Case 6-2012

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Presentation of Case

Dr. Clayton Knox (Medicine): A 45-year-old man with a history of alcoholism was admitted to this hospital because of rapid cognitive decline and worsening jaundice.

During the previous 3 months, increasing fatigue and cough productive of yellow sputum and flecks of blood had developed, with post-tussive vomiting. Eleven days earlier, the patient had traveled to Europe for a week for a family event, during which he had consumed 10 to 20 alcoholic beverages per day. He had stopped drinking alcohol on his return, 3 days before admission, when nausea and vomiting developed. The next day, he called his physician's office. He reported no recent alcohol use and no fever, headache, diarrhea, or abdominal pain. Azithromycin was prescribed, and fluids and follow-up were advised. During the 36 hours before admission, jaundice developed, his urine darkened, and somnolence, slow and slurred speech, difficulty putting words together, and repetitions of questions and phrases developed. His girth gradually increased and his appetite decreased, without weight loss, tremulousness, or seizure activity. He was taken to the emergency department at a local affiliated hospital.

On examination, the patient was lethargic but oriented to person, place, and time and able to follow simple commands. The vital signs and oxygen saturation while he was breathing ambient air were normal. Scleral icterus, bilateral facial telangiectasias, and crackles in the right lower lung were evident, as was abdominal distention, with the edge of the liver palpable and slight tenderness in the right upper quadrant. The remainder of the physical and neurologic examination was normal. The blood levels of glucose, alanine aminotransferase, lipase, amylase, troponin I, and ammonia were normal, as were the results of renal-function tests; testing for hepatitis B and C viruses, alcohol, and salicylates was negative. Other results are shown in Table 1.

