Progressive Multifocal Leukoencephalopathy: Clinical and MR Response to Treatment

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Summary: Progressive multifocal leukoencephalopathy (PML) is a fatal demyelinating disease that occurs in immunocompromised hosts. We describe two patients with biopsy-proved PML who showed improvement clinically and radiologically after medical therapy. These cases reveal that interval improvement can in rare instances be consistent with a diagnosis of PML.

Index terms: Brain, diseases; Demyelinating disease; Immune deficiency

The usual course of progressive multifocal leukoencephalopathy (PML) is an inexorable deterioration in the patient's clinical status and an increase in the number and size of lesions on magnetic resonance (MR) images. Sometimes, a patient's clinical status may improve, and this may be accompanied by resolution of the lesions seen on MR images. In this article, we present a review of the literature and report two cases of PML in which the patients' clinical status and MR findings improved with medical therapy.

Case Reports

Case 1

A 59-year-old woman with a long history of Crohn disease presented with ataxia, nausea, and vomiting. She was initially treated with steroids for a presumed flare-up of her inflammatory bowel disease. However, she developed nystagmus, dysarthria, and increasingly severe ataxia. She became completely bedbound and dependent. MR images revealed multiple nonenhancing lesions in the deep white matter, the largest being in the posterior fossa (Fig 1). Her clinical status continued to deteriorate, and a repeat MR image 1 month later showed diffuse white matter abnormalities. A stereotaxic needle biopsy was performed and established the diagnosis of PML. The patient was then started on combination therapy consisting of cytarabine, interferon alfa, and gamma globulin. Her neurologic status improved dramatically. MR imaging performed 2 months after initiation of therapy showed an interval decrease in the extent of white matter lesions, especially in the area of the left cerebellar peduncle. Subsequent MR images obtained over a 14-month follow-up period showed no interval changes. Neurologically, the patient has residual dysarthria and moderate ataxia.

Case 2

A 34-year-old man with human immunodeficiency virus had an 8-week history of increasing light-headedness, unsteady gait, dizziness, and confusion. On physical examination the patient had nystagmus, a right-sided homonymous hemianopia, and mildly unsteady gait. An MR image revealed multiple nonenhancing lesions, the largest being in the posterior fossa (Fig 2). A stereotaxic biopsy was performed and confirmed the diagnosis of PML. One month later, therapy with cytarabine was started. Five courses of chemotherapy were administered over the subsequent 5-month period. Physical examination after chemotherapy showed partial resolution of his neurologic deficits. Follow-up MR imaging performed 3 months after initiation of chemotherapy showed an interval decrease in the size and intensity of the previously documented lesions (Fig 2).

Discussion

PML is a demyelinating disease of the central nervous system that occurs in an immunocompromised host. Clinically, it presents as relentlessly progressive focal central nervous system dysfunction, such as hemiparesis, aphasia, cortical blindness, or altered mental states (1). The usual course of the disease is rapid neurologic deterioration ending in coma and death. The causative agent, the JC virus, invades oligoden-

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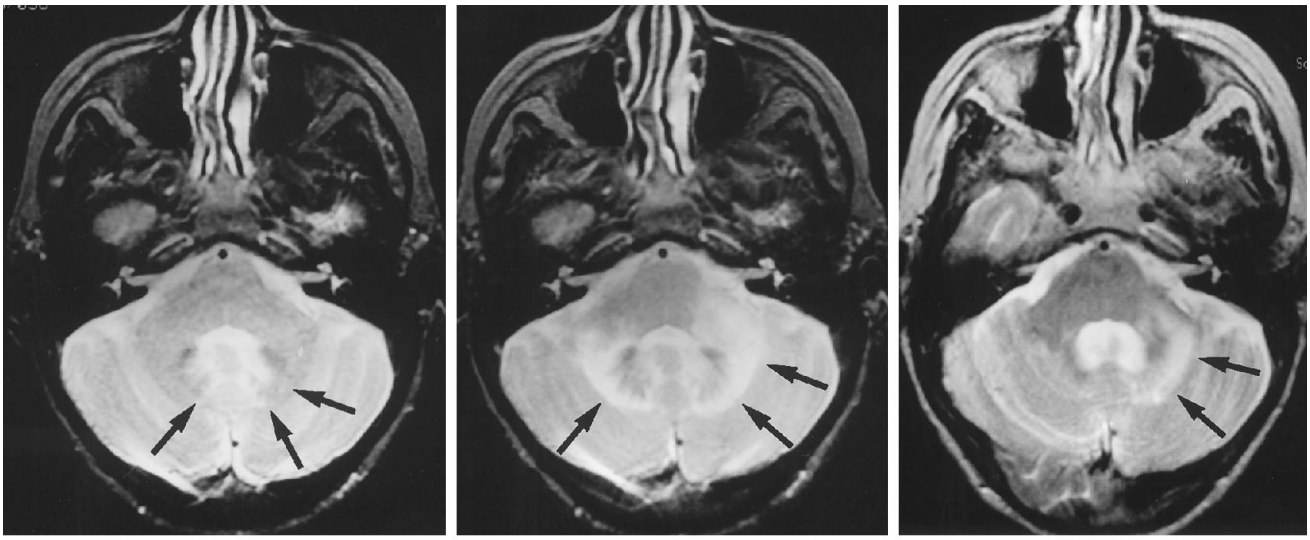

Fig 1. Axial T2-weighted MR images in a 59-year-old woman with Crohn disease, nausea, and vomiting.

