Elderly Patients on Immunosuppressive Medications

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Abstract
Unlike primary central nervous system lymphomas (PCNSLs) in patients with AIDS or organ transplants, PCNSLs in the elderly are usually not considered to be mediated by Epstein Barr virus (EBV); hence, diagnostic studies for EBV are not routinely performed. We encountered 4 patients, 65 years or older, who developed EBV-associated PCNSLs and who had been treated with a variety of immunosuppressive drugs for different autoimmune/collagen vascular disorders, including autoimmune polyneuropathy (mycophenolate mofetil for 5 years), polymyositis (prednisone for 16 years with intermittent methotrexate, azathioprine, and cyclophosphamide), myasthenia gravis (azathioprine >10 years), and rheumatoid arthritis (methotrexate >10 years). All patients had multifocal, necrotic brain lesions typical of EBV-positive PCNSLs on neuroimaging. Withdrawing immunosuppressives lead to PCNSL regression in some patients. The patient who had received mycophenolate mofetil was treated successfully for his EBV-associated PCNSL with rituximab and methotrexate, but later developed fatal systemic malignant melanoma, which was likely immunosuppression related.

The striking feature of these cases is the variety of underlying diseases—and hence accompanying medications—that can be associated with EBV-associated PCNSLs. They serve as a diagnostic alert for neuropathologists and suggest that increased testing of PCNSLs for EBV by immunohistochemistry or in situ hybridization may be warranted in any patient on any immunosuppressive medication, but particularly the elderly.

Key Words: Azathioprine, Cell Cept, Epstein Barr virus, Immunosuppressant, Immunosuppression, Malignant melanoma, Mycophenolate mofetil, Prednisone, Primary lymphoma.

INTRODUCTION
Primary central nervous system lymphomas (PCNSLs) are aggressive lymphoid neoplasms that are almost always of B-cell origin (1). Although they were rare 30 years ago and accounted for only approximately 1% of all primary brain tumors (2), the incidence of PCNSLs increased sharply in the era of acquired immunodeficiency syndrome (AIDS); this caused some authors to predict that PCNSLs would surpass glioblastomas as the most frequent brain tumor type by the year 2000 (3).

The advent of highly active retroviral therapy has made this possibility not come true, and a decrease in AIDS-related PCNSLs had already been detected by 2002 (4). Primary central nervous system lymphomas in immunocompetent patients have not shown a similar decline in incidence, nor have those that occur in the setting of solid organ transplantation (4).

Primary central nervous system lymphomas that arise in immunocompetent individuals differ considerably from those seen in the setting of severe immunocompromising conditions, particularly AIDS. These differences include the usual age of the patient affected (5), the neuroimaging features of the lesion(s) (5, 6), and clinical outcomes (5, 7).

A signature feature of PCNSLs in immunosuppressed patients (AIDS-related and transplantation-related) as opposed to PCNSLs in immunocompetent individuals is the almost uniform association with Epstein Barr virus (EBV) in the immunosuppressed group (8). This also affords the opportunity to use cerebrospinal fluid (CSF) polymerase chain reaction (PCR) testing for EBV as a less invasive diagnostic tool to detect PCNSLs in immunosuppressed, but not in immunocompetent, patients.

For PCNSLs related to organ transplantation, the degree of immunosuppression of the patient can often be manipulated via reduction or withdrawal of the medications. Extended months of survival or even long-term remission can be achieved, although usually additional antilymphoma therapies are also necessary to control the PCNSL.

