2006-12-21

Case records of the Massachusetts General Hospital. Case 39-2006. A 24-year-old woman with systemic lupus erythematosus, seizures, and right arm weakness.

Jang-Ho J. Cha
Harvard Medical School

Et al.

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 39-2006: A 24-Year-Old Woman with Systemic Lupus Erythematosus, Seizures, and Right Arm Weakness

Jang-Ho J. Cha, M.D., Ph.D., Karen Furie, M.D., Jonathan Kay, M.D., Rochelle P. Walensky, M.D., M.P.H., Mark E. Mullins, M.D., Ph.D., and E. Tessa Hedley-Whyte, M.D.

From the Departments of Neurology (J.-H.J.C., K.F.), Rheumatology (J.K.), Medicine and Infectious Disease (R.P.W.), Radiology (M.E.M.), and Pathology (E.T.H.-W.), Massachusetts General Hospital; and the Departments of Neurology (J.-H.J.C., K.F.), Medicine (J.K., R.P.W.), Radiology (M.E.M.), and Pathology (E.T.H.-W.), Harvard Medical School.

N Engl J Med 2006;355:2678-89

PRESENTATION OF CASE

Dr. Sherry Chou (Neurology): A 24-year-old woman was transferred to this hospital because of seizures and a lesion in the brain.

A diagnosis of systemic lupus erythematosus (SLE) had been made 6 years earlier, associated with polyarthritis, myalgia, malar rash, facial swelling, photosensitivity, pancytopenia, fevers, Raynaud's syndrome, pericardial and pleural effusion, membranous glomerulonephritis, and alopecia. She had been treated continuously with corticosteroids, with the addition of methotrexate, azathioprine, mycophenolate, leflunomide, and etanercept at various times, and dapsone prophylaxis. Her compliance with her medication regimen had been poor, and she had stopped taking dapsone 6 months earlier.

For several months, the patient had experienced intermittent numbness of her tongue and slurred speech. Two weeks before admission, she was hospitalized elsewhere because of fever (peak temperature, 39.4°C) and joint pain. A diagnosis of lupus flare was made; her symptoms responded to dexamethasone, and she was discharged home.

Six days before admission to this hospital, she had transient tingling and shaking of her right arm. The next day, she had a generalized tonic–clonic seizure and was admitted to another hospital. Treatment with diphenylhydantoin was started, and no additional seizures occurred. Magnetic resonance imaging (MRI) of the brain revealed a small ovoid lesion in the left parietal lobe. Laboratory-test results are summarized in Table 1. Stains, cultures, and tests for antigens in the cerebrospinal fluid were negative for bacteria, mycobacteria, cryptococcus, *Neisseria meningitidis, Streptococcus pneumoniae,* group B streptococcus, and influenza B virus. The tingling in her right arm continued, and pain and weakness developed. A repeated MRI scan on the fourth hospital day showed enlargement of the lesion in the brain, with vasogenic edema involving the subcortical white matter of the left frontal and parietal lobes. Treatment with ceftriaxone and acyclovir was started. The patient was transferred to this hospital 6 days after admission to the other hospital.

The patient had a history of depression. She had been treated for narcotic and alcohol dependency in the past, but did not currently use either intravenous drugs or alcohol to excess. She smoked one pack of cigarettes daily. She was a native of Cape Verde but had lived most of her life in Massachusetts. She lived with her husband and was not employed because of her illness. Both of her parents had died of human immunodeficiency virus (HIV) infection. She was allergic to sulfa medications. In addition to antibiotics and diphenylhydantoin, her medications included fluoxetine, pantoprazole, prednisone (30 mg daily), lorazepam, a nicotine patch, and a fentanyl patch for the pain in her arm.

On examination, the patient was not in acute distress and answered questions appropriately. The temperature was 37.4°C, the pulse 100 beats per minute, the blood pressure 98/63 mm Hg, and the respirations 16 per minute; oxygen saturation was 100% while she was breathing ambient air. She had oral thrush and a blistering lesion consistent with herpes on her lower lip. The remainder of the general physical examination was normal. On neurologic examination, she was alert and oriented, with normal attention and speech; short-term memory was mildly impaired. There was slight flattening of the right nasolabial fold; the other cranial nerves were normal. The motor strength was 4+/5 in the right arm and was otherwise normal. Deep tendon reflexes were 3+ in the right arm and 2+ elsewhere; there was an extensor right plantar response. Sensation was normal. The gait was narrow-based, with small steps, and she had difficulty with tandem gait. The Romberg test was negative. Levels of serum electrolytes, amylase, and lipase and tests of coagulation and renal function were normal. Serologic testing for antibodies to toxoplasma, histoplasma, cryptococcus, blastomyces, coccidioides, bartonella, brucella, *Coxiella burnetii*, HIV, *Borrelia burgdorferi*, and Lyme disease and nucleic acid testing of blood for *Tropheryma whippelii* were negative. Lumbar puncture was performed (Table 1); stains and cultures for bacteria and fungi were negative, as was nucleic acid testing for cytomegalovirus and varicella–zoster, Epstein–Barr, herpes simplex type 1 and 2, and JC viruses. Results of other tests are summarized in Table 1.

Repeated MRI of the brain with T_2-weighted and fluid-attenuated inversion recovery (FLAIR) images the next day confirmed the presence of an area of hyperintensity involving the posterior left frontal and parietal lobe white matter, with patchy enhancement at the superior margin of the lesion. Levetiracetam, pyrimethamine, leucovorin (folinic acid), dapsone, ampicillin, and fluconazole were added, and diphenylhydantoin was discontinued. During the next 5 days, the temperature rose intermittently to 40.0°C. Repeated MRI on the fourth hospital day showed slightly increased enhancement but no change in the size of the lesion. Magnetic resonance spectroscopy showed a normal ratio of choline to creatine and the presence of a lactate peak. Computed tomographic (CT) scanning of the chest and abdomen showed no abnormalities. Repeated lumbar puncture (Table 1) showed no evidence of malignant cells on cytologic examination, and cultures for nocardia and listeria were negative.

