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## Multiple cerebral lesions complicating therapy with interleukin-2

B. Illowsky Karp, MD; J. C. Yang, MD; M. Khorsand, MD; R. Wood, MD; and T. C. Merigan, MD

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**Article abstract**—We reviewed the records and radiologic studies of eight patients who developed new focal neurologic abnormalities while receiving interleukin-2 (IL2)-based immunotherapy for malignancy or HIV infection. Initial confusion and delirium in the patients evolved into coma, ataxia, hemiparesis, seizures, and cortical syndromes including aphasia, apraxia, and cortical blindness. Imaging studies showed multiple white and gray matter lesions with a predilection for the occipital poles, centrum semiovale, and cerebellum. After cessation of IL2 treatment, seven patients improved to normal or near-normal neurologic function paralleled by resolution of the lesions on scans. One patient improved only minimally. Possible etiologies for the lesions include an IL2-induced cerebral vasculopathy, a direct toxic effect of IL2, or immunologically mediated damage.

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Interleukin-2 (IL2) is a lymphokine effective against advanced metastatic malignancies in some patients,<sup>1,3</sup> which may also act against the human immunodeficiency virus.<sup>4,5</sup> IL2 is used alone, in a long-acting preparation conjugated to polyethylene glycol (PEG-IL2), in combination with activated lymphocytes as part of adoptive immunotherapy, or with other cytokines such as alpha-interferon (alpha-IFN) or granulocyte-macrophage colony stimulating factor (GM-CSF).<sup>1,6</sup>

Systemic side effects of IL2 such as fever, chills, malaise, nausea, vomiting, and diarrhea are common. Fluid extravasation from a capillary leak syndrome may lead to hypotension, multiorgan failure, and arrhythmias.<sup>1,7</sup> The most common neurologic side effect of IL2 therapy is a reversible encephalopathy characterized by confusion, lethargy, and poor concentration.<sup>8-10</sup>

It can progress to delirium with psychotic features or to coma. Over the past several years, there have been a few case reports of focal neurologic deficits in patients receiving IL2. Aphasia, hemiparesis, seizures, visual distortions, and ataxia have occurred as well as brachial plexopathy and carpal tunnel syndrome.<sup>11-17</sup> Vecht et al.<sup>16</sup> reported an acute fatal demyelinating leukoencephalopathy in a patient receiving IL2.

As therapy with IL2 has become more widespread, neurologic illness has become an important cause of morbidity and a treatment-limiting complication. We describe eight patients who developed neurologic deficits and lesions on brain imaging during IL2-based treatment of malignancy or HIV infection.

**Methods.** From 1985-1994, over 1,500 patients received IL2-based therapy for malignancy at our institution, in-

From the National Institute of Neurological Disorders and Stroke (Dr. Illowsky Karp), the National Cancer Institute (Dr. Yang), National Institutes of Health, Bethesda, MD; the Comprehensive Cancer Center (Dr. Khorsand), University of Wisconsin, Madison, WI; the Center for AIDS Research (Drs. Wood and Merigan), Stanford University, Stanford, CA.

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Address correspondence and reprint requests to Dr. Barbara I. Karp, Building 10, Rm. 5N-226, NINDS, NIH, Bethesda, MD 20892.

cluding five who developed neurologic illness with abnormalities on magnetic resonance imaging (MRI) during or shortly after treatment. No patient had metastases to the nervous system or a history of neurologic disease or stroke prior to receiving IL2. The medical records and imaging studies were reviewed. Three additional patients (cases 4, 7, and 8) receiving IL2 for HIV infection or malignancy at other institutions with similar neurologic symptoms, courses, and imaging studies were also studied.

**Case reports.** *Patient 1.* A 53-year-old man with renal cell carcinoma underwent nephrectomy and radiotherapy before referral for IL2. His immunotherapy included alpha-IFN and IL2. Five days after the start of treatment, the patient became progressively confused and lethargic and lapsed into coma. He had intermittent left focal seizures, which stopped spontaneously within 24 hours. Peritoneal dialysis was begun on the 10th hospital day for renal failure. Two days after beginning dialysis, the patient was alert but disoriented with hallucinations. The symptoms improved over the next week. On the 22nd hospital day, left focal seizures recurred and were followed by a generalized seizure. He was started on phenytoin.