We present 4 cases of elderly patients older than 65 years whose ages were typical for PCNSLs in immunocompetent patients but whose tumors showed neuroimaging features typical for PCNSLs in immunocompromised patients (i.e. multifocal and ring-enhancing lesions), which prompted some clinical confusion before biopsy confirmation of the diagnosis. Epstein Barr virus positivity was found in the lymphoma tissue by in situ hybridization studies for Epstein Barr early regions (EBERs); the patients also had strikingly high CSF PCR levels for EBV when this was tested. All patients were under treatment with immunosuppressive medications for a variety of nontransplantation,
non-AIDS-related disorders. Survival durations ranged from 1 to 13 months after withdrawal or reduction in immunosuppressive medications; these are generally longer than in patients with AIDS-related PCNSLs, even in the highly active retroviral therapy era (7). In one patient, there was a total remission of his PCNSL based on resolution of clinical, neuroimaging, and CSF PCR EBV titers; he died because a second neoplasm (malignant melanoma), which was also likely related to his immunosuppressive medications, mycophenolate mofetil, and rituximab. To our knowledge, this case represents the first association between development of malignant melanoma and either of these medications but follows very recent reports linking malignant melanoma with another immunosuppressive drug, natalizumab (9, 10).

MATERIALS AND METHODS

Tissue sections were formalin-fixed and paraffin-embedded, and 4-μm-thick sections were cut. Sections were selected, stained with Harris hematoxylin and eosin, by immunohistochemistry for CD20 and CD3, and by in situ hybridization for EBER (for EBV-encoded RNA, digoxigenin-labeled EBER riboprobe; all from Ventana, Tucson, AZ). Immunohistochemistry was also performed using antibodies to S100 (polyclonal), HMB-45 (monoclonal), kappa and lambda light chains (polyclonal), and CD138 (monoclonal) (all from Dako, Carpinteria, CA).

In situ hybridization for EBER was performed on a Ventana autostainer (Ventana, Tucson, AZ) following the manufacturer’s recommendations, as listed in the following steps: Deparaffinization of 6-μm-thick sections, cell conditioning, and protease treatment followed by application of the EBER probe with digoxigenin recognition system and light hematoxylin counterstain for 4 minutes.

Immunoglobulin heavy chain gene rearrangement and clonal T-cell receptor γ gene rearrangement analysis using PCR testing and capillary electrophoresis methods were conducted. In this assay, the immunoglobulin heavy chain gene was analyzed using the InVivoScribe Technologies (San Diego, CA) IGH Gene Rearrangement Assay kit, and T-cell γ receptors were analyzed using the InVivoScribe Technologies T Cell Receptor Gamma Gene Rearrangement Assay kit. Three proprietary IgH gene primer pairs, which are located on FR1-JH, FR2-JH, and FR3-JH, and 2 proprietary T-cell γ primer pairs, which are located on Vγ 1–8, 9 and Jγ1/2, were used in conjunction with PCR to amplify portions of the IgH gene and the TCRγ gene according to manufacturer’s instructions (95°C for 7 minutes, 94°C for 30 seconds, 55°C for 30 seconds, 72°C for 1 minute for 35 replicates, 72°C for 10 minutes, 4°C forever). A region of the HLA-DQα gene is also amplified from each patient sample as a DNA control. The resulting PCR products are then separated and analyzed for peak presence using the

![FIGURE 1. Case 1. (A, B) Magnetic resonance imaging (MRI) scan demonstrates several of this patient’s ring-enhancing lesions, located in the left temporal lobe, left posterior frontal lobe near the vertex, right basal ganglia, and right corpus callosum. Note the edema surrounding the ring-enhancing lesions. T1-weighted coronal MRI with gadolinium. (C) Biopsy shows high-grade, highly necrotic, lymphoma. The lymphoma was immunopositive for CD20. Hematoxylin and eosin stain, original magnification: 100×. (D) Biopsy demonstrates strong nuclear signal by in situ hybridization for Epstein Barr early region (EBER), documenting that this was an Epstein Barr virus (EBV)-associated lymphoma. Digoxigenin-labeled EBER riboprobe for EBV-encoded RNA with light hematoxylin counterstain, original magnification: 600×.](image-url)
Beckman Coulter (Beckman Coulter, Inc, Fullerton, CA) Vidiera Nucleic Sample Detection capillary electrophoresis analysis and software system.

