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Progressive Multifocal Leukoencephalopathy After Fludarabine Therapy for Low-Grade Lymphoproliferative Disease

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Fludarabine is becoming the initial therapy for low-grade lymphoproliferative malignancies, such as CLL and follicular lymphoma. Fludarabine is highly immunosuppressive in addition to being myelosuppressive and has been associated with neurotoxicity. Progressive multifocal leukoencephalopathy (PML) is an infection with JC virus of the white matter of the central nervous system seen mostly in immunosuppressed patients. We describe two patients treated with fludarabine who developed PML. Immunolabeling was positive for JCV in both patients, but PCR was repeatedly negative in one of them. We suggest that fludarabine may increase the risk of PML in patients with lymphoproliferative diseases. Am. J. Hematol. 70:51–54, 2002. © 2002 Wiley-Liss, Inc.

Key words: fludarabine; lymphoproliferative diseases; chronic lymphocytic leukemia; JC virus; progressive multifocal leukoencephalopathy

INTRODUCTION

Indolent lymphoproliferative diseases such as chronic lymphocytic leukemia (CLL) and follicular low-grade non-Hodgkin's lymphomas (NHL) are common malignancies, especially in the elderly. These diseases are incurable with current therapy [1]. The nucleoside analog fludarabine phosphate is fast becoming the first-line treatment of choice for such diseases [2]. Treatment with fludarabine has the best overall response rates and increases disease-free survival, although overall survival may not be prolonged [3]. The adverse effect profile of fludarabine is different from regimens employing alkylating agents that have been traditionally used for indolent lymphoproliferative disorders. Adverse effects include immunosuppression on top of myelosuppression, leading to increased risk of serious infection [4] and neurotoxicity [5]. Administration of fludarabine to patients who are more likely to have neurological problems due to their age and who have a disease that itself causes immunodeficiency, therefore, is fraught with difficulties. We describe two patients with indolent lymphoproliferative diseases treated with fludarabine who developed rapidly progressive and ultimately fatal neurological disorders. Autopsy examination revealed progressive multifocal leukoencephalopathy (PML) caused by JC virus. We raise the difficult question of whether fludarabine may increase the known risk of patients with lymphoproliferative diseases to develop PML.

CASE REPORT 1

A 74-year-old HIV-negative male with a 6-year history of questionable bile duct carcinoma with biliary stent placement and a 5-year history of indolent CLL was admitted to the University of Wisconsin Hospital and Clinics because of partial bilateral visual loss and increasing ataxia. Other history included coronary artery disease with bypass surgery 16 years previously, cerebrovascular disease with left carotid

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endarterectomy 6 years previously, chronic atrial fibrillation with an episode of blindness in the right eye 4 years previously, and life-threatening hemorrhage while on warfarin. Three months prior to the admission, the patient had received fludarabine phosphate, 25 mg/m^2/day for 5 days, for intra-abdominal lymphadenopathy and lymphocytic infiltration of the liver associated with biliary tract obstruction despite external drainage. The absolute lymphocyte count dropped from 16.0×10^9/L to 4.0×10^9/L. Immunoglobulin levels remained in the normal range. Over the next 4 weeks, the patient developed progressive disequilibrium. Magnetic resonance imaging (MRI) of the brain revealed two small lesions in the cerebellar white matter and extensive peri-ventricular white matter changes thought to be ischemic in nature. When the ataxia progressed and dysphagia and gradual visual loss were noted, a repeat MRI showed new white matter lesions in the frontal lobe but otherwise stable disease. Fludarabine neurotoxicity was suspected, but ischemia could not be ruled out. Therefore, anticoagulation was started. These neurologic symptoms continued to worsen, and the patient expired 2 weeks later. Autopsy revealed bilateral, multifocal, irregular, chalky white, soft, granular white matter lesions. Microscopically, these lesions were characterized by patches of white matter breakdown, foamy macrophages, large reactive astrocytes with bizarre nuclei, and oligodendrocytes containing enlarged homogenous amphophilic nuclei. Immunolabeling with anti-JC virus antibody was strongly positive in the enlarged nuclei of the oligodendrocytes. Microscopy demonstrated infiltration by CLL in multiple organs, including liver and periportal nodes. In addition, there was co-existing infiltration of major hepatic ducts with bile duct carcinoma.