Following the seizure, he had a left spastic hemiparesis. Cerebrospinal fluid (CSF) was normal except for a slight elevation in protein to 56 mg/dL. An electroencephalogram (EEG) showed diffuse background slowing with right temporal lobe periodic epileptiform discharges. A CT of the head showed nonenhancing white matter lucencies extending from occipital areas forward into the centrum semi-ovale. White matter hyperintensities, which were especially prominent occipitally, were seen on MRI.

He improved rapidly and was fully awake 48 hours after the seizure. A repeat MRI 3 weeks later was unchanged, and an EEG was improved. On discharge from the hospital on the 38th hospital day, the patient had persistent reflex asymmetry but an otherwise normal neurologic examination. MRI 1 month after discharge showed resolution of the white matter abnormalities.

**Patient 2.** A 41-year-old man with renal cell carcinoma started IL2 2 months after a radical nephrectomy. He received seven doses of IL2, then three weekly doses of PEG-IL2. During the second week of PEG-IL2 treatment, he developed right proximal arm weakness, sensory loss, and shoulder pain with winging of the scapula. Deep tendon reflexes were normal. MRI of the cervical spine showed bony degeneration and bulging disks at C-5 through C-7. MRI of the head showed a few small areas of high signal in the cerebral white matter.

A second cycle of therapy began 1 month later. He received five doses of IL2 followed by PEG-IL2 for 3 weeks. Two days after the last PEG-IL2 dose, he became delirious and was treated with haloperidol. On examination, the patient was lethargic but able to state his name and open his eyes on command. There was no visual fixation or response to visual threat. The pupils were small and reactive to light. A right gaze preference was present. Both legs moved spontaneously, but the right arm was immobile and hyperreflexic. The left arm withdrew to noxious stimuli only. Plantar responses were extensor. The patient had a generalized tonic-clonic seizure, which was treated with phenytoin.

At the time of neurologic deterioration, the white blood

cell (WBC) count was 23,000/mm<sup>3</sup> with 46% eosinophils. Coagulation studies, serum sodium, magnesium, calcium, and liver function tests were normal. There was mild renal insufficiency. CK was markedly elevated at 1,024 U/L. A nonenhanced CT of the head showed no lesions. MRI showed new cortical, subcortical, and cerebellar lesions, including bilateral occipital lesions that did not enhance with gadolinium (figure 1A). The CSF had 3 white blood cells and 44 red blood cells/mm<sup>3</sup>. CSF protein, glucose, and cultures were normal. An EEG done 4 days after the seizure showed diffuse slowing without epileptiform activity.

The patient remained intubated and pharmacologically paralyzed for 5 days after the seizure. When paralysis and sedation were discontinued, he gradually awoke. He was able to read and identify objects and colors, but complained of difficulty locating objects visually. The right arm remained weak and atrophic. MRI of the head 1 week later showed persistence of the brain lesions, which now enhanced with gadolinium (figure 1B).

Two months later, his mental status and vision were completely normal. The right arm weakness had improved. An MRI 5 months after admission showed only those small white matter lesions that had been present prior to the second cycle of IL2.