**CASE HISTORIES**

**Case 1**

The patient was a 65-year-old man with a 10-year history of an immune-mediated small fiber neuropathy (autoimmune polyneuropathy) that manifested predominantly as autonomic dysfunction, sensory loss, and gait imbalance. At diagnosis in 1996, he was briefly treated with high-dose prednisone alone; he then received a combination of prednisone (9–30 mg/day) and azathioprine (dose titrated to 200 mg/day) for 2 years before transitioning to a combination of prednisone (6–35 mg/day) and methotrexate (7.5–30 mg weekly) for an additional 3 years. Mycophenolate mofetil (MMF; CellCept, Hoffmann-La Roche Inc., Nutley, NJ) was initiated in January 2001 (dose titrated to 2,500 mg/day), and he was able to taper off of prednisone 10 months later in October 2001. His medical history also included remote granulomatous lung disease, reactive airway disease, and coronary artery disease.

In October 2006, he presented with a 6- to 12-week history of slowly progressive gait imbalance, word finding difficulties, alexia, mood swings, and a 1-week history of low-grade fever and diplopia. There was a 5-pound weight loss during the previous month. During his hospital admission, laboratory data showed a white blood cell count of 10.4 and a sedimentation rate of 51. Cerebrospinal fluid studies demonstrated 61 white blood cells, protein 61, and glucose 67.

Computed tomographic studies of chest and abdomen showed only multiple calcifications in mediastinal lymph nodes, liver, and spleen. Neuroimaging revealed 7 ring-enhancing brain lesions (Figs. 1A, B). CSF cytology showed atypical cells, flow cytometry revealed polyclonal and T-cell populations, and CSF PCR testing for EBV was positive (7,982 copies viral DNA/ml). He underwent a stereotactically guided left posterior temporoparietal craniotomy on November 3, 2006, with excision of one of the enhancing lesions. Biopsy showed high-grade, highly necrotic B-cell lymphoma (Fig. 1C) that was immunopositive for CD20 and showed strong nuclear signal by in situ hybridization for EBER, documenting that it was an EBV-associated lymphoma (Fig. 1D). A monoclonal B-cell population was detected by PCR gene rearrangement studies (Fig. 2, IgH gene rearrangement illustrated).

Rituximab was started in November 6, 2006, and the patient received dexamethasone for brain edema. Mycophenolate mofetil (CellCept) was tapered and discontinued within 1 week of the lymphoma diagnosis. He was hospitalized soon thereafter (December 2006) for diarrhea and complications of his therapy, including cytomegalovirus (CMV) enteropathy (PCR was positive for virus on biopsy), probable interstitial pneumonia secondary to CMV, neutropenia and thrombocytopenia thought to be due to his CMV infection, nephrotic syndrome secondary to membranous glomerulonephritis (needle biopsy of the kidney on December 27, 2006), hemorrhagic cystitis due to BK virus (urine positive by PCR), and EBV-related hyperplasia of the colon (proven by in situ hybridization) on colonic biopsy (December 18, 2006). Repeat CSF PCR for EBV on December 26, 2006 showed no detectable viral genome. Dexamethasone was discontinued, and he recovered on intravenous and oral ganciclovir.

Thereafter, he received rituximab 375 mg/m² weekly for 6 doses then 750 mg/m² for 6 doses achieving a major partial radiographic response in his brain lesions and clinical improvement. During treatment, however, he was noted to have worsening ataxia and a new left lower extremity weakness, with new right periventricular enhancing mass. On February 7, 2007, his CSF PCR for EBV showed 56,160 viral copies/ml. He was admitted for high-dose methotrexate therapy. By February 15, 2007, his CSF viral load had returned to low levels—7,370 viral copies/ml. His autoimmune polyneuropathy was stable during this period, with treatment with neurontin and physical therapy. Repeat CSF PCR for EBV on March 5, 2007 and March 26, 2007 (his last recorded assessment) showed no detectable viral genome.

