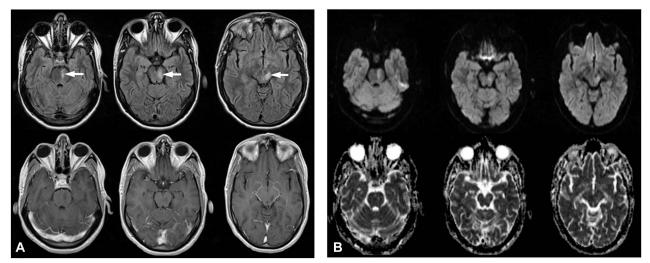


FIG. 4. Case 3: Magnetic resonance imaging of progressive multifocal leukoencephalopathy. **A**. Top panel, Axial fluidattenuated inversion recovery images reveal hyperintensive lesion in left pons extending into left cerebral peduncle (*arrows*). Bottom panel, Postcontrast T1 axial scans show the lesion to be hypointensive with enhancement. **B**. Top panel, Axial diffusion-weighted imaging shows the lesion to be hyperintense. Bottom panel, apparent diffusion coefficient (ADC) images fail to show evidence of restricted diffusion.

copies per mL of JC virus DNA by PCR. In his blood, he had 120,000 copies per mL of HIV-1 RNA.

Infratentorial PML

Infratentorial demyelinating lesions may occur in isolation or with supratentorial lesions (12,109,156-158). The cerebellum is more commonly involved than the brainstem probably as a consequence of greater volume and due to a unique cerebellar syndrome from the causative virus referred to as JC virus granule call neuronopathy (159). Patients with brainstem findings may have concurrent involvement of the cerebellum seen on imaging or on pathological investigations (157). Infratentorial (cerebellar and brainstem) abnormalities were noted on neuroimaging studies in 48% (20% isolated infratentorial lesions) of 154 PML cases in a large series (12). Infratentorial involvement on imaging studies does not necessarily translate to clinical abnormalities in as many as 50% of cases. This poor correlation could be artifactual (retrospective studies, brainstem signs either not elicited or recorded) or related to the natural history of the disease with chances of brainstem involvement being less when duration of PML is less than 2 and half months (109).

Brainstem involvement may cause nuclear, internuclear, and supranuclear palsies producing diplopia, facial weakness, and numbness, hypoacusis, dysarthria, dysphagia, and nystagmus. PML may cause isolated or multiple ocular motor cranial neuropathies, multiple cranial neuropathy (sixth and seventh), internuclear ophthalmoplegia (160), or abnormalities of ocular smooth pursuit, saccades, and nystagmus (12,161). PML with cerebellar JC viral granular neuronopathy may present with a combination of cerebellar and brainstem signs such as ataxia, nystagmus, diplopia, dysarthria, dysphagia, and vertigo (51,65,77,88,136,157,162,163). PML causing progressive brainstem disorder was reported in a patient with systemic lupus erythematosus being treated with etanercept and prednisone after she presented with diplopia, right face hypoesthesia, vertigo, dysarthria, right hemiparesis, hemiataxia, and gait problems. Brain MRI demonstrated lesions of bilateral pons and medulla, right middle cerebellar peduncle extending into the right cerebellar hemisphere, and left paramedian cerebellum (164).

Optic Nerve

Primary involvement of the optic nerve has not been reported in PML, which is surprising because the JC virus targets the oligodendroglia, which produces optic nerve myelin. Optic atrophy is usually secondary to underlying cause such as MS (5). The latter is particularly true in the patients with MS who have developed natalizumabassociated PML. Curiously, Brooks and Walker (30) in their review of 230 cases of PML, which predated the use of natalizumab for MS found optic atrophy in 1.4% of cases at the time of diagnosis.

DIAGNOSTIC CONSIDERATIONS

Demonstration of the JC virus in brain tissue or CSF is insufficient for diagnosis of PML because the virus may be found in these locations of normal individuals. Diagnostic criteria for PML have been published as a consensus statement from the American Academy of Neurology's Neuroinfectious Disease Section (See **Supplemental Digital Content**, Table E2, http://links.lww.com/WNO/A164) (165). The 2 diagnostic approaches used include demonstration of typical histopathological findings and JC virus in tissue specimen or a demonstration of JC virus in the CSF of patients who fulfill clinical and radiographic criteria. The characteristic histopathologic features of PML include multifocal demyelination, enlarged bizarre astrocytes with lobulated hyperchromatic nuclei, and enlarged oligodendroglial nuclei. The presence of JC virus in the specimen can be confirmed by electron microscopy, immunohistochemistry, or PCR techniques.

The imaging characteristics of PML are not diagnostic. Hypodense white matter lesions without mass effect or contrast enhancement are seen on computed tomography. Brain MRIs show hyperintense white matter lesions on T2 and FLAIR images, which are hypointense on T1 images. Gadolinium enhancement is seen in 15% of HIV-associated PML and 40% of natalizumab-associated PML (166).