The patient continued to have joint pain and severe headaches and required narcotics for pain control. On the sixth hospital day, CT scanning of the brain showed a heterogeneously enhancing lesion in the posterior aspect of the left frontal lobe. A stereotactic biopsy of the brain was performed, and microscopical examination of the biopsy specimen showed a subacute cerebritis that was more florid than typical lupus cerebritis; rare cells with prominent nucleoli were present that were thought to be histiocytes; special stains and immunohistochemical staining for bacteria, mycobacteria, fungi, varicella–zoster and herpes simplex viruses, and toxoplasma and nucleic acid testing for toxoplasma and bartonella DNA were negative. Results of laboratory tests are shown in Table 1. Lupus flare was diagnosed, and the patient was treated with prednisone at a dose of 60 mg daily.

During the next week, intermittent fevers continued; results of laboratory tests are listed in Table 1. Repeated MRI examination of the brain with T_2-weighted images on the 12th and 16th hospital days showed enlargement of the lesion in the left parietal lobe, with increased mass effect and surrounding edema, and new, nonenhancing, hyperintense lesions within the right caudate and corona radiata, right posterior frontal subcortical white matter, left anterior frontal gyrus, left lentiform nucleus, left occipital lobe, and left anterior thalamus. Magnetic resonance perfusion performed 3 days later showed decreased cerebral blood flow and cerebral blood volume in the left posterior frontal and anterior left parietal lobes. Positron-emission tomographic (PET) scanning of the brain showed mixed foci of hypo-

Table 1. Results of Laboratory Tests.

Variable	Normal Range	Other Hospital	This Hospital										
		Day 1	Day 1	Day 4	Day 6	Day 8	Day 11	Day 16	Day 19	Day 34	Day 40	Day 45	Day 52
Hematologic and blood chemical tests													
Hematocrit (%)	36.0–46.0	29.4	33.0		24.3	23.4	21.4	31.8			31.7		27.2
Hemoglobin (g/dl)	12.0–16.0	9.7	10.9		8.1	7.6	6.9	10.8			10.7		9.4
Mean corpuscular volume (μm^3)	80–100	103.6	103		102	101	102	93			93		92
White-cell count (per mm^3)	4,500–11,000	4,600	3,800		2,700	2,500	2,100	10,000			9,300		11,900
Differential count (%)													
Neutrophils	40–70	60.5	77			73	49	89			72		88
Band forms	0–10	0	0			0	0	0					
Lymphocytes	22–44	24.3	19			17	37	9			20		9
Monocytes	4–11	14.8	3			9	13	2			7		3
Eosinophils	0–8	0.1	1			1	1	0			1		0
Basophils	0–3	0.3	0			0	0	0			0		0
Platelet count (per mm^3)	150,000–350,000	218,000	331,000		241,000	225,000	280,000	536,000			535,000		701,000
Erythrocyte sedimentation rate (mm/hr)	1–25	47	64				109	132			59		92
Alanine aminotransferase (U/liter)	0–35	56	39		144	852	243	130			18		31
Aspartate aminotransferase (U/liter)	0–35	37	52		362	265	604	92			16		26
Alkaline phosphatase (U/liter)	30–120	87	75		69	348	507	887			174		168
Bilirubin (mg/dl)													
Total	0.3–1.0		0.2			1.0	1.8	1.8			0.4		0.2
Direct	0.1–0.3		0.1			0.5	0.9	0.9			0.2		0.1
Immunologic tests													
Antinuclear antibody	Negative (1:40)					1:1280 (homogeneous pattern)							
Anti–double-stranded DNA antibody	Negative at 1:10 dilution	1,871*				1:20							
Anti-Ro antibody	Negative					Positive							
Anti-La (SS-B) antibody	Negative					Negative							

Anti-RNP antibody	Negative	Negative			Negative					
Anti-Smith IgG	Negative	243†			Equivocal					
Antimitochondrial antibody	Negative					Negative				
Anti–smooth-muscle antibody	Negative at 1:20					Negative				
Anti–ribosomal P protein antibody (U/ml)	<20	92								
Anti–soluble liver antigen antibody (U/ml)	<5					Negative				
Anti–liver cytosol antibody (U/ml)	<15				1					
Anti–liver-kidney microsome antibody	<1:40				<1:40					
Total complement (U/ml)	63–145				11					
C3 (mg/dl)	86–184	37‡			27					
C4 (mg/dl)	20–58	11§			<10					
Cerebrospinal fluid analysis										
Opening pressure (mm H_2O)							12.5			9
Glucose (mg/dl)	50–75	59	55	135			41	42		34
Protein (mg/dl)	5–55	61	90	67			45	74		95
White cells (per mm^3)	0–5	63	3	1			84	49		15
Neutrophils (%)	0	5	30	19			21	60		12
Lymphocytes (%)	0	78	65	31			68	37		83
Monocytes (%)	0	17	5	49			11	3		4
Red cells (per mm^3)	0	2	5,111	3,889			3	8		33
IgG (mg/dl)	0.0–8.0							11.8		
Albumin (mg/dl)	11.0–50.9							43.6		
Agarose electrophoresis								No banding		

* The normal value was <5 IU per milliliter at the outside laboratory.
† The normal value was <100 U per milliliter at the outside laboratory.
‡ The normal range was 79 to 152 at the outside laboratory.
§ The normal range was 16 to 47 at the outside laboratory.

metabolism and hypermetabolism in the areas of abnormality detected on MRI; the areas of hypermetabolism suggested a malignant condition. Lumbar puncture was repeated (Table 1); repeated cultures were negative. West Nile virus nucleic acid, St. Louis and eastern equine encephalitis antibodies, and toxoplasmosis antibodies were not detected.