By May 2007, he had received 4 cycles of high-dose methotrexate and 12 cycles of rituximab, with good response and decrease in size of his CNS lesions; the patient complained only of headache. By June 2007, he had completed 7 cycles of high-dose methotrexate, and at that time, he was deemed to be in complete remission from his EBV-associated PCNSL. The patient was being maintained on monthly high-dose steroid pulses when in October 2007, he complained of new onset of bone pain, and bone scan showed multifocal hypermetabolic bone lesions. Core biopsy of the spine on October 4, 2007 (at that time, approximately 1 year after MMF treatment) revealed metastatic malignant melanoma with numerous cells containing melanin pigment and immunoreactivity for S100 protein, Melan-A, and HMB-45.

![FIGURE 2](image.png)
(Figs. 3A–C). No lymphoma was present in the biopsy. No cutaneous or intraocular primary melanotic lesion was identified, and there was no medical history of a melanotic skin lesion.

Within weeks of the melanoma diagnosis, he developed symptomatic metastatic disease involving liver, kidney, and lung. He was deemed not to be a candidate for further medical therapy and received comfort care only. He died in December 2007, approximately 13 months after diagnosis of his PCNSL. No autopsy was performed.

Case 2

This was a 65-year-old white woman with a 16-year history of polymyositis, treated continuously since diagnosis, with a prednisone at varying doses and intermittently with methotrexate, azathioprine, and cyclophosphamide. For 3 years preceding presentation, cyclophosphamide was provided in addition to a minimum dose of 20 mg prednisone a day. Three weeks before presentation, cyclophosphamide was discontinued because of pancytopenia. Medical history also included pulmonary fibrosis secondary to methotrexate,

(Figures 3 and 4).
severe aortic stenosis, hypothyroidism after treatment for hyperthyroidism, and gastroesophageal reflux disease.

The patient was transferred to University of Colorado Hospital on September 5, 2006, with a 3-day history of confusion, word finding difficulty, right greater than left upper extremity paresthesias and incoordination, and gait imbalance. She was found to have a ring-enhancing mass along the left splenium of the corpus callosum (Fig. 4A). Scattered hyperintensities on long TR-weighted sequences were also seen in bilateral subcortical and periventricular white matter, with at least 2 lesions forming transcallosal bands. Biopsy of the corpus callosum lesion on September 19, 2006, confirmed a high-grade, diffuse large B-cell lymphoma that showed strong diffuse immunoreactivity for CD20 (Fig. 4C) and was positive by in situ hybridization for EBV (Fig. 4D). Gene rearrangement studies showed rearrangements of both immunoglobulin heavy gene and the T-cell receptor gamma gene by PCR (Fig. 5). This so-called “lineage infidelity” denotes the clonal rearrangements of both IgH and TcR-γ in the same lymphoma; this feature is seen in up to 10% of both T-cell and B-cell lymphomas by PCR testing and may reflect either “dual rearrangement involving neoplastic B-cells” or “the presence of oligoclonal expansion of tumor-infiltrating T-lymphocytes” (11). Postbiopsy, CSF PCR testing for EBV was positive, with a high titer (46,116 copies of viral DNA/ml).

Initial CT scan of the chest/abdomen/pelvis on September 6, 2006, had shown a right adrenal mass, 2 consolidative lung masses (in the left upper and right lower lobes), and ground-glass opacity of the lungs. Chest x-rays done at the transferring hospital were felt to be unchanged from baseline chest x-rays and chest CT scans; these findings were attributed to long-standing pulmonary fibrosis. At this time, the adrenal mass was thought to be benign. Hence, her initial staging examination was felt to be negative and that she met the criteria for a PCNSL. After a large right paraspinal mass was seen on staging magnetic resonance imaging of the spine, however, repeat body CT scans on September 28, 2006, found extensive metastatic disease to lungs, adrenals, mesentery, perinephric adipose, right paraspinal region, right chest wall, and vertebrae. Rituximab and treatment for community-acquired pneumonia were initiated. Bone marrow biopsy on October 2, 2006 showed hypocellular marrow with dyserythropoiesis and increased immature myeloid cells. Due to widespread disease and declining respiratory status, the family requested comfort care only. The patient died on October 5, 2006, 1 month after presentation.