TREATMENT

Although there is no definitive pharmacological treatment for PML, management is aimed at reversal of the underlying immunosuppressive state, which includes treatment with HAART in patients with HIV/AIDS and removing offending immunosuppressive agents, such as natalizumab. Risk mitigation strategies used to prevent the development of PML include monitoring patients on natalizumab for JC virus antibody, limiting the cumulative total dose in those that are JC virus antibody positive and serial brain MRI scans to detect PML early (167). In JC virus antibodypositive individuals, the risk of PML after 24 months of treatment with natalizumab is as follows: in those without previous immunosuppressant use, the risk is estimated at 3 per 1000 and in those with previous immunosuppressant use, it is 13 per 1000 (https://medinfo.biogenidec.com). Discontinuing natalizumab in these circumstances requires an informed discussion with the patient. Although increasing the time interval between doses of natalizumab has been suggested to decrease the occurrence of PML, there are no well-controlled trials to demonstrate the efficacy of this strategy. There is no consensus about the drug of choice after natalizumab discontinuation. A patient with PML after dimethyl fumarate (Tecfidera) treatment has been reported in the absence of other prior or concomitant immunomodulatory therapy (Tecfidera product label, December 2014). A combination of lymphopenia and reduced leukocyte binding to VCAM by 33% induced by dimethyl fumarate (168) may underlie an increased risk for PML. These observations coupled with reports of PML with fumaric acid esters in the treatment of psoriasis raise concerns about its use in this population (21,22).

CONCLUSIONS

The neuro-ophthalmic manifestations of PML are protean and depend on the parts of the nervous system affected. Impaired vision from lesions of retrogeniculate visual pathway and association cortices appears to be one of the most common manifestations of PML. Ocular motility disorders result from involvement of the brainstem and cerebellum. Without awareness of these presentations, the diagnosis of PML may be missed in those patients who initially are seen by an ophthalmologist or neurologist with visual complaints. Approximately one-third of patients with PML present with visual disturbances. Homonymous hemianopia is the most common neuro-ophthalmological manifestation; however, a wide variety of abnormalities of afferent and efferent visual systems are observed. Visual complaints may not only herald PML but are frequently the most debilitating symptom.

STATEMENT OF AUTHORSHIP

Category 1: a. Conception and design: P. Sudhakar, D. M. Bachman, J. R. Berger, S. Kedar; b. Acquisition of data: P. Sudhakar, D. M. Bachman, A. S. Mark, J. R. Berger, S. Kedar; c. Analysis and interpretation of data: P. Sudhakar, D. M. Bachman, A. S. Mark, J. R. Berger, S. Kedar. Category 2: a. Drafting the manuscript: P. Sudhakar, D. M. Bachman, J. R. Berger, S. Kedar; b. Revising it for intellectual content: P. Sudhakar, J. R. Berger, S. Kedar. Category 3: a. Final approval of the completed manuscript: P. Sudhakar, D. M. Bachman, A. S. Mark, J. R. Berger, S. Kedar. Category 3: a. Final approval of the completed manuscript: P. Sudhakar, D. M. Bachman, A. S. Mark, J. R. Berger, S. Kedar.

REFERENCES

- Astrom KE, Mancall EL, Richardson EP Jr. Progressive multifocal leuko-encephalopathy; a hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin's disease. Brain. 1958;81:93–111.
- Padgett BL, Walker DL, ZuRhein GM, Eckroade RJ, Dessel BH. Cultivation of papova-like virus from human brain with progressive multifocal leucoencephalopathy. Lancet. 1971;1:1257–1260.
- Rockwell D, Ruben FL, Winkelstein A, Mendelow H. Absence of immune deficiencies in a case of progressive multifocal leukoencephalopathy. Am J Med. 1976;61:433–436.
- Zochodne DW, Kaufmann JC. Prolonged progressive multifocal leukoencephalopathy without immunosuppression. Can J Neurol Sci. 1987;14:603–607.
- Faris AA, Martinez AJ. Primary progressive multifocal leukoencephalopathy. A central nervous system disease caused by a slow virus. Arch Neurol. 1972;27:357–360.
- Richardson EP Jr. Progressive multifocal leukoencephalopathy 30 years later. N Engl J Med. 1988;318:315–317.
- Bolton CF, Rozdilsky B. Primary progressive multifocal leukoencephalopathy. A case report. Neurology. 1971;21:72– 77.
- Houff SA, Major EO, Katz DA, Kufta CV, Sever JL, Pittaluga S, Roberts JR, Gitt J, Saini N, Lux W. Involvement of JC virusinfected mononuclear cells from the bone marrow and spleen in the pathogenesis of progressive multifocal leukoencephalopathy. N Engl J Med. 1988;318:301–305.
- Silverman L, Rubinstein LJ. Electron microscopic observations on a case of progressive multifocal leukoencephalopathy. Acta Neuropathol. 1965;5:215–224.
- 10. **Smith JL**. Progressive multifocal leukoencephalopathy. Arch Ophthalmol. 1959;62:828–832.
- 11. **Berger JR**, Kaszovitz B, Post MJ, Dickinson G. Progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. A review of the literature

with a report of sixteen cases. Ann Intern Med. 1987;107:78–87.