During the next week, the patient's temperature rose intermittently to 40.0°C. The patient became less alert, with psychomotor slowing, dysphasia, dysarthria, naming slowness, and the new onset of right–left confusion. Motor strength on the right side decreased to 4/5 in the leg, 3/5 in the upper arm, and 2/5 in the distal arm. Repeated MRI on the 22nd hospital day showed no change. Antimicrobial management was changed to include atovaquone and clindamycin. An open biopsy of the brain on the 26th hospital day showed granulomatous inflammation, coagulative necrosis, and granulation tissue; special stains and cultures for microorganisms were negative.

On the 40th hospital day, the patient had a headache and was lethargic. She followed commands but did not speak. Strength in the right arm and leg and muscle tone in the right arm were decreased. An MRI of the brain showed an increase in the size and number of lesions and possible leptomeningeal involvement. A transesophageal echocardiogram obtained the next day showed no vegetations. The patient became progressively more somnolent. A magnetic resonance cerebral angiogram performed on the 43rd hospital day showed progression of the lesions. A conventional cerebral angiogram showed no evidence of vasculitis. Lumbar puncture was repeated on the 45th day (Table 1), and caspofungin and voriconazole were added to her medications. On the 46th day, the patient was mute but followed commands. Repeated T_2-weighted MRI showed progression of the existing lesions and a new, enhancing, hyperintense focus in the right superior frontal gyrus.

A trial of intravenous pulse methylprednisolone (Solu-Medrol, Pfizer) at a dose of 1 g per day for 3 days was begun on the 51st hospital day. On the 52nd day, the patient was obtunded, with decorticate posturing and increased respiratory effort; the trachea was intubated, and she was transferred to the neurologic intensive care unit. Her antimicrobial regimen consisted of caspofungin, voriconazole, clindamycin, atovaquone, meropenem, vancomycin, and pyrimethamine. A urine culture was positive for vancomycin-resistant enterococci, and a sputum culture was positive for *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*; linezolid and cefepime were added to her medications.

On the 54th hospital day, the patient's pupils were fixed and dilated. CT scanning of the brain showed new areas of hypoattenuation in the right hemisphere and transtentorial and uncal herniation. An intracranial pressure monitor was placed, and the intracranial pressure on Licox insertion was 50 mm H_2O. Despite therapy with mannitol and induced hypertension, the patient's intracranial pressure increased to 130 mm H_2O, and the cerebral perfusion pressure was less than 10 mm Hg. She met clinical criteria for brain death by the evening of that day.

An autopsy was performed.

DIFFERENTIAL DIAGNOSIS

NEUROLOGIC LOCALIZATION OF THE LESION

Dr. Jang-Ho J. Cha: The first task of the neurologist who is treating a patient with a neurologic deficit is to locate the responsible lesion in time and space. When I first saw this patient, she had had intermittent numbness of the tongue and slurred speech for several months. Although I am aware of the diagnosis in this case, these symptoms suggest the presence of a spatially fixed lesion in the brain, with a number of possible localizations. The symptom of numbness is ambiguous, since it can imply either altered sensation or motor difficulty. The presence of slurred speech makes a motor problem more likely.

The transient shaking of the right arm that occurred 6 days before admission was most likely due to a focal seizure. This information is an important clue to localization, pointing to a lesion within the cortical surface of the left hemisphere. The area of the motor cortex that controls the arm is located near the area that controls the tongue and face; therefore, the numbness of the tongue, the facial weakness, and the seizure and weakness involving the right arm can be attributed to a single lesion most likely located within the junction

of the gray and white matter, an area where the clinical manifestation of lesions is likely to be seizures. Since language is largely preserved, there is no widespread damage within the left hemisphere. However, the fact that there is an extensor plantar response of the right toe suggests that this is a large lesion, since the area of the motor cortex that controls the leg and foot is located some distance from the area that controls the face and arm. May we see the imaging studies?

Dr. Mark E. Mullins: MRI scans of the brain obtained on the second hospital day (Fig. 1A and 1B) show a dominant lesion within the perirolandic region of the left hemisphere, associated with some contrast enhancement, hyperintensity on FLAIR and T_2-weighted images, and mild swelling. Some areas of restricted diffusion, which is consistent with vasogenic and cytotoxic edema, are associated with the dominant lesion. On the fourth hospital day, a repeated examination with spectroscopy showed diffusely decreased peaks within the areas of abnormal enhancement, suggesting some neuronal loss. The ratio of choline to creatine was approximately 1, a result suggesting that a tumor was not present.

Scans from repeated brain MRI on the 12th hospital day (Fig. 1C and 1D) show prominent changes in the dominant lesion, including hyperintensity on a T_1-weighted image and decreased signal intensity on the gradient–echo sequence, indicating the presence of hemorrhage. The lesion now has the appearance of a space-occupying enhancing lesion surrounded by a large area of edema.

PET scans of the brain obtained on the 19th hospital day show mixed hypermetabolism and hypometabolism in the dominant lesion (see Fig. 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org); these findings are consistent with cerebritis but also could suggest a neoplasm. The number of lesions has increased dramatically as compared with previous images. FLAIR images from another MRI scan (Fig. 1E and 1F) now show multiple areas of intraparenchymal swelling and hyperintensity on FLAIR images, in addition to the original lesion. The findings on MRI perfusion scans did not suggest the presence of a brain tumor.