A, Findings on the initial MR image (2500/90/1 [repetition time/echo time/excitations]), obtained shortly after the onset of neurologic symptoms, were almost normal, showing only subtle areas of high signal intensity adjacent to the fourth ventricle (*arrows*).

B, Two months after onset of symptoms, MR image (2500/90/1) shows bilateral large lesions deep in the cerebellar hemispheres and cerebellar peduncles (*arrows*). Biopsy results established a diagnosis of PML. Chemotherapy was begun at this point and clinical symptoms improved.

C, Four months later (8 months after the onset of neurologic deficit), a repeat MR image (2500/90/1) shows substantial reduction in lesion size (*arrows*).

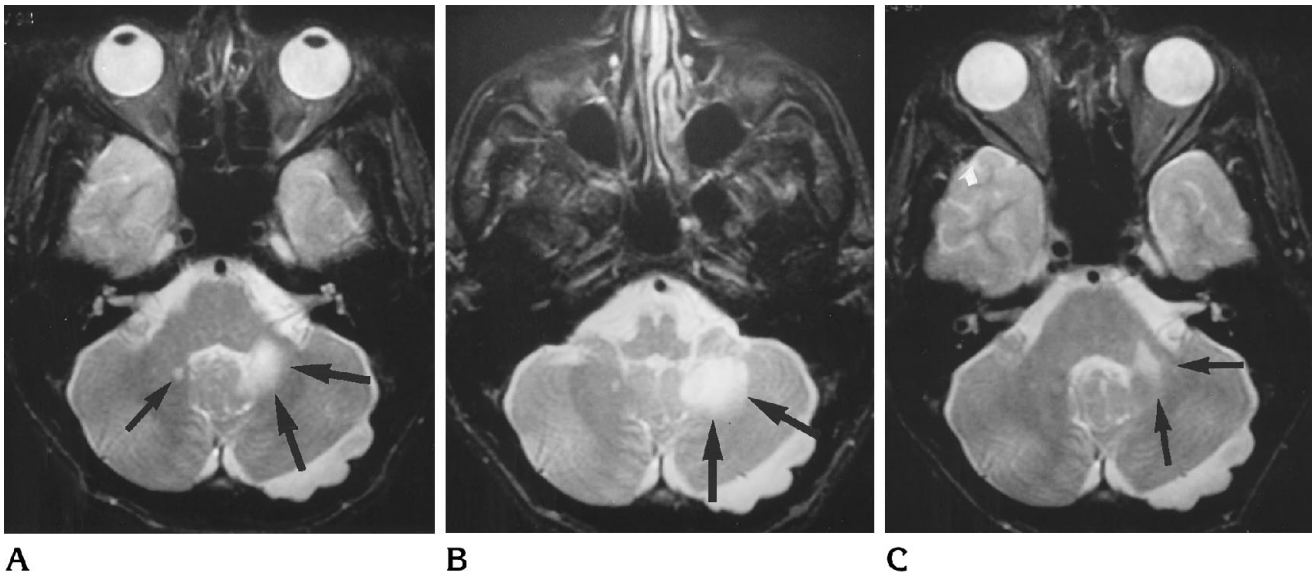

Fig 2. Axial T2-weighted MR images in a 34-year-old man with human immunodeficiency virus infection.

A, Findings on the initial MR image (2500/90/1), obtained shortly after the onset of neurologic symptoms, showed bilateral lesions (*arrows*) in the middle cerebellar peduncles, the left-sided lesion being larger. The contrast-enhanced MR image (not shown) revealed no enhancement.

B, Two months later, MR image (2500/90/1) shows the left-sided lesion (*arrows*) to be markedly larger. Biopsy results established the diagnosis of PML. Chemotherapy was begun at this time.

C, One month after initiation of chemotherapy, MR image (2500/90/1) shows marked reduction in the size of the lesions (*arrows*).