- Berger JR, Pall L, Lanska D, Whiteman M. Progressive multifocal leukoencephalopathy in patients with HIV infection. J Neurovirol. 1998;4:59–68.
- Holman RC, Torok TJ, Belay ED, Janssen RS, Schonberger LB. Progressive multifocal leukoencephalopathy in the United States, 1979–1994: increased mortality associated with HIV infection. Neuroepidemiology. 1998;17:303–309.
- 14. **Zelman IB**, Mossakowski MJ. Opportunistic infections of the central nervous system in the course of acquired immune deficiency syndrome (AIDS). Morphological analysis of 172 cases. Folia Neuropathol. 1998;36:129–144.
- Khanna N, Elzi L, Mueller NJ, Garzoni C, Cavassini M, Fux CA, Vernazza P, Bernasconi E, Battegay M, Hirsch HH; Swiss HIV Cohort Study. Incidence and outcome of progressive multifocal leukoencephalopathy over 20 years of the Swiss HIV Cohort Study. Clin Infect Dis. 2009;48:1459–1466.
- Tan CS, Koralnik IJ. Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol. 2010;9:425–437.
- Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. N Engl J Med. 2005;353:369–374.
- Langer-Gould A, Atlas SW, Green AJ, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. N Engl J Med. 2005;353:375–381.
- Van Assche G, Van Ranst M, Sciot R, Dubois B, Vermeire S, Noman M, Verbeeck J, Geboes K, Robberecht W, Rutgeerts P. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med. 2005;353:362–368.
- Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, Lee S, Plavina T, Scanlon JV, Sandrock A, Bozic C. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012;366:1870–1880.
- van Oosten BW, Killestein J, Wattjes MP. Case reports of PML in patients treated for psoriasis. N Engl J Med. 2013;369:1081–1082.
- 22. Ermis U, Weis J, Schulz JB. PML in a patient treated with fumaric acid. N Engl J Med. 2013;368:1657–1658.
- Stolt A, Sasnauskas K, Koskela P, Lehtinen M, Dillner J. Seroepidemiology of the human polyomaviruses. J Gen Virol. 2003;84:1499–1504.
- 24. Berger JR, Khalili K. The pathogenesis of progressive multifocal leukoencephalopathy. Discov Med. 2011;12:495–503.
- Richardson EP Jr, Webster HD. Progressive multifocal leukoencephalopathy: its pathological features. Prog Clin Biol Res. 1983;105:191–203.
- Bayliss J, Karasoulos T, McLean CA. Frequency and large T (LT) sequence of JC polyomavirus DNA in oligodendrocytes, astrocytes and granular cells in non-PML brain. Brain Pathol. 2012;22:329–336.
- Wuthrich C, Koralnik IJ. Frequent infection of cortical neurons by JC virus in patients with progressive multifocal leukoencephalopathy. J Neuropathol Exp Neurol. 2012;71:54–65.
- Mossakowski MJ, Zelman IB. Pathomorphological variations of the AIDS-associated progressive multifocal leukoencephalopathy. Folia Neuropathol. 2000;38:91–100.
- Clifford DB, De Luca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. Lancet Neurol. 2010;9:438–446.
- 30. **Brooks BR**, Walker DL. Progressive multifocal leukoencephalopathy. Neurol Clin. 1984;2:299–313.
- Bernal-Cano F, Joseph JT, Koralnik IJ. Spinal cord lesions of progressive multifocal leukoencephalopathy in an acquired immunodeficiency syndrome patient. J Neurovirol. 2007;13:474–476.

- Wein F, Francis GS, Gans MS, Connolly WE, Burnier MN Jr. Neuro-ophthalmic findings in progressive multifocal leukoencephalopathy. Can J Ophthalmol. 1998;33:270–275.
- Ormerod LD, Rhodes RH, Gross SA, Crane LR, Houchin KW. Ophthalmologic manifestations of acquired immune deficiency syndrome-associated progressive multifocal leukoencephalopathy. Ophthalmology. 1996;103:899–906.
- Richardson EP Jr. Progressive multifocal leukoencephalopathy. N Engl J Med. 1961;265:815–823.
- Levy RM, Bredesen DE, Rosenblum ML. Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): experience at UCSF and review of the literature. J Neurosurg. 1985;62:475–495.
- Aksamit AJ, Gendelman HE, Orenstein JM, Pezeshkpour GH. AIDS-associated progressive multifocal leukoencephalopathy (PML): Comparison to non-AIDS PML with in situ hybridization and immunohistochemistry. Neurology. 1990;40:1073–1078.
- Snider WD, Simpson DM, Nielsen S, Gold JW, Metroka CE, Posner JB. Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. Ann Neurol. 1983;14:403–418.
- Adams JH, Short IA. Progressive multifocal leucoencephalopathy. Scott Med J. 1965;10:195–202.
- Aksamit AJ, Sever JL, Major EO. Progressive multifocal leukoencephalopathy: JC virus detection by in situ hybridization compared with immunohistochemistry. Neurology. 1986;36:499–504.
- Aksamit AJ, Mourrain P, Sever JL, Major EO. Progressive multifocal leukoencephalopathy: investigation of three cases using in situ hybridization with JC virus biotinylated DNA probe. Ann Neurol. 1985;18:490–496.
- 41. **Appen RE**, Roth H, ZuRhein GM, Varakis JN. Progressive multifocal leukoencephalopathy. A cause of visual loss. Arch Ophthalmol. 1977;95:656–659.
- 42. **Bateman O,** Squires G, Thannhauser S. Hodgkin's disease associated with Schilder's disease. Ann Intern Med. 1945;22:426–431.
- Bedri J, Weinstein W, DeGregorio P, Verity MA. Progressive multifocal leukoencephalopathy in acquired immunodeficiency syndrome. N Engl J Med. 1983;309:492–493.
- 44. **Behar A**. Progressive multifocal leukoencephalopathy in a case of acute lymphatic leukemia. Isr J Med Sci. 1965;1:650–654.
- 45. **Berger JR**, Mucke L. Prolonged survival and partial recovery in AIDS-associated progressive multifocal leukoencephalopathy. Neurology. 1988;38:1060–1065.
- 46. **Bernick C**, Gregorios JB. Progressive multifocal leukoencephalopathy in a patient with acquired immune deficiency syndrome. Arch Neurol. 1984;41:780–782.
- 47. **Bethlem J,** Van G, Den Hartog Jager WA. Progressive multifocal leucoencephalopathy associated with multiple myeloma. Acta Neuropathol. 1964;3:525–528.
- Blum LW, Chambers RA, Schwartzman RJ, Streletz LJ. Progressive multifocal leukoencephalopathy in acquired immune deficiency syndrome. Arch Neurol. 1985;42:137– 139.
- 49. **Bauer WR**, Turel AP Jr, Johnson KP. Progressive multifocal leukoencephalopathy and cytarabine. Remission with treatment. JAMA. 1973;226:174–176.
- Boerman RH, Arnoldus EP, Raap AK, Peters AC, ter Schegget J, van der Ploeg M. Diagnosis of progressive multifocal leucoencephalopathy by hybridisation techniques. J Clin Pathol. 1989;42:153–161.
- Boudin G, Mikol J, Vernant JC, Bydlowski M, Bouchet N. Progressive multifocal leukoencephalopathy. Anatomo-clinical study of 2 cases, one of which with extension to the brain stem and cerebellum. Rev Neurol (Paris). 1974;130:89–102.
- 52. **Buckman R**, Wiltshaw E. Letter: progressive multifocal leucoencephalopathy successfully treated with cytosine arabinoside. Br J Haematol. 1976;34:153–158.
- 53. **Carroll BA**, Lane B, Norman D, Enzmann D. Diagnosis of progressive multifocal leukoencephalopathy by computed tomography. Radiology. 1977;122:137–141.