Full autopsy demonstrated extensive lymphoma involving the lungs, adrenal glands, bilateral kidneys, the hepatic surface, chest wall, mediastinal lymph nodes, and serosa of the small bowel. The brain demonstrated translucent leptomeninges without hemorrhage or infiltrates. Coronal sections revealed a friable, ill-defined, partially necrotic yellowish lesion (3.5 × 3.5 × 3.0 cm) in the splenium of the corpus callosum (Fig. 4B). Other areas of white matter were less obviously involved grossly; however, on microscopic examination, cohesive masses of lymphoma cells, perivascular lymphoma cell collections, and individual lymphoma cell infiltration of white matter were identified throughout the brain at all levels. Only 2 of 22 sampled sections failed to show histological evidence of PCNSL, underscoring the “whole brain” nature of the disease.

Case 3

The patient was an 80-year-old man with a medical history of myasthenia gravis diagnosed in the early 1990s. At that time, he had presented with ocular complaints and had been placed on azathioprine (Imuran) 100 mg twice daily. He had undergone thymectomy approximately 9 years before admission. He had undergone thymectomy approximately 9 years before admission. His recent problems related to a 2-week history of gradual slurring of speech and right lower face droop, first noticed by a friend. On the morning of admission, he also...
had an episode of complete loss of speech for approximately 10 minutes, followed by persistently slurred speech, which prompted him to seek medical attention. He reported no weakness. He was admitted to the hospital for further workup.

Cranial CT scan showed 2 large lesions, 2 to 4 cm in diameter, in the right parieto-occipital and left parietal region. Magnetic resonance imaging with gadolinium showed a ring-enhancement pattern in both areas (Figs. 6A, B). These were presumed to be metastatic lesions; hence, CSF PCR testing for EBV was not considered. Thoracic, abdomen, and pelvic CT scanning showed a 7-mm-diameter nodule in the left lower lobe of the lung, bilateral kidney cysts, and an enlarged prostate. There was otherwise no evidence of a primary lesion. A CT-guided biopsy of the left lower lung nodule was considered, but a thoracotomy would have been required to reach the lesion. The patient instead elected to undergo a craniotomy and biopsy of the right parieto-occipital mass. The diagnosis was high-grade, B-cell lymphoma that was positive with in situ hybridization probe for EBER (Figs. 6C–E). This EBV-related PCNSL was tested for clonality, but no evidence was found for a monoclonal or polyclonal B-cell or T-cell population by immunoglobulin heavy chain or T-cell receptor gamma locus PCR. This testing was performed retrospectively on formalin-fixed tissue, and, as is always the case, the negative result on PCR testing of formalin fixed tissue could not entirely exclude the presence of a monoclonal population in the specimen.

The patient did well initially but received his care elsewhere, and the details of his medical course and treatment from that point on were not available. He died, however, 8 months later, with the cause of death listed as thrombophlebitis. No autopsy was performed. This case was mentioned briefly in a previous publication by one of the authors (B.K.D.) (12).

**Case 4**

The patient was a 78-year-old woman whose case was seen in consultation by one of the authors (C.G.) and whose medical history was significant for long-standing rheumatoid arthritis. She had been treated for this disease with standard dose methotrexate for more than 10 years, but no other details regarding the specifics of her medications were known. In June 2002, she presented with neurological symptoms to an outside hospital and was found to have 10 or more multiple CNS-enhancing lesions with central necrosis.