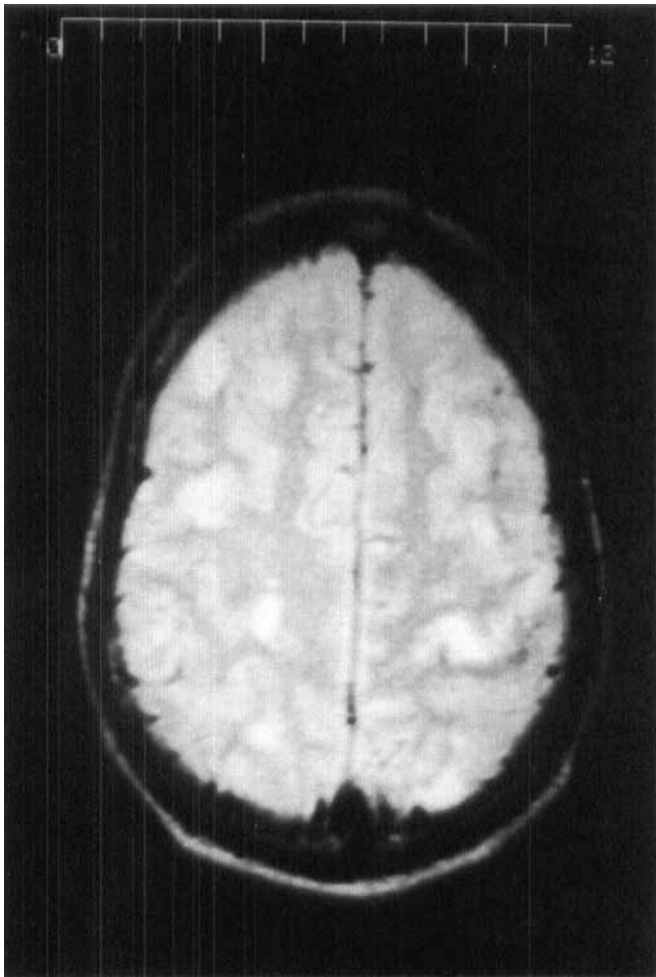
**Patient 3.** A 63-year-old woman with renal cell carcinoma of the sternum tolerated an initial course of IL2 followed after 1 week by PEG-IL2. A second, higher dose of PEG-IL2 was given 1 week later. Forty-eight hours after the second PEG-IL2 administration, she became confused, agitated, incontinent, and progressively somnolent. Her speech was dysarthric. Strength, tone, and deep tendon reflexes were decreased in the left arm and leg. Snout, root, and bilateral grasp reflexes were present. The left toe was upgoing. CSF analysis was normal. An MRI of the head showed possible bilateral occipital hyperintensities that had not been present on a baseline scan before admission.

The patient deteriorated. By the next day she was obtunded and unable to follow any commands and had intermittent decorticate posturing of her right arm. A repeat MRI showed multifocal white matter and cortical hyperintensities including definite bilateral occipital lesions (figure 2A). An EEG showed generalized slowing. Because the first two patients had seizures in a similar clinical setting, this patient was given phenytoin prophylactically.

At the time of neurologic deterioration, she had mild respiratory insufficiency, hypotension, and oliguria. Her WBC count was 29,000/mm<sup>3</sup> with 50% eosinophils. Her serum CK rose to 694. The prothrombin time was slightly prolonged at 18.6; other coagulation studies were normal.

The patient continued to worsen. By the fifth day after the last IL2 infusion, she could open her eyes spontaneously but did not focus visually, follow objects, or respond consistently to visual threat. Her pupils were equal and reactive. She appeared unaware of her surroundings and did not follow commands. There was no spontaneous movements of her arms or legs, and the left side did not withdraw to pain.

Over the next several weeks, the left spastic hemiparesis persisted. Noxious stimuli to the right side of the body elicited flexor posturing. Myoclonic jerks were intermittently present in the right arm. A CT without contrast



A



B

*Figure 1. (A) T<sub>2</sub>-weighted MRI of patient 2 showing multiple cortical lesions. The lesions did not enhance with gadolinium. (B) T<sub>1</sub>-weighted MRI with gadolinium obtained 1 week after that in A showing new enhancement of lesions.*

showed multiple well-circumscribed lucencies throughout the cerebral hemispheres (figure 2B).

There was only slight improvement over the second month of hospitalization. Although she became responsive to her surroundings and was able to speak, she had irritability and marked deficits in attention and concentration. She was able to recognize her family and some objects. All limbs were spastic and hyperreflexic, and she had no movement of her right hand. Bilateral grasps persisted. She was transferred to a rehabilitation facility 7 weeks after receiving her final dose of IL2.

**Patient 4.** A 43-year-old HIV-seropositive man on azidothymidine began weekly doses of PEG-IL2. Approximately 60 hours after the sixth infusion, he became confused and unsteady. The following day he complained of mild bifrontal headache and was unable to feed or clothe himself properly. On examination, he was alert and oriented to person and place, but not date. His answers were slow, and he was unable to follow multi-step commands or do even simple arithmetic. Left-right confusion and perseveration were present. He could neither write clearly nor copy figures.