- 54. Castaigne P, Escourolle R, Derouesne C, Cathala F, Hauw JJ, Duclos H, Goust JM. A case of progressive multifocal leukoencephalopathy. Anatomoclinical and immunological study. Isolation of a new papova strain virus from cerebral biopsy. Rev Neurol (Paris). 1973;128:85–94.
- Castaigne P, Rondot P, Escourolle R, Ribadeau dumas JL, Cathala F, Hauw JJ. Progressive multifocal leukoencephalopathy and multiple gliomas. Rev Neurol (Paris). 1974;130:379–392.
- Castleman B, Scully RE, McNeely BU. Case records of the Massachusetts general hospital. Weekly clinicopathological exercises. Case 39–1972. N Engl J Med. 1972;287:656– 663.
- 57. Cavanagh JB, Greenbaum D, Marshall AH, Rubinstein LJ. Cerebral demyelination associated with disorders of the reticuloendothelial system. Lancet. 1959;2:524–529.
- Chaisson RE, Griffin DE. Progressive multifocal leukoencephalopathy in AIDS. JAMA. 1990;264:79–82.
- Chandor SB, Forno LS, Wivel NA. Progressive multifocal leucoencephalopathy. J Neurol Neurosurg Psychiatry. 1965;28:260–271.
- 60. **Christensen E,** Fog M. A case of Schilder's disease in an adult with remarks to the etiology and pathogenesis. Acta Psychiatr Neurol Scand. 1955;30:141–154.
- Conomy JP, Beard NS, Matsumoto H, Roessmann U. Cytarabine treatment of progressive multifocal leukoencephalopathy. Clinical course and detection of viruslike particles after antiviral chemotherapy. JAMA. 1974;229:1313–1316.
- Conway B, Halliday WC, Brunham RC. Human immunodeficiency virus-associated progressive multifocal leukoencephalopathy: apparent response to 3'-azido-3'deoxythymidine. Rev Infect Dis. 1990;12:479–482.
- Cunningham ME, Kishore PR, Rengachary SS, Preskorn S. Progressive multifocal leukoencephalopathy presenting as focal mass lesion in the brain. Surg Neurol. 1977;8:448– 450.
- D'Agostino AN, Pease GL, Kernohan FW. Cerebral demyelination associated with polycythemia vera. J Neuropathol Exp Neurol. 1963;22:138–147.
- Davies JA, Hughes JT, Oppenheimer DR. Richardson's disease (progressive multifocal leukoencephalopathy). A study of four cases. Q J Med. 1973;42:481–501.
- 66. **Dawson DM**. Progressive multifocal leukoencephalopathy in myasthenia gravis. Ann Neurol. 1982;11:218–219.
- Deep WD, Fraumeni JF, Tashima CK, McDivitt R. Leukoencephalopathy and dermatomyositis in Hodgkin's disease. A case report. Arch Intern Med. 1964;113:635– 640.
- DelDuca V Jr, Morningstar WA. Multiple myeloma associated with progressive multifocal leukoencephalopathy. JAMA. 1967;199:671–673.
- 69. **Dolman CL,** Cairns AR. Leukoencephalopathy associated with Hodgkin's disease. Neurology. 1961;11:349–353.
- Dolman CL, Furesz J, Mackay B. Progressive multifocal leukoencephalopathy: two cases with electron microscopic and viral studies. Can Med Assoc J. 1967;97:8–12.
- Dupuis M, Fernandes Xavier FG, Gonsette RE, Brucher JM. Progressive multifocal leukoencephalopathy mimicking multiple sclerosis as the sole clinical manifestation of acquired immunodeficiency syndrome. Acta Neurol Belg. 1986;86:285–296.
- Egan JD, Ring BL, Reding MJ, Wells IC, Shuman RM. Reticulum cell sarcoma and progressive multifocal leukoencephalopathy following renal transplantation. Transplantation. 1980;29:84–86.
- Ellison GW. Progressive multifocal leukoencephalopathy (PML). I. Investigation of the immunologic status of a patient with lymphosarcoma and PML. J Neuropathol Exp Neurol. 1969;28:501–506.
- Farrell DF. The EEG in progressive multifocal leukoencephalopathy. Electroencephalogr Clin Neurophysiol. 1969;26:200–205.