CASE REPORT 2

A 63-year-old HIV-negative male was diagnosed with stage IV follicular mixed malignant lymphoma at the Landspitalinn University Hospital. A partial response (PR) was obtained after 6 monthly cycles of fludarabine (25 mg/m^2/day for 5 days). Gradual progression led to re-treatment 6 months later with chlorambucil and prednisolone (5-week cycles). PR was obtained after 6 cycles. Two months later, when the patient again showed disease progression, therapy with fludarabine, mitoxantrone, and dexamethasone (FND) was instituted. Once again, PR was seen after 6 cycles. The patient's absolute lymphocyte count had been persistently in the $(0.5-1.0) \times 10^9$/L range following the first course of fludarabine and dropped even lower, to $(0.3-0.7) \times 10^9$/L, with FND. Shingles developed during the initial course of FND that responded to acyclovir therapy. After the 2nd cycle of FND, intermittent low-grade fevers, night sweats, and oral ulcers with dysphagia developed that were unresponsive to acyclovir. Cultures and PCR for herpes simplex were negative. These symptoms continued intermittently, and varicella zoster also re-activated twice in the same dermatome. Progressive memory loss and right-sided visual disturbances were noted shortly thereafter. A brain MRI revealed a left-sided parieto-occipital lesion suggestive of PML. Increased anxiety and agitation ensued, eventually leading to unresponsiveness. Repeat MRI confirmed progressive leukodystrophy. The patient died shortly thereafter. At autopsy, bilateral subcortical demyelination, abnormal astrocytes with hyperchromatic nuclei, and oligodendrocytes with enlarged nuclei and "ground glass" appearance were noted, diagnostic of PML (Fig. 1). Inflammatory infiltrate was sparse. Although PCR of spinal fluid and brain tissue for JC virus was repeatedly negative, immunolabeling of glial cells with anti-JC virus antibody was strongly positive (Fig. 2).

DISCUSSION

PML is a progressive demyelinating disorder of the central nervous system [6], caused by opportunistic infection with JC papovavirus, with only few case reports implicating another human polyomavirus, similar to SV-40 [7]. A majority of the population has antibodies to JCV due to a prior benign exposure [6]. PML is seen in immunosuppressed patients, most often with the acquired immunodeficiency syndrome (AIDS), but it has also been described in patients with long-standing progressive CLL [8]. Various immunosuppressive agents such as interferon-α [9], cyclosporine [10], fluorouracil/levamisole [11], and chlorambucil/methylprednisolone [12], have also been implicated in PML. The clinical course is usually rapid and fatal. No good therapies are currently available, although cytosine arabinoside has been reported to be beneficial in a few cases [13].

Fludarabine is both myelosuppressive and immunosuppressive. The immunosuppression is partially due to absolute lymphopenia and a decrease in helper (CD4) T-cells. Such lymphopenia lasts from several months up to a year following therapy with fludarabine with increased risk of opportunistic infections [4,14]. Fludarabine, particularly at high doses, is also associated with diffuse white matter loss on CNS imaging and can cause neurologic complications, such as blindness and encephalopathy [5]. Because of the neurotoxicity, it may be difficult to determine the reason for neurologic deterioration following treatment with fludarabine, i.e., whether it is due to