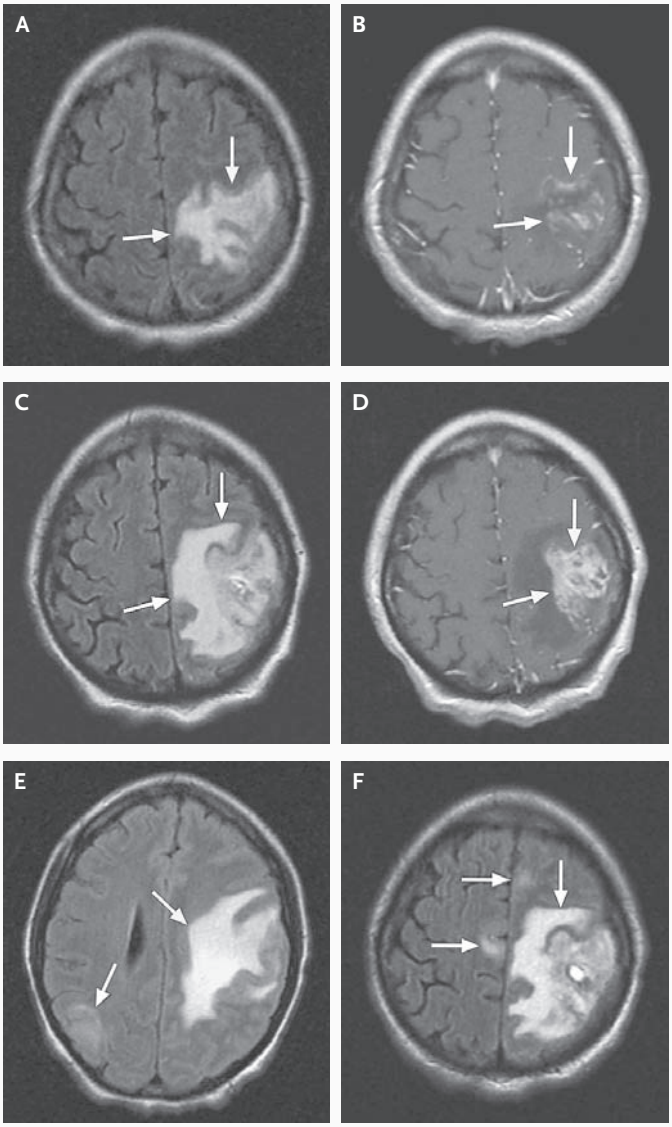

Figure 1. MRI Scans of the Brain.

A FLAIR image obtained on the second hospital day shows mild swelling and hypointensity in the left frontoparietal, perirolandic region, which is most consistent with edema (Panel A, arrows), with subtotal enhancement on a T_1-weighted image obtained after gadolinium enhancement (Panel B, arrows). A FLAIR image on the 12th hospital day shows a left frontoparietal lesion that has increased in size (Panel C, arrows), with enhancement and surrounding edema on a T_1-weighted image obtained after gadolinium enhancement (Panel D, arrows). FLAIR images of the brain on the 19th hospital day (Panels E and F) show multifocal, parenchymal hyperintensities that are most consistent with edema; most of these lesions (arrows) are new. There is involvement of the deep gray matter, subcortical white matter, and corpus callosum.

RADIOLOGIC DIFFERENTIAL DIAGNOSIS

The findings on the imaging studies are most consistent with cerebritis. Ongoing seizure activity can produce similar results, which may be the primary disorder or may occur in combination with other underlying conditions. The findings on PET scans suggest that this is not a typical bacterial infection.[1] Inflammatory disorders, including lupus cerebritis and sarcoidosis, should also be considered. Atypical tumors such as lymphoma or glioma may be included in the differential diagnosis in a case like this, when no other diagnosis is apparent. The imaging findings do not suggest simple ischemia or infarction.

Dr. Jonathan Kay: In this patient with SLE and the new onset of fever, seizures, weakness, and a brain lesion, the major question for the rheumatology consultants was whether these were the result of lupus disease activity itself or of a complication such as infection or a malignant tumor such as lymphoma.

LUPUS DISEASE ACTIVITY

Fever is one of the most common clinical manifestations of SLE, and disease activity accounts for more than 66% of febrile episodes in patients with this condition.[2] This patient did not have shaking chills or an elevated absolute neutrophil count, but she did have elevated titers of anti–double-stranded DNA and anti–ribosomal P antibodies, leukopenia, and hypocomplementemia — findings that are more characteristic of lupus disease activity than of infection. Various autoantibodies have been associated with neuropsychiatric lupus[3-5]; this patient had anti–double-stranded DNA antibodies and anti–ribosomal P antibodies, and she had had elevated IgG anticardiolipin antibodies in the past. Anti–double-stranded DNA antibodies cross-react with NR2 glutamate receptors in the brain,[5] and anticardiolipin antibodies may confer a predisposition to coagulation, resulting in the neurologic consequences of ischemic injury. Anti–ribosomal P antibodies have been detected in patients with lupus who had psychosis or depression, neither of which was present in this patient.

NEUROPSYCHIATRIC SLE

Central nervous system (CNS) involvement in SLE[6-12] includes inflammation of the brain (cerebritis) or intracranial blood vessels (vasculitis) and ischemic complications of vasculitis.[4] The most common manifestations are cognitive dysfunction, headache, seizures, and psychiatric conditions; aseptic meningitis, stroke, encephalopathy, movement disorders, and myelopathy are also seen.[3,13,14] This patient had seizures, cognitive dysfunction, and headache.