- Fermaglich J, Hardman JM, Earle KM. Spontaneous progressive multifocal leukoencephalopathy. Neurology. 1970;20:479–484.
- Field AM, Gardner SD, Goodbody RA, Woodhouse MA. Identity of a newly isolated human polyomavirus from a patient with progressive multifocal leucoencephalopathy. J Clin Pathol. 1974;27:341–347.
- Gagne F, Bouchard JP, Bernier JP. Progressive multifocal leucoencephalopathy. observation with predominant pontocerebellar lesions and association with congenital immune deficiency. Acta Neuropathol. 1977;38:167–169.
- Fisher CM, Williams HW, Wing ES Jr. Combined encephalopathy and neuropathy with carcinoma. J Neuropathol Exp Neurol. 1961;20:535–547.
- Gallai M, Eckhardt A, Ambrozy G. On a case of progressive multifocal leukoencephalopathy accompanying hodgkin's disease. Psychiatr Neurol (Basel). 1963;145:356–368.
- Guilleux MH, Steiner RE, Young IR. MR imaging in progressive multifocal leukoencephalopathy. AJNR Am J Neuroradiol. 1986;7:1033–1035.
- Hayashi T, Sumiyoshi A, Tanaka M, Araki S, Minamishima Y. Progressive multifocal leukoencephalopathy. A case report with special reference to SV40 etiology. Acta Pathol Jpn. 1985;35:173–181.
- Headington JT, Umiker WO. Progressive multifocal leukoencephalopathy. A case report. Neurology. 1962;12:434–439.
- 83. Hecker R, Reid RT. Cerebral demyelination in Whipple's disease. Med J Aust. 1962;49:211–212.
- Hedley-Whyte ET, Smith BP, Tyler HR, Peterson WP. Multifocai, leukoencephalopathy with remission and five year survival. J Neuropathol Exp Neurol. 1966;25:176.
- Ho JL, Poldre PA, McEniry D, Howley PM, Snydman DR, Rudders RA, Worthington M. Acquired immunodeficiency syndrome with progressive multifocal leukoencephalopathy and monoclonal B-cell proliferation. Ann Intern Med. 1984;100:693–696.
- Hulette CM, Downey BT, Burger PC. Progressive multifocal leukoencephalopathy. Diagnosis by in situ hybridization with a biotinylated JC virus DNA probe using an automated histomatic code-on slide stainer. Am J Surg Pathol. 1991;15:791–797.
- Jakobsen J, Diemer NH, Gaub J, Brun B, Helweg-Larsen S. Progressive multifocal leukoencephalopathy in a patient without other clinical manifestations of AIDS. Acta Neurol Scand. 1987;75:209–213.
- Loken AC. Progressive multifocal leucoencephalography. A neuropathological and electronmicroscopical study of two cases. Acta Pathol Microbiol Scand Suppl. 1974;248 (suppl):127–132.
- Johnston RF, Green RA, Headington JT. Progressive multifocal leukoencephalopathy. Arch Intern Med. 1963;111:353–362.
- Jones HR Jr, Hedley-Whyte ET, Freidberg SR, Kelleher JE Jr, Krolikowski J. Primary cerebellopontine progressive multifocal leukoencephalopathy diagnosed premortem by cerebellar biopsy. Ann Neurol. 1982;11:199–202.
- Kepes JJ, Chou SM, Price LW Jr. Progressive multifocal leukoencephalopathy with 10-year survival in a patient with nontropical sprue. Report of a case with unusual light and electron microscopic features. Neurology. 1975;25:1006–1012.
- King JO, Hart DH, Sullivan JR, Surtees VM, Anderson RM. Progressive multifocal leukoencephalopathy. Clin Exp Neurol. 1981;17:125–134.
- Knight A, O'Brien P, Osoba D. "Spontaneous" progressive multifocal leukoencephalopathy. Immunologic aspects. Ann Intern Med. 1972;77:229–233.
- Krupp LB, Lipton RB, Swerdlow ML, Leeds NE, Llena J. Progressive multifocal leukoencephalopathy: clinical and radiographic features. Ann Neurol. 1985;17:344–349.
- Legrain M, Graveleau J, Brion S, Mikol J, Kuss R. Progressive multifocal leukoencephalopathy following kidney transplantation. J Neurol Sci. 1974;23:49–62.

Sudhakar et al: J Neuro-Ophthalmol 2015; 35: 296-305

Copyright © North American Neuro-Ophthalmology Society. Unauthorized reproduction of this article is prohibited.