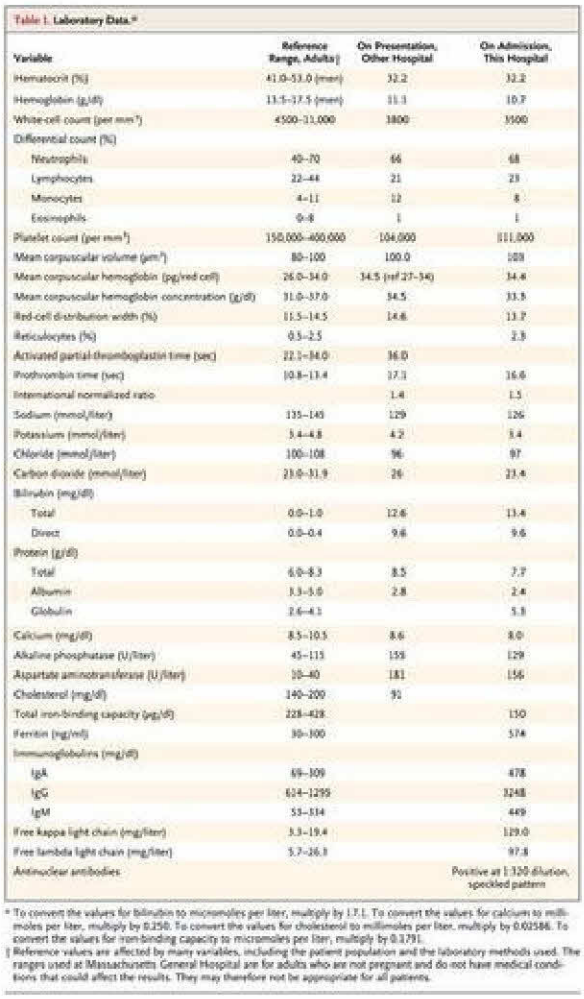

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Presentation, Other Hospital	On Admission, This Hospital
Hematocrit (%)	41.0–53.0 (men)	32.2	32.2
Hemoglobin (g/dl)	13.5–17.5 (men)	11.1	10.7
White-cell count (per mm³)	4500–11,000	3800	3500
Differential count (%)			
Neutrophils	40–70	66	68
Lymphocytes	22–44	21	23
Monocytes	4–11	12	8
Eosinophils	0–8	1	1
Platelet count (per mm³)	150,000–400,000	104,000	111,000
Mean corpuscular volume (μm³)	80–100	100.0	103
Mean corpuscular hemoglobin (pg/red cell)	26.0–34.0	34.5 (ref 27–34)	34.4
Mean corpuscular hemoglobin concentration (g/dl)	31.0–37.0	34.5	33.3
Red-cell distribution width (%)	11.5–14.5	14.6	13.7
Reticulocytes (%)	0.5–2.5		2.3
Activated partial-thromboplastin time (sec)	22.1–34.0	36.0	
Prothrombin time (sec)	10.8–13.4	17.1	16.6
International normalized ratio		1.4	1.5
Sodium (mmol/liter)	135–145	129	126
Potassium (mmol/liter)	3.4–4.8	4.2	3.4
Chloride (mmol/liter)	100–108	96	97
Carbon dioxide (mmol/liter)	23.0–31.9	26	23.4
Bilirubin (mg/dl)			
Total	0.0–1.0	12.6	13.4
Direct	0.0–0.4	9.6	9.6
Protein (g/dl)			
Total	6.0–8.3	8.5	7.7
Albumin	3.3–5.0	2.8	2.4
Globulin	2.6–4.1		5.3
Calcium (mg/dl)	8.5–10.5	8.6	8.0
Alkaline phosphatase (U/liter)	45–115	159	129
Aspartate aminotransferase (U/liter)	10–40	181	156
Cholesterol (mg/dl)	140–200	91	
Total iron-binding capacity (μg/dl)	228–428		130
Ferritin (ng/ml)	30–300		574
Immunoglobulins (mg/dl)			
IgA	69–309		478
IgG	624–1295		3248
IgM	53–334		449
Free kappa light chain (mg/liter)	3.3–19.4		129.0
Free lambda light chain (mg/liter)	5.7–26.3		97.8
Antinuclear antibodies			Positive at 1:320 dilution, speckled pattern

* To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for iron-binding capacity to micromoles per liter, multiply by 0.1791.
† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

Table 1:

Laboratory Data.

An electrocardiogram was normal. A chest radiograph showed findings consistent with atelectasis in the base of the right lung, unchanged from 5 years earlier, and was otherwise normal. Computed tomography (CT) of the head obtained without the administration of contrast material revealed hypodensity and mass effect in the right temporal lobe and insula, with preservation of the adjacent cortex and without intracranial herniation or hydrocephalus. Magnetic resonance imaging (MRI) after the administration of contrast material revealed a solitary lesion (2.6 cm in diameter) in the right insula, with thin, smooth, peripheral enhancement and extensive surrounding edema and mild mass effect. The patient was transferred to this hospital.

The patient reported no fever, chills, diarrhea, abdominal pain, chest pain, dyspnea, weakness, numbness, tingling, paresthesias, or altered sensation, taste, or smell. He had a history of elevated results of liver-function tests, anxiety, depression, gout, erectile dysfunction, and bursitis of the right shoulder; he had undergone a hemorrhoidectomy 7 years earlier after an episode of rectal bleeding and iron-deficiency anemia requiring hospitalization. He had a long history of alcohol abuse (up to 1 liter of vodka per day). He had declined detoxification treatment, disulfiram therapy, and referral to support groups for alcoholism. He did not smoke or use illicit drugs. Medications included allopurinol, citalopram,

sildenafil, and vitamins; he had taken celecoxib for bursitis for 3 months, stopping 3 months earlier. He had no known allergies. He grew up on a farm in Europe, immigrated to the United States two decades ago, returned to Europe often for family events, lived with his wife and children, and had worked in the food-service industry and with heavy machinery. His mother, 89 years of age, had cancer, and his father died at 84 years of age with bone cancer; a cousin had tuberculosis.