Parenchymal lesions, which are seen on imaging studies in up to 36% of patients, are usually located in the periventricular and subcortical white matter or corticomedullary junction. These lesions are thought to be a consequence of perivascular microinfarction. In this patient, however, the neuroradiographic appearance of the lesions did not suggest ischemia or demyelinating disease, and a cerebral angiogram did not show vasculitis.

INFECTION

Infections are common in patients with SLE,[15] accounting for about 20% of episodes of fever,[2] and are a leading cause of death in hospitalized patients.[2,16] CNS infection occurs infrequently,[17] most often in patients who have received corticosteroid treatment within the previous 6 months as well as concurrent immunosuppressive therapy with cyclophosphamide, azathioprine, or other agents. Our patient had important risk factors for infection, including active SLE with lymphopenia,[18] renal involvement, hypoalbuminemia, and the receipt of high doses of corticosteroids. She had also received other immunosuppressive therapy, including etanercept, a tumor necrosis factor (TNF) antagonist that may interfere with the host defense against opportunistic infections, including *Mycobacterium tuberculosis, Histoplasma capsulatum,* and *Listeria monocytogenes*.[19]

Although neuropsychiatric lupus is a possible explanation for this patient's symptoms, her risk factors for infection suggested that an unusual infection could not be ruled out, even in the presence of negative cultures and serologic studies for potential pathogens.

Dr. Karen Furie: The fulminant nature of this patient's illness, lack of response to immunosuppressive therapy, and rapid progression are not characteristic features of neuropsychiatric lupus. Since the patient was receiving immunosuppressive therapy for an autoimmune disease, possible infectious causes included bacterial, viral, fungal, and parasitic pathogens; in addition, we considered neoplastic and demyelinating conditions (Table 2).

Table 2. Differential Diagnosis of an Enhancing Hemispheric Lesion in This Patient.

- Lupus
  - Vasculitis
  - Lupus cerebritis
  - Demyelinating disease
  - Ischemia
- Infections
  - Bacterial
    - *Tropheryma whippelii* (Whipple's disease)
    - Listeria
    - Nocardia
    - Bartonella
    - Mycobacteria
  - Viruses
    - JC virus (progressive multifocal leukoencephalopathy)
    - Cytomegalovirus
    - Herpes simplex virus
    - Varicella–zoster virus
    - West Nile virus
    - Eastern equine encephalitis
- Protozoa
  - *Toxoplasma gondii*
  - Ameba
- Fungi
  - Candida
  - Mucormycosis
  - Cryptococcus
  - Histoplasmosis
  - Coccidioidomycosis
  - Aspergillus
  - Blastomycosis
- Helminths
  - Schistosomiasis
  - Neurocysticercosis
- Neoplasms
  - Lymphoma
  - Glioma
  - Metastases
  - Sarcoma

INFECTIONS IN IMMUNOCOMPROMISED PATIENTS

Cerebral toxoplasmosis has been reported in patients with SLE as a result of immunosuppression from the disease itself or from disease-modifying agents.[20,21] This patient's clinical course and the findings on imaging studies were consistent with the diagnosis of *Toxoplasma gondii;* however, biopsy of the brain and serologic tests of the cerebrospinal fluid were negative. Nevertheless, because of a strong suspicion for this diagnosis, she was treated for toxoplasmosis with dapsone and pyrimethamine, since her allergy to sulfa drugs precluded treatment with trimethoprim–sulfamethoxazole.

Progressive multifocal leukoencephalopathy is a demyelinating disease caused by the JC virus, affecting immunocompromised hosts. Patients with progressive multifocal leukoencephalopathy typically present with rapidly progressive focal neurologic deficits, although the onset can be subacute, and seizures can occur. Imaging studies characteristically show nonenhancing lesions of the white matter. The clinical scenario in this patient was suggestive of progressive multifocal leukoencephalopathy; however, the imaging findings were atypical, nucleic acid testing for the JC virus was negative, and two brain biopsies did not show the characteristic findings.

Patients with CNS cryptococcosis usually present with subacute symptoms such as encephalopathy, headache, and fever, and this diagnosis would be a consideration in this case. However, the results of imaging studies, negative cerebrospinal fluid test for cryptococcal antigen, and negative cerebrospinal fluid culture essentially rule out this diagnosis. Patients with neurocysticercosis, which is caused by the larval stage of the pork tapeworm, *Taenia solium,* commonly present with seizures[22,23]; headache, altered sensorium, and focal deficits have also been described. This patient was a native of Cape Verde, where neurocysticercosis has been reported.[24] However, the acute febrile illness and rapid progression are not characteristic of neurocysticercosis, and the imaging studies did not support this diagnosis.

LYMPHOMA

Finally, primary CNS lymphoma is a rare subtype of non-Hodgkin's lymphoma, usually of B-cell origin, that affects the eyes, brain, and leptomeninges. It occurs more commonly in immunocompromised than in immunocompetent persons, including patients treated with agents that block the activity of TNF.[25] Some of the imaging findings in this patient were thought to be consistent with lymphoma. However, two biopsies showed no evidence of lymphoma. We considered performing a third biopsy but could not do so because of

the rapid deterioration of the patient's neurologic status.

Dr. Cha: Because of the patient's deteriorating condition and her lack of response to a broad spectrum of antimicrobial therapies, we were left with a presumptive diagnosis of lupus cerebritis. A trial of high-dose corticosteroids was initiated in an attempt to treat this condition, but her disorder worsened and she died.