- Lloyd OC, Urich H. Acute disseminated demyelination of the brain associated with lymphosarcoma. Lancet. 1959;2:529– 530.
- Lyon LW, McCormick WF, Shochet SS Jr. Progressive multifocal leukoencephalopathy. Arch Intern Med. 1971;128:420–426.
- Macher AM, Parisi JE, Aksamit AJ, Smirniotopoulos JG, Chase R, Lu AT, Bauserman SC, Grant KF, Nelson AM, Connor DH. Case for diagnosis. AIDS. Mil Med. 1986;151: M25–M32.
- Malas D, Weiss S. Progressive multifocal leukoencephalopathy and cryptococcal meningitis with systemic lupus erythematosus and thymoma. Ann Neurol. 1977;1:188–191.
- Manz HJ, Dinsdale HB, Morrin PA. Progressive multifocal leukoencephalopathy after renal transplantation. Demonstration of papova-like virions. Ann Intern Med. 1971;75:77–81.
- Marriott PJ, O'Brien MD, Mackenzie IC, Janota I. Progressive multifocal leucoencephalopathy: remission with cytarabine. J Neurol Neurosurg Psychiatry. 1975;38:205–209.
- Mathews T, Wisotzkey H, Moossy J. Multiple central nervous system infections in progressive multifocal leukoencephalopathy. Neurology. 1976;26:9–14.
- McCormick WF, Schochet SS Jr, Sarles HE, Calverley JR. Progressive multifocal leukoencephalopathy in renal transplant recipients. Arch Intern Med. 1976;136:829–834.
- 104. Miller JR, Barrett RE, Britton CB, Tapper ML, Bahr GS, Bruno PJ, Marquardt MD, Hays AP, McMurtry JG III, Weissman JB, Bruno MS. Progressive multifocal leukoencephalopathy in a male homosexual with T-cell immune deficiency. N Engl J Med. 1982;307:1436–1438.
- Morecki R, Porro RS. Progressive multifocal leukoencephalopathy. Identification of virions in paraffinembedded tissues. Arch Neurol. 1970;22:253–258.
- Mosher MB, Schall GL, Wilson J. Progressive multifocal leukoencephalopathy; positive brain scan. JAMA. 1971;218:226–228.
- Nagashima K, Yamaguchi K, Yasui K, Ogiwara H. Progressive multifocal leukoencephalopathy. neuropathology and virus isolation. Acta Pathol Jpn. 1981;31:953–961.
- O'Riordan T, Daly PA, Hutchinson M, Shattock AG, Gardner SD. Progressive multifocal leukoencephalopathyremission with cytarabine. J Infect. 1990;20:51–54.
- Parr J, Horoupian DS, Winkelman AC. Cerebellar form of progressive multifocal leukoencephalopathy (PML). Can J Neurol Sci. 1979;6:123–128.
- 110. Peters AC, Versteeg J, Bots GT, Boogerd W, Vielvoye GJ. Progressive multifocal leukoencephalopathy: immunofluorescent demonstration of simian virus 40 antigen in CSF cells and response to cytarabine therapy. Arch Neurol. 1980;37:497–501.
- 111. **Portegies P**, Algra PR, Hollak CE, Prins JM, Reiss P, Valk J, Lange JM. Response to cytarabine in progressive multifocal leucoencephalopathy in AIDS. Lancet. 1991;337:680–681.
- 112. **Price MJ**, Feldman RG, Adelberg D, Kayne H. Abnormalities in color vision and contrast sensitivity in Parkinson's disease. Neurology. 1992;42:887–890.
- 113. **Rhodes RH,** Ward JM, Walker DL, Ross AA. Progressive multifocal leukoencephalopathy and retroviral encephalitis in acquired immunodeficiency syndrome. Arch Pathol Lab Med. 1988;112:1207–1213.
- 114. **Rand KH,** Johnson KP, Rubinstein LJ, Wolinsky JS, Penney JB, Walker DL, Padgett BL, Merigan TC. Adenine arabinoside in the treatment of progressive multifocal leukoencephalopathy: use of virus-containing cells in the urine to assess response to therapy. Ann Neurol. 1977;1:458–462.
- 115. **Richardson EP Jr**, Johnson PC. Atypical progressive multifocal leukoencephalopathy with plasma-cell infiltrates. Acta Neuropathol Suppl. 1975;6(suppl);247–250.