**FIGURE 6.** Case 3. (A, B) Magnetic resonance imaging scan demonstrates a discrete right parieto-occipital mass with surrounding edema (A) and a second, ring-enhancing left frontal lobe lesion (B). (C) Photomicrograph illustrates the high-grade, cytologically monomorphic lymphoma with prominent mitotic figures. Hematoxylin and eosin stain, original magnification: 600×. (D) The lymphoma shows strong diffuse immunostaining for CD20. Note the negative blood vessels (BV) in the tumor. Immunohistochemistry with light hematoxylin counterstain, original magnification: 600×. (E) Lymphoma nuclei demonstrate a strong positive signal with the Epstein Barr early region (EBER) in situ hybridization probe. Digoxigenin-labeled EBER riboprobe for Epstein Barr virus–encoded RNA; original magnification: 600×.
Biopsy of one of these cerebral lesions was undertaken and it revealed 2 processes. The first was that of cerebral toxoplasmosis with extensive necrosis, vascular thrombosis, large numbers of tachyzoites, and occasional cysts characteristic of this disease. Intimately associated with this lesion was a polymorphous, lymphoplasmacytic EBV-associated lymphoproliferative disorder (Fig. 7). The neoplastic process was immunopositive for CD138, both kappa and lambda (and hence was not clonal), and showed strong nuclear reaction for EBV by in situ hybridization (Fig. 7).

The patient received specific treatment for her toxoplasmosis, and methotrexate was stopped, but no additional treatment for a lymphoproliferative disorder was given. Her neurological deficits markedly improved. Approximately 3 months later, however, she developed renal failure and subsequent multiorgan failure attributable to her rheumatoid arthritis and died.

An autopsy was performed, and the brain was referred to one of us for consultation (C.G.). Microscopic examination disclosed that active necrotizing granulomatous vasculitis was still identifiable, but both of the patient’s disorders had responded to therapy. No residual Toxoplasma species could be identified, and the polymorphous, lymphoplasmacytic EBV-associated lymphoproliferative disorder had almost completely resolved. Epstein Barr virus studies were conducted on multiple autopsy blocks and were negative.

**DISCUSSION**

Mycophenolate mofetil (CellCept) is a widely used oral immunosuppressive agent that suppresses lymphocyte proliferation via inhibiting an enzyme in the synthesis of guanosine nucleotides. Mycophenolate mofetil is used in solid organ transplantation recipients to prevent rejection and,
because it does not cause neutropenia or anemia, is starting to be used more frequently in patients with myasthenia gravis and other autoimmune disorders. It is becoming apparent that the drug is not without risk because there have been several reports of the development of PCNSL in persons treated with MMF. O’Neill et al detailed 4 patients who developed CNS lymphoproliferative disorders associated with MMF use; these patients (aged 57 to 88 years) had CNS vasculitis, relapsing polychondritis, myasthenia gravis, or dermatomyositis (13, 14). Patients with lupus erythematosus have also been reported with MMF-related PCNSLs (15, 16). The drug is considered to have fewer side effects than steroids and thus to be “steroid-sparing” (17), thereby prompting a widening variety of conditions to be treated with MMF. Waning immunity with age may plausibly interact with the added immunosuppression afforded by the MMF to yield increased risk of PCNSL. The duration of receipt of the drug and other unknown host factors may also influence the risk.

In the study by O’Neill et al (13), the duration of receipt of drug before PCNSL development was 8, 11, 37, and 46 months. Two of the 4 patients had polymorphous lymphoplasmacytic infiltrates of the brain and 2 had monomorphic B cell PCNSLs. In situ hybridization for EBER was positive in all 4 patients. As in our case 1, whose PCNSL resolved with rituximab and high-dose methotrexate therapy, all 4 of the patients in that report responded after MMF withdrawal and administration of rituximab (13). This ability to achieve possible successful therapeutic intervention underscores the importance of the neuropathologist for recognizing this association between the patient’s immunosuppressive medication and the development of their EBV-associated PCNSL. It also may suggest that the presence or absence of clonality does not directly influence, or predict, which patients with PCNSLs might respond to withdrawal of their MMF.