CLINICAL DIAGNOSIS

SLE with probable lupus cerebritis.

Possible CNS infection.

PATHOLOGICAL DISCUSSION

Dr. E. Tessa Hedley-Whyte: The two brain biopsy specimens showed an inflammatory process, which in the first biopsy specimen comprised predominantly lymphocytes and polymorphonuclear leukocytes, with occasional pale cells that were thought to be histiocytes (see Fig. 2 of the Supplementary Appendix). The second biopsy specimen showed a granulomatous reaction with coagulative necrosis and granulation tissue, but no recognizable organisms.

At autopsy, the entire left hemisphere of the brain was disintegrating (Fig. 2A). The thalamus

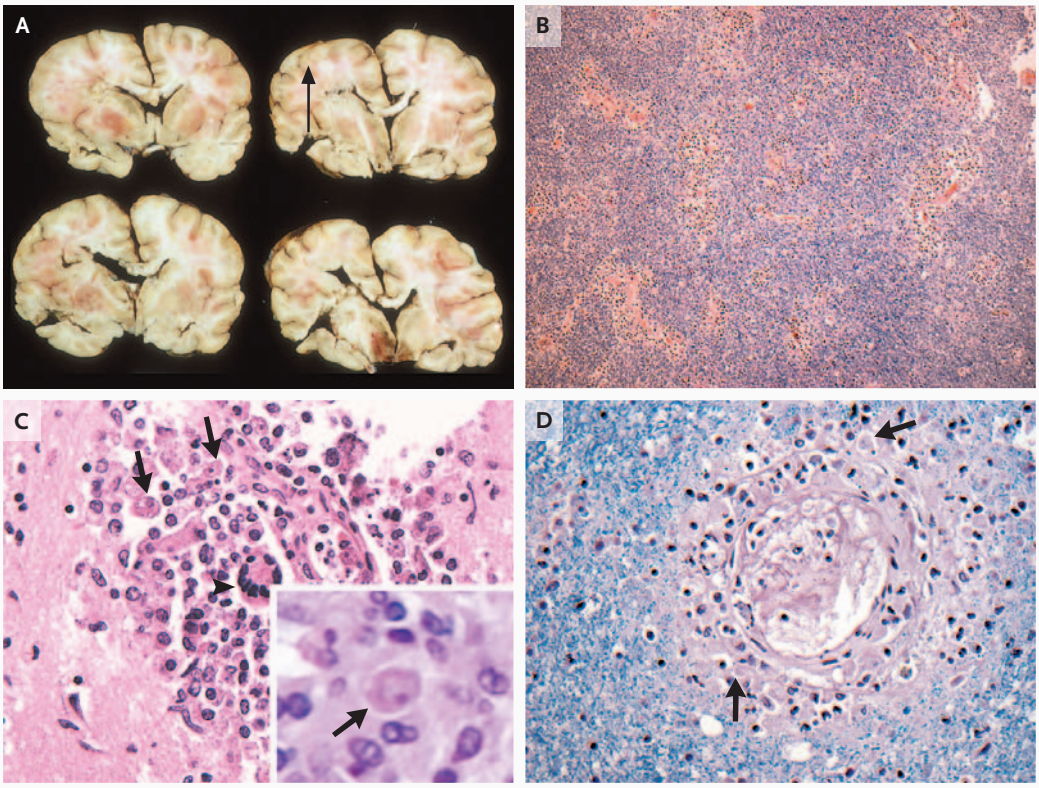

Figure 2. Sections of the Brain at Autopsy.

Coronal sections of the formalin-fixed brain show flattening of the gyri and obliteration of the sulci, findings indicative of severe brain swelling, and loss of delineation between gray and white matter (Panel A). The left hemisphere (on the left side of the photograph) is disintegrating. The left and right midbrain and caudal left thalamus are hemorrhagic. The biopsy site is marked by an arrow. A histologic section of central white matter from the left hemisphere contains multiple areas of inflammation and necrosis, predominantly in a perivascular distribution (Panel B, Luxol fast blue–hematoxylin and eosin staining for myelin and cells). At a higher magnification, there are perivascular lymphocytes, plasma cells, a multinucleated giant cell (black arrowhead), and a few amebas (black arrows) (Panel C, hematoxylin and eosin). The inset shows a viable ameba (arrow) in the white matter with only a mild inflammatory response (hematoxylin and eosin). There is necrosis of a blood-vessel wall (Panel D, Luxol fast blue–hematoxylin and eosin), which is a typical finding in amebic encephalitis. Several disintegrating amebas are mixed with the inflammatory cells (arrows).

and the upper brain stem were hemorrhagic and necrotic. Lesions were also evident within the cerebellum. Microscopical examination showed perivascular and parenchymal inflammation with multinucleated giant cells, lymphocytes, plasma cells, and neutrophils throughout the brain (Fig. 2B). There were numerous amebas, which are easily mistaken for histiocytes (Fig. 2C). Amebas were present even in areas that appeared normal on gross examination, with only a minor inflammatory response. Encysted amebas were present in small numbers. A characteristic of amebic encephalitis is the dissolution of the blood-vessel walls, which probably accounts for the hemorrhage in the most involved areas (Fig. 2D).