On examination, the blood pressure was 142/89 mm Hg; other vital signs were normal. The conjunctivae were icteric, the tongue was smooth and dry, and there was dried blood in the mouth. A systolic murmur, grade 2/6, was heard at the apex, radiating toward the axilla. The abdomen was distended, with periumbilical striae, bulging flanks, and a prominent venous pattern over the upper abdomen, without tenderness, rebound, or guarding. The edge of the liver was four fingerbreadths below the right costal margin in the midclavicular line. The skin was jaundiced, and there were petechiae on the legs. The patient followed commands and spoke fluently and spontaneously, without aphasia or dysarthria. The pupils constricted briskly (the right pupil from 5 mm to 4 mm, and the left pupil from 4 mm to 3 mm), and the remainder of the examination was normal.

Blood levels of phosphorus, magnesium, alanine aminotransferase, lactate dehydrogenase, iron, vitamin B12 , and folate were normal. Serum protein electrophoresis and immunofixation showed five small bands (two IgG kappa, one IgG lambda, and two IgM kappa, all <0.25 g per deciliter), features consistent with an oligoclonal immune response. Other test results are shown in Table 1.

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Table 1:

Laboratory Data.

The urine contained 3+ bilirubin and trace urobilinogen, glucose, and ketones; screening for toxins in the urine revealed lorazepam. Thiamine, folic acid, allopurinol, citalopram, levetiracetam, and multivitamins were administered.

During the next 3 days, the patient was intermittently lethargic, with slurred speech. Testing for IgG antibodies to Epstein-Barr virus (EBV) capsid antigen and nuclear antigen was positive; the level of EBV DNA was 1000 copies per milliliter by polymerase chain reaction. Testing for IgM antibodies to EBV; antibodies to cytomegalovirus and smooth muscle; and hepatitis A, B and C viruses was negative, as was a skin test for tuberculosis. Ultrasonography of the abdomen showed hepatic and splenic enlargement and a thickened gallbladder wall. CT of the chest revealed scattered nodules, 2 to 5 mm in diameter, in the middle lobe and a minor fissure of the right lung, bilateral hilar lymphadenopathy, and trace pleural effusions bilaterally. CT of the abdomen showed hepatosplenomegaly, mild lymphadenopathy, and a small amount of ascites. On the third day, repeat MRI of the brain obtained after the administration of contrast material showed a T2-weighted hyperintense lesion (3.4 cm in diameter) with thin, smooth peripheral enhancement and heterogeneous foci of restricted diffusion centrally. Lactulose was administered.

On the fifth hospital day, the level of total bilirubin was 18.6 mg per deciliter (318 μmol per liter), and the direct bilirubin 11.8 mg per deciliter (202 μmol per liter).

A test result was received, and a diagnostic procedure was performed.

Differential Diagnosis

Dr. Tracey A. Cho: This 45-year-old man with chronic alcoholic liver disease presented with subacute fatigue, cough, and hemoptysis; acute liver decompensation; and fluctuating mental status. He had variable somnolence, slow and slurred speech, difficulty putting words together, and frequent repetition during conversational speech. Results of his mental-status examination and his level of arousal fluctuated, without clear focal deficits, but note was made of anisocoria, with the right pupil larger than the left pupil, and worsening somnolence.

Syndromic Diagnosis

Neuroanatomical localization is fairly broad at this point. Somnolence may result from abnormalities in the bilateral cortexes, reticular activating system (rostral brain stem), or bilateral medial thalami. Slow speech and difficulty putting words together may be indicative of aphasia due to dominant frontal-lobe or temporal-lobe dysfunction or could represent bradyphrenia, which may be caused by global, diffuse subcortical, extrapyramidal, or psychiatric dysfunction. Alternatively, difficulty putting words together could represent impaired attention resulting from global dysfunction, lesions in the prefrontal cortex, parietal lesions, or a psychiatric cause. Conversational repetition could be explained by impaired attention or by short-term memory impairment, attributable to the medial temporal lobe and limbic circuits (thalamus, mammillary bodies, and their connections). Slurred speech or dysarthria may be due to lesions in the corticobulbar tract, brain-stem motor nuclei, cranial nerves, cerebellum, extrapyramidal system, or vocal cords. The findings of somnolence (in the absence of signs of aphasia or amnesia), slow speech, difficulty putting words together, conversational repetition, and slurred speech suggest global hemispheric dysfunction. However, anisocoria with the right pupil larger than the left pupil suggests dysfunction of the