- 116. **Rosenbloom MA**, Uphoff DF. The association of progressive multifocal leukoencephalopathy and sarcoidosis. Chest. 1983;83:572–575.
- 117. **Scherneck S,** Geissler E, Janisch W, Rudolph M, Vogel F, Zimmermann W. Isolation of a SV40-like virus from a patient with progressive multifocal leukoencephalopathy. Acta Virol. 1981;25:191–198.
- 118. Schlitt M, Morawetz RB, Bonnin J, Chandra-Sekar B, Curtiss JJ, Diethelm AG Jr, Whelchel JD, Whitley RJ. Progressive multifocal leukoencephalopathy: three patients diagnosed by brain biopsy, with prolonged survival in two. Neurosurgery. 1986;18:407–414.
- 119. **Sibley WA**. Demyelinating disease of the brain in chronic lymphatic leukemia: occurrence of a case in the husband of a patient with multiple sclerosis. Arch Neurol. 1961;5:300–307.
- 120. **Slavin ML,** Mallin JE, Jacob HS. Isolated homonymous hemianopsia in the acquired immunodeficiency syndrome. Am J Ophthalmol. 1989;108:198–200.
- 121. **Smith CR**, Sima AA, Salit IE, Gentili F. Progressive multifocal leukoencephalopathy: failure of cytarabine therapy. Neurology. 1982;32:200–203.
- 122. **Speelman JD**, ter Schegget J, Bots GT, Stam J, Verbeeten B Jr. Progressive multifocal leukoencephalopathy in a case of acquired immune deficiency syndrome. Clin Neurol Neurosurg. 1985;87:27–33.
- 123. Case records of the massachusetts general hospital. Weekly clinicopathological exercises. Case 13-1980. N Engl J Med. 1980;302:795–803.
- 124. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 32-1983. Acquired immunodeficiency syndrome and cranial-nerve abnormalities. N Engl J Med. 1983;309:359–369.
- 125. Trotot PM, Vazeux R, Yamashita HK, Sandoz-Tronca C, Mikol J, Vedrenne C, Thiébaut JB, Gray F, Cikurel M, Pialoux G. MRI pattern of progressive multifocal leukoencephalopathy (PML) in AIDS. Pathological correlations. J Neuroradiol. 1990;17:233–254.
- 126. **Horn GV**, Bastian FO, Moake JL. Progressive multifocal leukoencephalopathy: failure of response to transfer factor and cytarabine. Neurology. 1978;28:794–797.
- Vanderhaeghen JJ, Perier O. Progressive multifocal leukoencephalitis. Demonstration of viral particles by electron microscopy. Acta Neurol Psychiatr Belg. 1965;65:816–837.
- 128. **Vuia 0**. Progressive multifocal leucoencephalopathy and rosenthal fibres. Eur Neurol. 1976;14:198–208.
- 129. Weiner LP, Herndon RM, Narayan O, Johnson RT, Shah K, Rubinstein LJ, Preziosi TJ, Conley FK. Isolation of virus related to SV40 from patients with progressive multifocal leukoencephalopathy. N Engl J Med. 1972;286:385–390.
- 130. Weiner LP, Narayan O, Penney JB Jr, Herndon RM, Feringa ER, Tourtellotte WW, Johnson RT. Papovavirus of JC type in progressive multifocal leukoencephalopathy. rapid identification and subsequent isolation. Arch Neurol. 1973;29:1–3.
- 131. Weinstein VF, Woolf AL, Meynell MJ. Progressive multifocal leucoencephalopathy and primary hypersplenism. with a note on the association between disease of the reticuloendothelial system and progressive multifocal leucoencephalopathy. J Clin Pathol. 1963;16:405–418.
- 132. **Weitzman S,** Kaufman S, Wolpow E, Hinton RC, Richardson EP Jr. Case report. Simultaneous fungal and viral infection of the central nervous system. Am J Med Sci. 1978;276:127–132.
- 133. Wiley CA, Grafe M, Kennedy C, Nelson JA. Human immunodeficiency virus (HIV) and JC virus in acquired immune deficiency syndrome (AIDS) patients with progressive multifocal leukoencephalopathy. Acta Neuropathol. 1988;76:338–346.
- 134. **Willoughby E**, Price RW, Padgett BL, Walker DL, Dupont B. Progressive multifocal leukoencephalopathy (PML): in vitro cell-mediated immune responses to mitogens and JC virus. Neurology. 1980;30:256–262.
- 135. Wolinsky JS, Johnson KP, Rand K, Merigan TC. Progressive multifocal leukoencephalopathy: clinical pathological

correlates and failure of a drug trial in two patients. Trans Am Neurol Assoc. 1976;101:81–82.

- Woodhouse MA, Dayan AD, Burston J, Caldwell I, Adams JH, Melcher D, Urich H. Progressive multifocal leukoencephalopathy: electron microscope study of four cases. Brain. 1967;90:863–870.
- **Zurhein G,** Chou SM. Particles resembling papova viruses in human cerebral demyelinating disease. Science. 1965;148:1477–1479.
- 138. **Zu Rhein GM**. Association of papova-virions with a human demyelinating disease (progressive multifocal leukoencephalopathy). Prog Med Virol. 1969;11:185–247.
- Hamann KU, Shults WT, Hoyt WF. Impaired visual perception in progressive multifocal leukoencephalopathy; a clinical diagnosis based on sequential computerized axial tomography [in German]. Klin Monbl Augenheilkd. 1978;172:94–99.
- Mark AS, Atlas SW. Progressive multifocal leukoencephalopathy in patients with AIDS: appearance on MR images. Radiology. 1989;173:517–520.
- 141. Engsig FN, Hansen AB, Omland LH, Kronborg G, Gerstoft J, Laursen AL, Pedersen C, Mogensen CB, Nielsen L, Obel N. Incidence, clinical presentation, and outcome of progressive multifocal leukoencephalopathy in HIVinfected patients during the highly active antiretroviral therapy era: a nationwide cohort study. J Infect Dis. 2009;199:77–83.
- 142. Pandey A, Bandivdekar K, Ramchandani S, Ramchandani S. Progressive multifocal leukoence–phalopathy presenting as homonymous hemianopia in a patient with acquired immunodeficiency syndrome. Indian J Ophthalmol. 2012;60:574–576.
- 143. von Einsiedel RW, Fife TD, Aksamit AJ, Cornford ME, Secor DL, Tomiyasu U, Itabashi HH, Vinters HV. Progressive multifocal leukoencephalopathy in AIDS: a clinicopathologic study and review of the literature. J Neurol. 1993;240:391– 406.
- 144. Diller R, Thompson K. Visual loss secondary to acquired immunodeficiency virus-related progressive multifocal leukoencephalopathy demonstrating clinical improvement with highly active antiretroviral therapy. Optometry. 2007;78:63–70.
- 145. Yoganathan K, Brown D, Yoganathan K. Remission of progressive multifocal leukoencephalopathy following highly active antiretroviral therapy in a man with AIDS. Int J Gen Med. 2012;5:331–334.
- 146. **Herold TR**, Jakl V, Graser A, Eibl-Lindner K. Hemianopia and visual loss due to progressive multifocal leukoencephalopathy in natalizumab-treated multiple sclerosis. Clin Ophthalmol. 2012;6:1131–1133.
- McCalmont V, Bennett K. Progressive multifocal leukoencephalopathy: a case study. Prog Transpl. 2007;17:157–160.
- 148. Ayuso-Peralta L, Jiménez-Jiménez FJ, Tejeiro J, Vaquero A, Cabrera-Valdivia F, Madero S, Cabello A, García-Albea E. Progressive multifocal leukoencephalopathy in HIV infection presenting as Balint's syndrome. Neurology. 1994;44:1339– 1440.
- Moulignier A, de Saint Martin L, Mahieux F, Manifacier MJ, Dupont B. Balint's syndrome. Neurology. 1995;45:1030– 1031.
- 150. Uyama E, Uchino M, Ando M. Balint's syndrome. Neurology. 1995;45:2118–2119.
- 151. **Paytubi Gari C**, Lopez-Balaguer JM, Balmana J, Cadafalch J. Balint's syndrome secondary to progressive multifocal