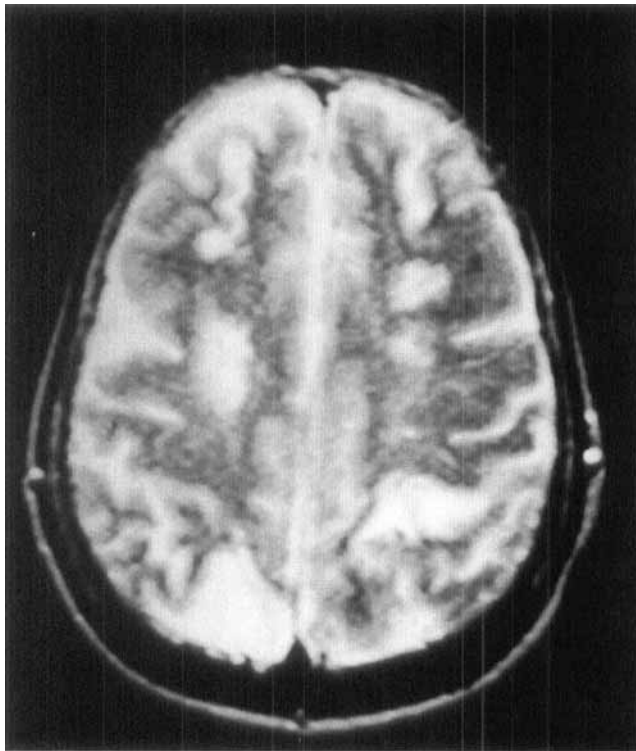
Cranial nerve examination was normal as was sensation to pinprick, light touch, vibration, and position. He

had agraphesthesia and astereognosis. Strength was normal. Rapid alternating movements were performed poorly, and he was unable to walk with a tandem gait. Babinski responses were present bilaterally.

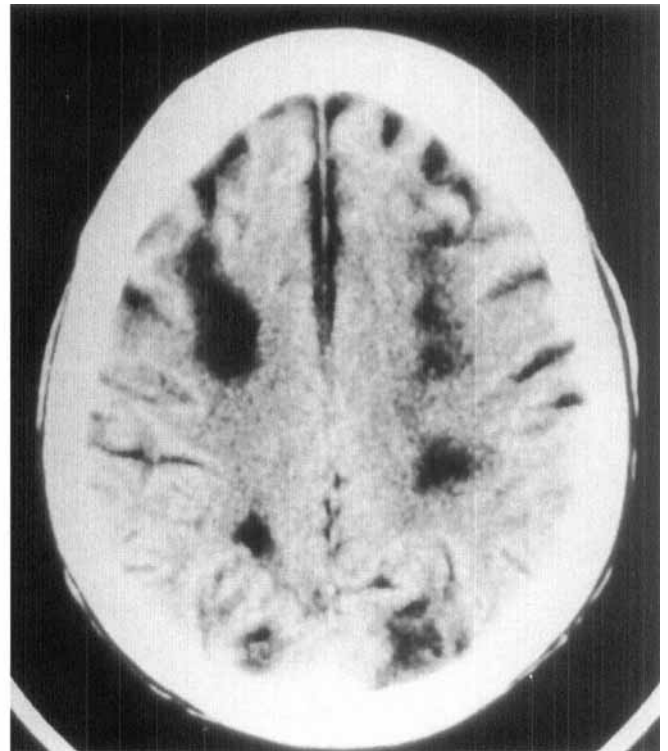
Laboratory studies included a WBC count of 18,700/mm<sup>3</sup> with 41% eosinophils. CD4 count was 450 cells/μL. LDH was elevated at 2,286 IU/L, and AST at 139 IU/L. Renal function was normal. The CSF contained nine RBCs/mm<sup>3</sup> and five WBCs/mm<sup>3</sup>. The CSF protein was 57 mg/dL.

Two CTs were unrevealing. MRI 3 days after admission showed diffuse, nonenhancing white and gray matter lesions. An EEG showed left temporal slowing with bursts of frontal intermittent rhythmic delta activity. The patient improved rapidly and was neurologically normal at discharge on the fifth hospital day.