The size of the amebas was compatible with acanthamoeba, balamuthia, and entamoeba. Entamoeba is not associated with this type of inflammatory response and has no capsule. To ascertain whether this organism was acanthamoeba or balamuthia, samples of the tissue were sent to the Centers for Disease Control and Prevention. Immunofluorescence staining of the formalin-fixed brain tissue with rabbit antibodies to acanthamoeba species confirmed the diagnosis of infection with acanthamoeba species (see Fig. 3 of the Supplementary Appendix).[26] An analysis of nucleic acid amplified by means of polymerase chain reaction from frozen brain tissue revealed the genus-specific amplicon ASA.S1, genotype T1. This amplicon has been seen in isolates of acanthamoeba obtained from granulomatous amebic encephalitis but not from the environment.[27,28]

The anatomical diagnosis is granulomatous amebic encephalitis due to acanthamoeba species. The rest of the autopsy showed inactive membranous glomerulonephritis. No amebas were seen outside the brain.

The diagnosis of granulomatous amebic encephalitis is notoriously difficult to establish.[27] Even after we knew that the diagnosis was amebic encephalitis, we were not confident that there were recognizable amebas in the biopsy specimens. In retrospect, some of the cells identified as histiocytes in the specimens were probably amebas (see Fig. 2 of the Supplementary Appendix). Three other cases of granulomatous amebic encephalitis due to acanthamoeba have been reported in patients with SLE, all diagnosed post mortem.[29-31]

DISCUSSION OF MANAGEMENT

Dr. Rochelle P. Walensky: Free-living amebas cause three types of disease in humans: amebic keratitis, primary amebic meningoencephalitis, and granulomatous amebic encephalitis. Table 3 compares the characteristics of primary amebic meningoencephalitis and granulomatous amebic encephalitis. Our patient had a typical clinical presentation of granulomatous amebic encephalitis due to acanthamoeba species, with subacute to long-term onset of symptoms related to a space-occupying lesion, including seizures, focal nerve deficits, and alteration in mental status. Death generally occurs within weeks after the onset of symptoms, often from herniation of the brain due to increased intracranial pressure; this was the case with the patient under discussion.[32]

Acanthamoeba species presumably enter the CNS through hematogenous spread from a usually transient primary infection in the lungs, skin, or paranasal sinuses in an immunocompromised host. The diagnosis is challenging, since acanthamoeba species are rarely isolated from cerebrospinal fluid[33] and serologic testing is not useful.[34] Brain biopsy, which was nondiagnostic on two occasions in this patient, is the only way to make a definitive diagnosis. The diagnosis is most often made on postmortem examination, as in this case.

Table 3. Comparison of the Features of Granulomatous Amebic Encephalitis and Primary Amebic Meningoencephalitis.

Characteristic	Granulomatous Amebic Encephalitis	Primary Amebic Meningoencephalitis
Infective agent	Acanthamoeba species *Balamuthia mandrillaris*	*Naegleria fowleri*
Predisposition	Occurs in immunodeficient persons Associated with chronic debilitating illness	Occurs in healthy persons Associated with exposure to contaminated water
Clinical course	Subacute	Acute, with death occurring within days
Pathological findings	Cysts and trophozoites present Hemorrhagic necrosis Vasculitis Inflammation with or without granulomas	Only trophozoites present Hemorrhagic necrosis Purulent meningoencephalitis

In nearly all cases of successful treatment of infections due to acanthamoeba species, the disease is localized to the skin or sinuses, without CNS involvement. In rare cases, patients with granulomatous amebic encephalitis have survived, usually when a single brain lesion could be excised.[32,35] For this patient, there would have been limited therapeutic options had the diagnosis been made before death.[35] Most available antimicrobial agents are amebostatic rather than amebicidal, are too toxic, or do not penetrate the CNS.[35] The use of corticosteroids to decrease intracranial pressure may exacerbate immune dysfunction.[32]

Dr. Kay: Because TNF plays a crucial role in granuloma formation, organisms that stimulate a granulomatous response, such as *M. tuberculosis* and *H. capsulatum*, may disseminate with TNF antagonist therapy. Although we do not know the timing or duration of etanercept therapy in this patient, its use may have predisposed her to disseminated amebic infection by interfering with granuloma formation.

ANATOMICAL DIAGNOSIS

Granulomatous amebic encephalitis due to acanthamoeba species.

Dr. Cha reports receiving consulting fees from Sirna Therapeutics and lecture fees from Pfizer; Dr. Furie, receiving consulting fees from Amersham Biosciences–GE Healthcare and grant support from Pfizer and Boehringer Ingelheim; Dr. Kay, receiving consulting fees from Amgen, Biogen Idec, Centocor, Genentech, Novartis, and Wyeth and grant support from Amgen, Centocor, Elan Pharmaceuticals, and Genentech; and Dr. Hedley-Whyte, having equity ownership in Becton Dickinson. No other potential conflict of interest relevant to this article was reported.

We thank Govinda S. Visvesvara, Ph.D., and Ms. Rama Sriram of the Division of Parasitic Diseases at the Centers for Disease Control and Prevention, Atlanta, for performing the immunofluorescence testing; and Greg Booton, Ph.D., Departments of Molecular Genetics and Evolution, Ecology, and Organismal Biology, Ohio State University, Columbus, for performing the nucleic acid testing for acanthamoeba.