Summary of PML cases in which patients improved with chemotherapy

Author	Associated Disease	Treatment	Survival, mo	Biopsy Performed
Lortholary (8)	HIV	Zidovudine	>60	Yes
Steiger (9)	Sarcoidosis	Acyclovir, cytarabine, interferon alfa	13	Yes
deTruchis (10)	HIV	Cytarabine, intrathecal cytarabine,* zidovudine	9	Yes
Colosimo (11)	Non-Hodgkin	Intramuscular interferon alfa	18	No
Nicoli (12)	HIV	Cytarabine,* zidovudine	10	Yes
	HIV	Cytarabine,* zidovudine	7	No
Portegies (13)	HIV	Cytarabine,* zidovudine	–	No
	HIV	Cytarabine,* zidovudine	6	No
	HIV	Cytarabine	–	No
Conway (14)	HIV	Zidovudine	10	Yes
O'Riordan (15)	Non-Hodgkin	Cytarabine, intrathecal cytarabine*	14	No
Berger (16)	HIV	Acyclovir,* zidovudine	30	Yes
	HIV	Dexamethasone	24	Yes
Fiala (17)	HIV	Zidovudine	1	No
Tashiro (18)	None identified	Vidarabine, interferon beta, cytarabine, intrathecal interferon beta*	16	Yes

Note.—PML indicates progressive multifocal leukoencephalopathy; and HIV, human immunodeficiency virus.
* Drug considered responsible for improvement in patients receiving multiple drugs.

droglial cells causing multiple foci of demyelination. Isolation of the JC virus with brain biopsy confirms a clinical diagnosis of PML.

Originally, over 60% of cases of PML occurred in the setting of immunologic compromise from lymphoproliferative or myeloproliferative disorders (1). However, in the past two decades the epidemiology of the disease has changed and the majority of cases now occur in association with acquired immunodeficiency syndrome (AIDS) (2). Other cases occur in patients with iatrogenic immunosuppression. The association with AIDS has dramatically increased the frequency of and death rate from PML (1).

MR imaging is the preferred imaging method for diagnosis of PML. Typically, PML appears as widespread, asymmetric lesions in the white matter. On T2-weighted images they have increased signal intensity with little or no mass effect, and usually do not enhance after contrast administration. Contrast enhancement may be seen in some cases, particularly with techniques such as magnetization transfer contrast that suppress the background signal intensity of white matter (3). The absence of mass effect and enhancement have been used to distinguish PML from other entities that occur frequently in the immunocompromised host, such as lymphoma and toxoplasmosis (4, 5).

Both patients described here had initial MR findings characteristic of PML, and both had significant clinical improvement associated with treatment. The decrease in the size of lesions seen on MR images associated with clinical improvement is notable. Interval improvement is an outcome that is so infrequent that it is generally not thought to be consistent with a diagnosis of PML. Our review of the literature indicates that partial resolution may occur spontaneously or, more commonly, after chemotherapy (6–18).

In our cases, reduction in the extent of the lesions on MR images was found after reversal of immunosuppression and treatment with cytarabine, interferon alfa, and gamma globulin in the first case, and after treatment with cytarabine in the second case. The Table contains a summary of articles that have reported cases in which treatment has been associated with prolonged survival of patients with PML. All but two authors also reported associated improvement in MR appearance of PML lesions (14, 17). These two authors did not mention radiologic findings in their reports (14, 17). There have also been reported cases of prolonged survival with untreated PML (5, 6). These cases of apparently spontaneous recovery occur after a reversal or stabilization of the underlying immunocompromised state.

No one treatment has been shown to be consistently effective. Although cytarabine is reported to have had a beneficial effect in several cases (Table), the inefficacy of cytarabine has

been reported in a series of 16 patients with AIDS, half of whom were treated with cytarabine. Of the eight treated, only one showed improvement. Overall, no increased survival with treatment with cytarabine was noted (10). Cytarabine may be useful in some cases of PML, but the parameters that make PML responsive to therapy with cytarabine have not been isolated. In addition, there seems to be some evidence that the use of interferon alfa, either alone or in combination with other chemotherapy, may be of some value. It has been used successfully in two cases listed in the Table as well as the one presented here, and seems to be worthy of further investigation. The effect of gamma globulin in our first case was also uncertain, and may warrant further study.

The one patient who responded to cytarabine therapy in the series reported by deTruchis had lesions that were isolated to the cerebellum on MR images (10). Both the patients reported here also had cerebellar lesions. Although neither patient had isolated cerebellar abnormalities on MR images, in both cases the lesions in the cerebellum showed the most improvement with therapy. In the first patient the decrease in the size of the cerebellar lesions was accompanied by significant recovery from the pancerebellar syndrome she had developed. It may be fruitful in the future to try to understand what effect, if any, the location of the lesion has on the course and severity of PML.

In summary, we have described two cases of PML in which there was interval clinical and MR improvement. Although the most common course of PML is rapid, fatal neurologic deterioration, a review of the literature shows that a fluctuating course with interval improvement is not inconsistent with the diagnosis of PML. MR imaging may be useful in following up the response to treatment of PML, and further studies of the treatment of PML should be carried out.

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