**Patient 5.** A 28-year-old woman with metastatic malignant melanoma received IL2 after failing to respond to conventional chemotherapy. After her seventh dose of IL2, she developed renal and respiratory insufficiency, hypotension, and peripheral edema. She required a brief period of respirator support. After extubation, the patient was confused. Although awake and alert, she was oriented to person only. She had little spontaneous speech, mild word-finding difficulty, poor repetition of words, and



A



B

*Figure 2. (A) T<sub>2</sub>-weighted MRI of patient 3 showing multiple cortical and subcortical lesions. (B) CT obtained 3 weeks after A. The lesions appear as multiple cortical and subcortical lucencies.*

perseveration. The deep tendon reflexes were brisk, and plantar responses were extensor. A head CT was normal. However, MRI showed a hyperintense lesion in the left parietal lobe. The CSF was normal. The patient's symptoms cleared completely over 5 days. The lesion was smaller but still visible on scans performed up to 10 months later.

**Patient 6.** A 56-year-old man with metastatic renal cell carcinoma was referred for immunotherapy after a radical nephrectomy. He completed the first course of eight doses of IL2 without difficulty. One week later, he was lethargic and had recurrent episodes of vertigo lasting about 15 minutes. He complained of unsteadiness while walking and a loss of grip strength in the left hand. The symptoms cleared for 2 days, then recurred along with blurred vision. A left homonymous hemianopia and bilateral limb ataxia were found on examination.

At the time the neurologic symptoms developed, renal function was normal, but the alkaline phosphatase and AST were slightly increased. The peripheral WBC count was 13,000/mm<sup>3</sup> with 2% eosinophils. The CSF contained 3 WBC/mm<sup>3</sup> and was otherwise normal. A head CT was normal, but an MRI showed multiple hyperintense lesions on the T<sub>2</sub>-weighted scan. Lesions involved both gray and white matter and were found in the occipital cortex, left thalamus, and cerebellar hemispheres. They did not enhance.

The patient improved over 8 days. MRI 1 week after the initial scan showed the earlier lesions, but additionally found that the right occipital lesion enhanced with gadolinium. All lesions were smaller on a scan obtained 6 weeks later.

**Patient 7.** A 48-year-old man with metastatic renal cell carcinoma became confused and lethargic after two infusions of IL2 and GM-CSF. His neurologic examination was otherwise normal, as was MRI. Further immunotherapy was stopped because his white blood cell count had risen to 95,700/mm<sup>3</sup> with 55% eosinophils. Hydrocortisone and hydroxyurea were given to decrease the white blood cell count. At the time neurologic symptoms began, his renal function was normal; LDH and alkaline phosphatase were elevated to twice normal levels.

One day later, the patient deteriorated. He complained of dizziness and a headache and was disoriented with cognitive difficulties, hallucinations, expressive aphasia, and right-hand weakness. An EEG showed generalized and right frontal slowing. The CSF was normal. A second MRI showed nonenhancing, white matter hyperintensities in both frontal lobes, occipital poles, right parietal lobe, and right parietotemporal junction. MR angiography was normal. A third MRI 1 day later showed the previous white matter lesions and new signal abnormalities in the gray matter of the medial frontal lobes bilaterally. The patient gradually improved. By 6 weeks after admission he noticed only a slight impairment of fine motor movements when playing piano.

**Patient 8.** A 52-year-old man who underwent nephrectomy for renal cell carcinoma in 1986 had a recurrence of disease in 1994. He received IL2 and GM-CSF for 4 days. The second week of therapy was interrupted by severe diarrhea. The doses of both drugs were halved when treatment was restarted, and that of GM-CSF was reduced further when the absolute eosinophil count reached 20,000. During the third week of treatment, the patient