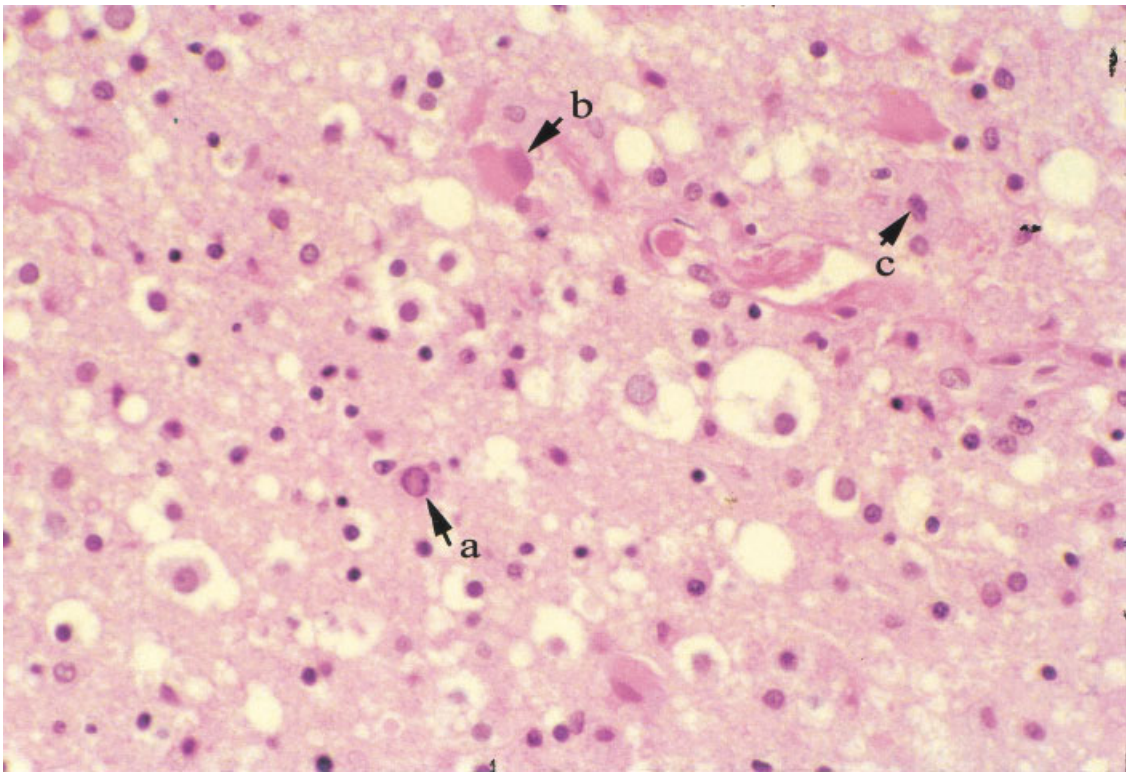

Fig. 1. H&E stained section revealing degenerating white matter, infiltrated by foamy macrophages (c) and reactive astrocytes with bizarre nuclei (b). Several of oligodendrocytes (a) reveal nuclear enlargement and amphophilia. Original objective magnification 40×. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

fludarabine CNS toxicity or to an opportunistic infection.

We report the development of PML in two patients with B-cell malignancies and treated with fludarabine. One patient, with CLL, was treated with only one cycle of fludarabine. The second patient had follicular lymphoma and was treated with 12 cycles of fludarabine. Two other papers describe an association of PML and low-dose fludarabine [15,16]. Of the four patients reported in these papers, all had CLL and had received from 3 to 16 cycles of fludarabine therapy prior to developing lesions on MRI consistent with PML. In only one of these previously reported patients was JC virus conclusively demonstrated on immunostaining. The immunosuppression that develops after fludarabine therapy is the most likely explanation for PML development even though the number of cycles given varies greatly. Other causes, such as idiosyncratic reactions, cannot be ruled out though. The two patients we report were 63 and 74 years old, respectively, but of the previously reported patients, three of four were younger than 60 years of age, the youngest being 45 years old. It is clear that the risk of developing PML is not restricted to older patients and may be affected by the number of fludarabine cycles given.