right optic nerve, the right pupillary constrictor muscles, the parasympathetic component of the right oculomotor nerve, or the left sympathetic pathway.

Many features of the patient's history and laboratory data could be accounted for by liver disease and a subacute confusional state. The differential diagnosis includes five major syndromes: hepatic encephalopathy, Wernicke's encephalopathy, alcohol withdrawal, occult seizures, and infection. However, the anisocoria seen on examination raises the possibility of mass effect on the right midbrain, which would compromise parasympathetic input to the pupil through the oculomotor nerve. In patients who are immunocompromised to any degree, such as this patient with liver disease, alterations in mental status should prompt CT of the head without the administration of contrast material, since multiple processes (e.g., both diffuse and focal mass lesions) may occur simultaneously.

May we review the imaging studies?

Dr. Mykol Larvie: The CT scan of the head without the administration of contrast material (Figure 1A) shows hypodensity involving the right insula and temporal lobe and extending superiorly into the corona radiata.

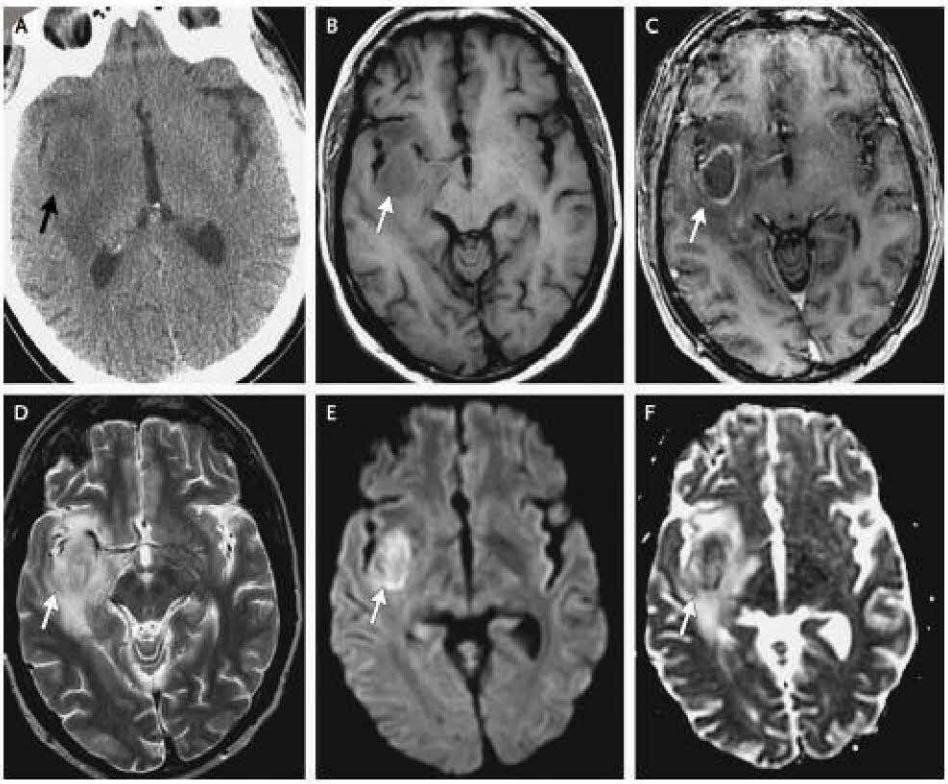


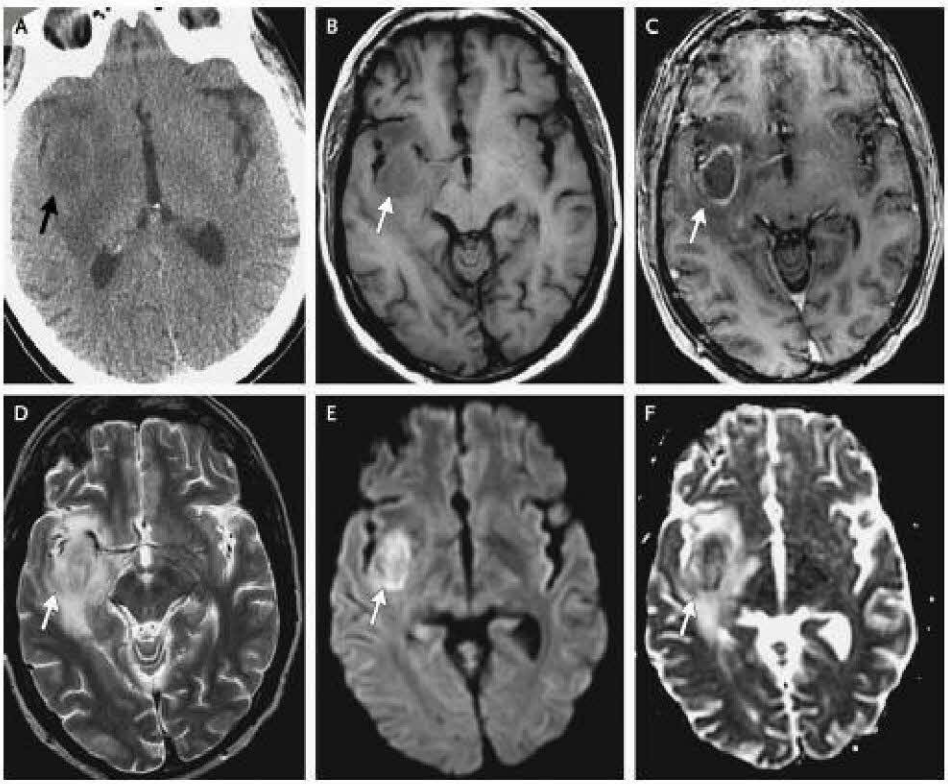
Figure 1:

Brain Imaging.

A CT scan of the head without the administration of contrast material (Panel A) reveals a hypodense lesion centered in the right insula (arrow). In addition, there is abnormal hypodensity extending into the adjacent parenchyma, including the right internal and external capsules and the right thalamus. There is mild mass effect. No calcifications are apparent. MRI scans in Panels B through F show a lesion centered

in the right insula (arrows). T1 -weighted images before (Panel B) and after (Panel C) the administration of contrast material reveal a peripherally enhancing lesion centered in the right insula, corresponding to the lesion seen on the CT scan (Panel A). There is heterogeneous T2 -weighted hyperintensity within the lesion (Panel D). In addition, there is more confluent hyperintensity in the adjacent parenchyma on T2 -weighted images, also extending into the right temporal lobe, with an appearance suggestive of perilesional edema. Diffusion-weighted imaging (Panel E) reveals hyperintensity within the right insular lesion, with corresponding hypointensity in the apparent-diffusion-coefficient image (Panel F), features consistent with restricted diffusion. The MRI scans also show the increased mass within the right insular lesion and surrounding tissue, with mild effacement of adjacent sulci and no intracranial brain herniation.