**Table Patient demographics and drug doses**

| Patient | Sex/Age | Diagnosis | Drug/Dose*                                                                                                                                                                                                                                                           | Time of Symptom Onset                       |
|---------|---------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| 1       | M/53    | RCC       | H-L IL2 4.5 mU/m <sup>2</sup> × 11 doses<br>alpha-IFN 3 mU × 11 doses                                                                                                                                                                                                | 22 days after start of treatment            |
| 2       | M/41    | RCC       | First course:<br>IL2: 720,000 IU/kg × 7 doses<br>PEG-IL2: 3 mU/m <sup>2</sup> × 1 dose<br>PEG-IL2: 6 mU/m <sup>2</sup> × 3 doses<br>Second course:<br>IL2: 720,000 IU/kg × 7 doses<br>PEG-IL2: 3 mU/m <sup>2</sup> × 1 dose<br>PEG-IL2: 6 mU/m <sup>2</sup> × 1 dose | 3 days after start of second PEG-IL2 course |
| 3       | F/63    | RCC       | IL2: 720,000 IU/kg × 7 doses<br>PEG-IL2: 3 mU/m <sup>2</sup> × 1 dose<br>PEG-IL2: 6 mU/m <sup>2</sup> × 1 dose                                                                                                                                                       | 3 days after second PEG-IL2 dose            |
| 4       | M/43    | HIV       | PEG-IL2: 3 mU/m <sup>2</sup> × 6 doses                                                                                                                                                                                                                               | 3 days after sixth PEG-IL2 dose             |
| 5       | F/28    | Melanoma  | IL2: 720,000 IU/kg × 7 doses                                                                                                                                                                                                                                         | 6 days after seventh IL2 dose               |
| 6       | M/56    | RCC       | IL2: 720,000 IU/kg × 8 doses                                                                                                                                                                                                                                         | 8 days after first course IL2 completed     |
| 7       | M/48    | RCC       | IL2: 1.5 mU/m <sup>2</sup> × 8 doses<br>GM-CSF: 5 µg/m <sup>2</sup>                                                                                                                                                                                                  | 6 days after eighth IL2 dose                |
| 8       | M/53    | RCC       | IL2: 1.5 mU/m <sup>2</sup> × 6 doses<br>GM-CSF: 5 µg/m <sup>2</sup>                                                                                                                                                                                                  | 2 days into second week of treatment        |

\* H-L IL2: Hoffman-LaRoche; other patients received the Chiron/Cetus preparation.

RCC = renal cell carcinoma.

became confused and restless. He was able to follow only simple commands and had poor attention with perseveration. A right homonymous hemianopia was present as well as right-sided neglect and ocular apraxia. There was right facial and arm weakness, hyperreflexia, and bilateral Babinski signs.

At the time of neurologic deterioration, the white blood cell count was 41,000/mm<sup>3</sup> with 50% eosinophils. The platelet count was 505,000/µL, and serum viscosity was increased to 4.3 (normal, 1.4 to 1.8). Serum protein electrophoresis was normal. Fibrinogen level was normal and fibrin split products were absent. CSF was normal. CT and MRI scans showed nonenhancing lesions in the left cerebellum and left frontal deep white matter. Repeat MRI several days later showed new nonenhancing lesions in both gray and white matter involving the thalamus, cerebellum, and occipital lobes. A third MRI the next day showed gadolinium enhancement in the left cerebellar, occipital, and posterior frontal lesions.

The patient gradually improved. Six weeks later, examination showed slight right arm weakness but was otherwise normal.

**Results.** The patients included six men and two women ranging in age from 28 to 63 years (mean age, 48 years). Six patients received IL2 for renal cell carcinoma, one for melanoma, and one for HIV infection (table). IL2 was the sole immunotherapeutic agent in five patients, three of whom received the long-acting preparation, PEG-IL2. One patient received alpha-IFN and two patients received GM-CSF in addition to IL2.

Neurologic symptoms did not begin immediately with the start of IL2 treatment. Five patients became symptomatic 3 to 8 days after completing a course of therapy, the other three during a course of treatment.

In each patient, the first sign of deterioration was a change in mental status with confusion, disorientation, and agitation. Three patients had hallucinations. Two patients became obtunded and one comatose. Two patients had seizures. Speech difficulties, including aphasia, dysarthria, and mutism, were present in four patients. Two patients had cortical blindness, and two had a homonymous hemianopia. Corticospinal tract involvement was manifest in seven of the eight patients who had weakness, spasticity, hyperreflexia, or Babinski signs. Three patients had perseveration, and one had primitive reflexes, including snout, bilateral grasp, and rooting reflexes. Four patients had limb or gait ataxia. Two patients had hemisensory deficits. One patient had left-right confusion, agraphesthesia, and astereognosis.

All patients had abnormal brain imaging. Multiple lesions were present in both gray and white matter in cortical and subcortical territories except for one patient who had an isolated left cortical parietal lesion. The lesions were not apparent or hypodense on CT (see figure 2B). On MRI, the lesions were either not visible or hypointense on T<sub>1</sub>-weighted images, and hyperintense on T<sub>2</sub>-weighted images. In one patient, the lesion enhanced with gadolinium on the first MRI scan obtained. In three other patients, lesions that did not enhance on the initial MRI scans did show enhancement on scans obtained 5 to 7 days later (see

figure 1). MR angiography, performed in only one patient, was normal.