The incidence of PML is difficult to ascertain. The diagnosis is based on clinical findings and not usually made until a post-mortem examination is done. The disease is defined by its histopathology, but demonstrating the JC virus, although helpful, is not necessary for making the diagnosis. PML should be considered in patients developing neurological symptoms or white matter changes on CNS imaging following fludarabine therapy for low-grade lymphoproliferative disease. The etiologic role of JC virus needs to be evaluated in the setting of lymphoproliferative disease treated with fludarabine. Of the 6 patients reported to date, only three have had the virus demonstrated. Of interest is the repeatedly negative PCR for the JC virus in one of our patients, even though immunohistochemistry was strongly positive. We suspect that immunohistochemistry examination in an experienced reference laboratory might demonstrate JC virus in the additional three cases. Such monitoring and analysis are important because of the widespread use of fludarabine as a first-line therapy for low-grade lymphoproliferative diseases.

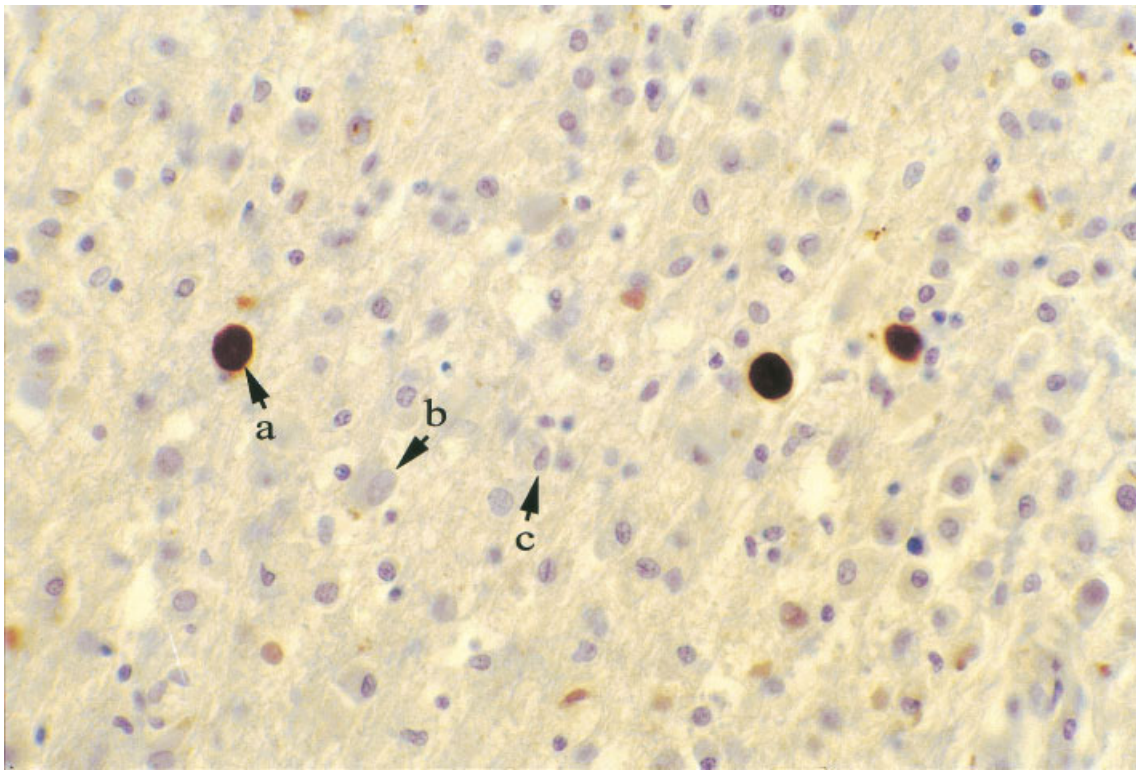

Fig. 2. Tissue section adjacent to section in Fig. 1, immunolabled with JC virus antibody. The enlarged nuclei of three oligodendrocytes (a) are positively immunolabled. (b) Reactive astrocytes with bizarre nuclei. (c) Foamy macrophages. Original objective magnification 40×. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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