REFERENCES

1. Lee BY, Newberg AB, Liebeskind DS, Kung J, Alavi A. FDG-PET findings in patients with suspected encephalitis. Clin Nucl Med 2004;29:620-5.
2. Stahl NI, Klippel JH, Decker JL. Fever in systemic lupus erythematosus. Am J Med 1979;67:935-40.
3. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599-608.
4. Senecal JL, Raymond Y. The pathogenesis of neuropsychiatric manifestations in systemic lupus erythematosus: a disease in search of autoantibodies, or autoantibodies in search of a disease? J Rheumatol 2004;31:2093-8.
5. DeGiorgio LA, Konstantinov KN, Lee SC, Hardin JA, Volpe BT, Diamond B. A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. Nat Med 2001;7:1189-93.
6. Hanly JG, Liang MH. Cognitive disorders in systemic lupus erythematosus: epidemiologic and clinical issues. Ann N Y Acad Sci 1997;823:60-8.
7. Hanly JG, Cassell K, Fisk JD. Cognitive function in systemic lupus erythematosus: results of a 5-year prospective study. Arthritis Rheum 1997;40:1542-3.
8. Jonsen A, Bengtsson AA, Nived O, Ryberg B, Sturfelt G. Outcome of neuropsychiatric systemic lupus erythematosus within a defined Swedish population: increased morbidity but low mortality. Rheumatology (Oxford) 2002;41:1308-12.
9. Petri M. Clinical features of systemic lupus erythematosus. Curr Opin Rheumatol 1994;6:481-6.
10. Rubin LA, Urowitz MB, Gladman DD. Mortality in systemic lupus erythematosus: the bimodal pattern revisited. Q J Med 1985;55:87-98.
11. Jennekens FG, Kater L. The central nervous system in systemic lupus erythematosus. 2. Pathogenetic mechanisms of clinical syndromes: a literature investigation. Rheumatology (Oxford) 2002;41:619-30.
12. *Idem.* The central nervous system in systemic lupus erythematosus. 1. Clinical syndromes: a literature investigation. Rheumatology (Oxford) 2002;41:605-18.
13. Afeltra A, Garzia P, Mitterhofer AP, et al. Neuropsychiatric lupus syndromes: relationship with antiphospholipid antibodies. Neurology 2003;61:108-10.
14. Ainiala H, Loukkola J, Peltola J, Korpela M, Hietaharju A. The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. Neurology 2001;57:496-500.
15. Petri M. Infection in systemic lupus erythematosus. Rheum Dis Clin North Am 1998;24:423-56.
16. Hellmann DB, Petri M, Whiting-O'Keefe Q. Fatal infections in systemic lupus erythematosus: the role of opportunistic organisms. Medicine (Baltimore) 1987;66:341-8.
17. Hung JJ, Ou LS, Lee WI, Huang JL. Central nervous system infections in patients with systemic lupus erythematosus. J Rheumatol 2005;32:40-3.
18. Iliopoulos AG, Tsokos GC. Immunopathogenesis and spectrum of infections in systemic lupus erythematosus. Semin Arthritis Rheum 1996;25:318-36.
19. Ehlers S. Why does tumor necrosis factor targeted therapy reactivate tuberculosis? J Rheumatol Suppl 2005;74:35-9.
20. Wilcox MH, Powell RJ, Pugh SF, Balfour AH. Toxoplasmosis and systemic lupus erythematosus. Ann Rheum Dis 1990;49:254-7.
21. Dubin HV, Courter MH, Harrell ER. Toxoplasmosis: a complication of corticosteroid- and cyclophosphamide-treated lupus erythematosus. Arch Dermatol 1971;104:547-50.
22. Wallin MT, Kurtzke JF. Neurocysticercosis in the United States: review of an important emerging infection. Neurology 2004;63:1559-64.
23. Nash TE, Del Brutto OH, Butman JA, et al. Calcific neurocysticercosis and epileptogenesis. Neurology 2004;62:1934-8.
24. Case Records of the Massachusetts General Hospital (Case 8-1993). N Engl J Med 1993;328:566-73.
25. Case Records of the Massachusetts General Hospital (Case 8-2006). N Engl J Med 2006;354:1178-84.
26. Shirwadkar CG, Samant R, Sankhe M, et al. Acanthamoeba encephalitis in patient with systemic lupus, India. Emerg Infect Dis 2006;12:984-6.
27. Booton GC, Visvesvara GS, Byers TJ, Kelly DJ, Fuerst PA. Identification and distribution of Acanthamoeba species genotypes associated with nonkeratitis infections. J Clin Microbiol 2005;43:1689-93.
28. Bloch KC, Schuster FL. Inability to make premortem diagnosis of Acanthamoeba species infection in a patient with fatal granulomatous amebic encephalitis. J Clin Microbiol 2005;43:3003-6.
29. Grunnet ML, Carron GH, Kushner LS. Fulminant amebic meningoencephalitis

due to Acanthamoeba. Neurology 1981;31:174-6.
30. Koide J, Okusawa E, Ito T, et al. Granulomatous amoebic encephalitis caused by Acanthamoeba in a patient with systemic lupus erythematosus. Clin Rheumatol 1998;17:329-32.
31. Uschuplich V, Mileusnic D, Johnson M. Pathologic quiz case: progressive fatal encephalopathy in an immunosuppressed patient with a history of discoid lupus erythematosus: subacute granulomatous meningoencephalitis (Acanthamoeba culbertsoni). Arch Pathol Lab Med 2004;128(9):e109-e111.
32. Marciano-Cabral F, Cabral G. Acanthamoeba spp. as agents of disease in humans. Clin Microbiol Rev 2003;16:273-307.
33. Pisani F, Costa C, Oteri G, Ioli A. Identification of amoebae in the CSF in a patient with meningoencephalitis. J Neurol Neurosurg Psychiatry 2003;74:1445-6.
34. Huang ZH, Ferrante A, Carter RF. Serum antibodies to Balamuthia mandrillaris, a free-living amoeba recently demonstrated to cause granulomatous amoebic encephalitis. J Infect Dis 1999;179:1305-8.
35. Deetz TR, Sawyer MH, Billman G, Schuster FL, Visvesvara GS. Successful treatment of Balamuthia amoebic encephalitis: presentation of 2 cases. Clin Infect Dis 2003;37:1304-12.