Seventy-five percent of the patients had occipital lobe involvement, which was often bilateral. Half had parietal lesions and half frontal lesions. The cerebellum was involved in 33% of patients and the thalamus in 25%. No patient had brainstem lesions.

EEGs, recorded in five patients, showed generalized slowing. Additional focal slowing was noted in two patients. One patient had periodic localizing epileptiform discharges, and one patient had frontal intermittent rhythmic delta activity. CSF analysis was usually normal. Two patients had a slight increase in CSF protein. Three patients had a mild lymphocytic pleocytosis.

At the time of neurologic compromise, one patient had renal failure and several others had mild renal or hepatic dysfunction. Two patients had hypotension, which improved with intravenous fluid infusion. Routine coagulation studies were usually normal. The serum viscosity was elevated in the single patient in whom it was measured. All patients except one had an IL2-induced eosinophilia. Eosinophilia was mild in one patient whose absolute eosinophil count was 700/mm<sup>3</sup>, but was marked in the others whose absolute eosinophil counts ranged from 1,372/mm<sup>3</sup> to 57,000/mm<sup>3</sup>.

No patient received additional IL2 after the development of neurologic symptoms. While patients did not receive specific treatment for their neurologic symptoms, all received supportive care. Several required medication for agitation or seizures. Seven patients had complete or nearly complete recovery of neurologic function. Improvement usually began within a week of the onset of neurologic symptoms. One patient, however, had only minimal recovery. This patient remained severely encephalopathic with a spastic quadriparesis.

**Discussion.** The patients presented here developed neurologic illness during or shortly after treatment with IL2 with corresponding cortical and subcortical lesions on imaging studies. The initial behavioral changes were often similar to the more common IL2-induced encephalopathy, but focal signs rapidly evolved reflecting the areas of the brain affected.

There was no evidence to suggest an infectious or malignant cause for the neurologic illness. Patients with nervous system metastases were excluded from the IL2 trials, and CSF cytology and cultures were negative. Metabolic disturbances, including hyponatremia, hepatic failure, renal insufficiency, or hypoxia, were present in some of our patients, but they are not likely to have caused the neurologic syndrome as they were often mild and transient. One patient had renal failure severe enough to require dialysis, but the others had only oliguria or a slight increase in BUN and creatinine. The disturbance in three patients was limited to transaminase elevation. No single abnormality was uniformly present in all patients, and none is known to cause focal symptoms with multiple cortical and subcortical lesions.

Two of the patients were co-treated with GM-CSF and one with alpha-IFN. The other five patients re-

ceived IL2 alone. Three of the patients received IL2 conjugated to polyethylene glycol (PEG), which decreases the clearance rate 15-fold.<sup>18</sup> The neurologic illness, however, cannot be due to GM-CSF, alpha-IFN, or the PEG moiety, since nonconjugated IL2 alone caused a similar picture and GM-CSF has no known neurologic complications. This neurologic toxicity occurred in 2 of 92 patients treated with PEG-IL2 at the National Cancer Institute. While PEG-IL2 may prolong exposure to high levels of IL2, in the absence of a prospective study it is not clear that neurologic complications are more frequent in patients receiving PEG-IL2 than in those receiving unconjugated IL2.

Patients with hypereosinophilia may develop peripheral neuropathy, cerebral infarction, or dementia with white matter lesions on MRI.<sup>19-22</sup> While we cannot dismiss the possibility that hypereosinophilia contributed to the development of neurologic symptoms, marked eosinophilia was not present in all of our patients, and there are no previous reports of this constellation of signs and reversible lesions in patients with idiopathic hypereosinophilia.