Fortunately, the vast majority of patients on MMF regimens do not develop PCNSLs, and the drug has proven clinical efficacy. In a trial of MMF treatment for 12 patients with dermatomyositis who were unresponsive to other medications, Edge et al (17) found that 10 of the 12 patients manifested clinical improvement in their dermatomyositis on MMF, most within 4 to 8 weeks after drug initiation. Only 1 of the 12 developed PCNSL, which occurred 13 months after starting MMF (17); also reported by Waldman and Callen (18). Fortunately, this PCNSL resolved during a 2-month period after cessation of the drug, without any further therapy (18). Because there are no current methods to predict which individual patient will develop PCNSL, increased vigilance is necessary for all patients on MMF.

Unfortunately, MMF is not the only immunosuppressive drug for which vigilance is necessary. Rare cases of PCNSLs developing in patients with myasthenia gravis who had been treated with long-term azathioprine have appeared (19). Case 3 of the present report with a 10-year duration of treatment has been previously briefly mentioned in a review article (12). Our case 4 also had had a long duration of treatment (i.e. greater than 10 years treatment of rheumatoid arthritis with methotrexate), and our case 2 had a 16-year history of polymyositis treated continuously since diagnosis with varying doses of prednisone and intermittently with other immunosuppressives. As noted above, decade-long treatment was not a prerequisite for the development of PCNSLs, at least with MMF usage; 2 of the 4 patients reported by O’Neill et al developed PCNSL within the first year after starting the drug (13). Hence, vigilance for EBV-related PCNSLs on the part of clinicians and pathologists must start soon after commencing treatment with any of these immunosuppressive drugs and must continue for the full duration of time that the patient is receiving treatment.

Finally, this report underscores the point that PCNSLs are not the only malignancy associated with the use of these drugs. The current study details for the first time a possible association between malignant melanoma and MMF use. It must be noted that a firm association cannot be made between melanoma development and MMF use because the patient was diagnosed with the metastatic melanoma 12 months after cessation of this drug. Patients on MMF trials are usually excluded if they have an active malignancy (17), and our patient had no known cancer and no known melanocytic cutaneous lesion at the time he was placed on MMF for his autoimmune polyneuritis. He eventually died due to metastatic malignant melanoma, not PCNSL.

Malignant melanoma is a well-known, non-AIDS defining malignancy seen in both HIV/AIDS patients and transplant recipients (20). When it occurs in transplant recipients, it can develop de novo many years after receiving the transplant (21) or a preexistent melanocytic lesion can become activated and have accelerated growth after the patient starts receiving immunosuppressive medications to facilitate organ retention. Malignant melanoma has also very recently been reported as a complication in 3 patients treated for multiple sclerosis with the immunosuppressive drug, natalizumab (9, 10). These reports come in the wake of previous reports linking this same multiple sclerosis medication to the development of progressive multifocal leukoencephalopathy (22–24).

In conclusion, PCNSLs mediated by EBV are characteristic of patients with AIDS or organ transplantation but are seldom found in immunocompetent individuals by in situ hybridization techniques (1, 25). Although elderly persons are a second, well-known patient group for PCNSLs, the disorder in the elderly has a differing etiology from HIV-related PCNSLs (26, 27). Primary central nervous system lymphomas in patients considered “immunocompetent” and not associated with HIV in the past have infrequently been positive for EBV by in situ hybridization techniques (8, 25). Hence, tumor tissue from PCNSLs in patients considered “immunocompetent” (i.e. those who are HIV-negative and not transplant recipients) has seldom been routinely tested for EBV in most neuropathology laboratories at the time of biopsy.

The cases in this report serve as a diagnostic alert for neuropathologists. Increased testing of PCNSLs for EBV by immunohistochemical or in situ hybridization may be warranted in any patient on any immunosuppressive medication. This is particularly true for elderly patients, but younger individuals such as those reported by Edge et al (17), Waldman and Callen (18), and Finelli et al (15), who were 40 and 42 years old, respectively, have been reported. Unknown
host factors in addition to advanced age may be operative in some patients to increase their risk for PCNSLs with immunosuppressive drug treatment.

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