leukoencephalopathy in a patient with acquired immunodeficiency syndrome [in Spanish]. Med Clin (Barc). 1998:111:357.

- 152. **Berger JR**, Whigham TE. Balint's syndrome in subacute HIV encephalitis. J Neurol Neurosurg Psychiatry. 1993;56:115.
- Schnider A, Landis T, Regard M. Balint's syndrome in subacute HIV encephalitis. J Neurol Neurosurg Psychiatry. 1991;54:822–825.
- 154. **Ouwens JP,** Haaxma-Reiche H, Verschuuren EA, Timens W, Steenhuis LH, de Boer WJ, van der Bij W; Groningen Lung Transplant Group. Visual symptoms after lung transplantation: a case of progressive multifocal leukoencephalopathy. Transpl Infect Dis. 2000;2:29–32.
- 155. Lewis AR, Kline LB, Pinkard NB. Visual loss due to progressive multifocal leukoencephalopathy in a heart transplant patient. J Clin Neuroophthalmol. 1993;13:237–241.
- 156. Whiteman ML, Post MJ, Berger JR, Tate LG, Bell MD, Limonte LP. Progressive multifocal leukoencephalopathy in 47 HIV-seropositive patients: neuroimaging with clinical and pathologic correlation. Radiology. 1993;187:233–240.
- 157. Rubin DI, Norris S, Flint R. Isolated pontine progressive multifocal leukoencephalopathy: unusual magnetic resonance imaging features. J Neuroimaging. 2002;12:63–66.
- 158. **Liptai Ž**, Papp E, Barsi P, Mihály I, Szalai E, Csomor J, Jelenik Z. Progressive multifocal leukoencephalopathy in an HIV-infected child. Neuropediatrics. 2007;38:32–35.
- 159. **Koralnik IJ,** Wüthrich C, Dang X, Rottnek M, Gurtman A, Simpson D, Morgello S. JC virus granule cell neuronopathy: a novel clinical syndrome distinct from progressive multifocal leukoencephalopathy. Ann Neurol. 2005;57:576–580.
- Zeller D, Markulin F, Monoranu CM, Solymosi L, Stoll G. Spreading along white matter tracts?—A case of progressive multifocal leukoencephalopathy with unusual MRI presentation. Clin Neurol Neurosurg. 2013;115:638–640.
- Hodel J, Outteryck O, Zéphir H, Rodallec M, Zins M, Vermersch P, Leclerc X. Cranial nerve involvement in infratentorial progressive multifocal leukoencephalopathy. Neurology. 2012;79:104–105.
- 162. **Martin JB**, Banker BQ. Subacute multifocal leukoencephalopathy with widespread intranuclear inclusions. Arch Neurol. 1969;21:590–602.
- 163. Sima AA, Finkelstein SD, McLachlan DR. Multiple malignant astrocytomas in a patient with spontaneous progressive multifocal leukoencephalopathy. Ann Neurol. 1983;14:183–188.
- Graff-Radford J, Robinson MT, Warsame RM, Matteson EL, Eggers SD, Keegan BM. Progressive multifocal leukoencephalopathy in a patient treated with etanercept. Neurologist. 2012;18:85–87.
- 165. **Berger JR**, Aksamit AJ, Clifford DB, Davis L, Koralnik IJ, Sejvar JJ, Bartt R, Major EO, Nath A. PML diagnostic criteria: consensus statement from the AAN neuroinfectious disease section. Neurology. 2013;80:1430–1438.
- 166. **Yousry TA**, Pelletier D, Cadavid D, Gass A, Richert ND, Radue EW, Filippi M. Magnetic resonance imaging pattern in natalizumab-associated progressive multifocal leukoencephalopathy. Ann Neurol. 2012;72:779–787.
- 167. **Chalkley JJ**, Berger JR. Progressive multifocal leukoencephalopathy in multiple sclerosis. Curr Neurol Neurosci Rep. 2013;13:408-013-0408-6.
- Rubant SA, Ludwig RJ, Diehl S, Hardt K, Kaufmann R, Pfeilschifter JM, Boehncke WH. Dimethylfumarate reduces leukocyte rolling in vivo through modulation of adhesion molecule expression. J Invest Dermatol. 2008;128:326–331.