There are a few reports of similar neurologic illness associated with IL2. Aphasia, hemiparesis, seizures, visual distortions, and ataxia occurred in a few patients receiving IL2<sup>12</sup> or PEG-IL2<sup>6</sup> for metastatic renal cell carcinoma reported by Philip et al. and Bukowski et al. Meyers and Yung<sup>23</sup> described a melanoma patient who developed a cerebellar syndrome and dementia 3 months after completing treatment with IL2 who had multiple white matter lesions on a later MRI scan.<sup>23</sup> The melanoma patient of Somers et al.<sup>15</sup> developed a spastic quadriparesis following IL2 with subcortical and cortical hyperintensities on MRI. The neurologic symptoms and the lesions gradually resolved. Bernard et al.<sup>11</sup> described two IL2 patients with brief episodes of focal neurologic deficits. Brain imaging was normal in both. Vecht et al.<sup>16</sup> reported a melanoma patient who developed a rapidly fatal encephalopathy with blindness, ataxia, and bilateral Babinski signs during an initial course of IL2. A CT was normal; MRI was not reported. At autopsy, the gray matter was normal but the white matter contained multiple small foci of perivascular demyelination. Because of the pathologic resemblance to acute perivenous encephalomyelitis, they postulated that the lesions were autoimmunologically mediated.

IL2 penetrates the blood-brain barrier. The CSF IL2 concentration averages 50% of serum level.<sup>24</sup> Specific cerebral IL2 binding sites are present in rat brain with highest density in the hippocampus. Similar receptors are likely present in human brain.<sup>25,26</sup> IL2 can alter adrenergic, dopaminergic, and cholinergic neurotransmission.<sup>25,27-30</sup> Direct neuromodulatory effects mediated by endogenous IL2 receptors may underlie the acute delirium frequently associated with IL2 therapy,<sup>28,29</sup> but are unlikely to have caused structural lesions.

IL2 can both promote the proliferation and matu-

ration of oligodendrocytes<sup>31</sup> and damage myelin.<sup>32,33</sup> Demyelination was the primary pathology in the case of fatal IL2 encephalopathy reported by Vecht et al.<sup>16</sup> There was, however, no clear evidence of myelin breakdown in our patients. The lesions affected both gray and white matter, and the CSF protein, which is often elevated in demyelinating diseases, was normal in six of the eight patients.

IL2 causes a systemic capillary leak syndrome.<sup>34</sup> Although Elison et al.<sup>32</sup> reported increased cerebral vascular permeability in cats, others have not found blood-brain barrier disruption with IL2 infusion.<sup>35,36</sup> The absence of gadolinium enhancement at the time of disease onset in our patients argues against blood-brain barrier dysfunction as a precipitating factor in the illness.

The brain lesions in our patients were not typical of arterial strokes. Multiple arterial territories were affected simultaneously and lesions resolved quickly. The subacute evolution of lesions, absence of hemorrhage, and lack of an embolic source make it unlikely that the lesions were caused by emboli.

IL2 induces IL1 and tumor necrosis factor (TNF) which affect endothelial cell function and coagulation.<sup>2,34,37,38</sup> TNF alone can damage axons and myelin in vitro and can cause a transient aphasia and focal neurologic deficits in patients.<sup>10,37,39</sup> IL2 may, therefore, cause neurologic dysfunction by inducing other cytokines.

IL2 can prolong the prothrombin time (PT) and partial thromboplastin time (PTT) and decrease coagulation factors,<sup>40,41</sup> but the PT and PTT were usually normal in our patients. More extensive monitoring of coagulation at one of our institutions showed an increase in von Willebrand's factor, but no abnormalities in protein C, protein S, antithrombin III, fibrinogen, PT, or PTT in patients receiving IL2.

The pattern of illness and distribution of lesions associated with IL2 are similar to those complicating cyclosporine therapy and occasionally seen with chemotherapy, alpha-IFN, hypertensive encephalopathy, and eclampsia.<sup>42-53</sup> The etiology of neurologic disease in these circumstances is unknown, but has been attributed to direct toxic effects of medications, cortical venous thrombosis, or a local vasculopathy with fluid extravasation. Cytokine activation is also likely in all these circumstances.

In summary, we describe eight patients who developed cortical and subcortical neurologic signs and cerebral lesions during treatment with IL2-based immunotherapy. The etiology of this illness is not known, but the similarity to neurologic complications of cyclosporine, chemotherapy, and other immunotherapy suggests a common pathogenesis.

The occurrence of new neurologic signs and lesions in patients receiving IL2 should not be presumed to be progression of the underlying disease. Since the neurologic illness associated with IL2 may be completely reversible, further IL2 infusion should be stopped and supportive care provided to maximize neurologic recovery.

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