There is mild mass effect, with slight effacement of the right lateral ventricle. T2 -weighted images from MRI of the head (Figure 1D) show a region of relatively mild hyperintensity centered in the right insula,



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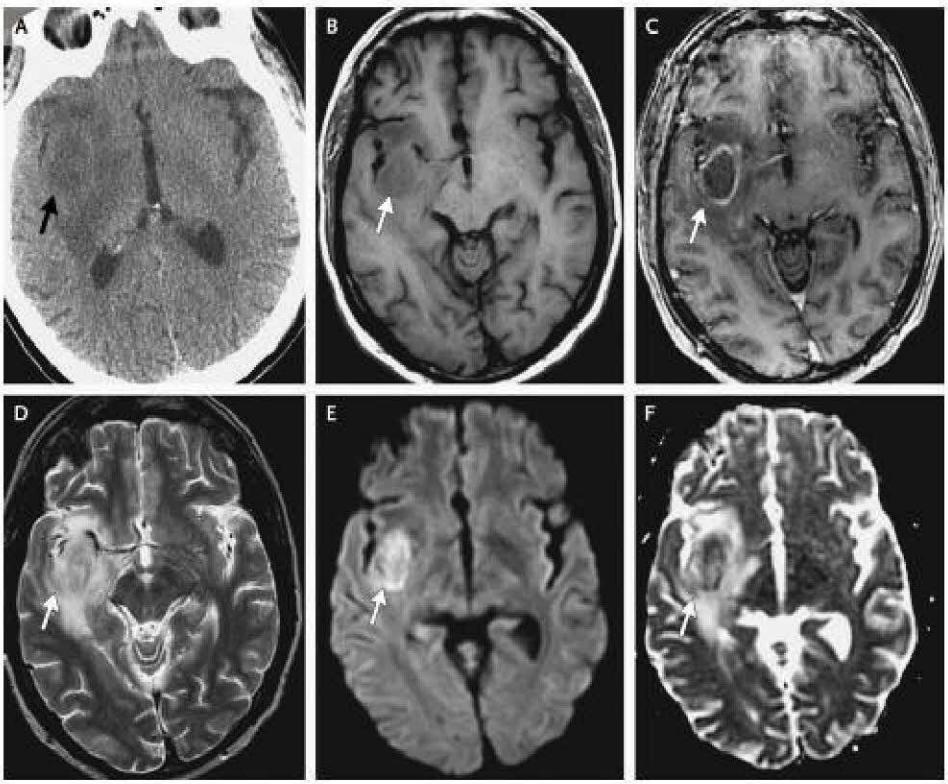
perilesional edema. Diffusion-weighted imaging (Panel E) reveals hyperintensity within the right insular lesion, with corresponding hypointensity in the apparent-diffusion-coefficient image (Panel F), features consistent with restricted diffusion. The MRI scans also show the increased mass within the right insular lesion and surrounding tissue, with mild effacement of adjacent sulci and no intracranial brain herniation.

as well as confluent hyperintensity in the adjacent parenchyma that is consistent with edema. The pattern suggests a central lesion with perilesional edema. There is no evidence of hemorrhage, and mild, heterogeneous restricted diffusion corresponds to the mildly hyperintense region seen on T2 -weighted imaging. Images obtained after the administration of contrast material (Figure 1C) show a lesion that is delineated by thin,



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consistent with restricted diffusion. The MRI scans also show the increased mass within the right insular lesion and surrounding tissue, with mild effacement of adjacent sulci and no intracranial brain herniation.

smooth peripheral enhancement and that is centered in the right insula. The lesion extends to involve the insular cortex and, together with the associated edema, causes mild mass effect on adjacent structures. In broad terms, the lesion has features of an infectious abscess, although a tumor could have this appearance; an inflammatory or demyelinating process is much less likely.

The imaging studies confirm Dr. Cho's observations. The mass effect from the lesion in the insula slightly effaces the perimesencephalic cisterns and impinges on the brain stem, which could account for impairment of the oculomotor-nerve nuclei in the brain stem and the resulting anisocoria. Regions of the ventral attention network -- the right temporoparietal region and the right ventral frontal lobe -- are markedly perturbed by the lesion and the surrounding edema, possibly contributing to the fluctuating mental status and attention difficulties. Involvement of the right temporal lobe, which may be the language-dominant region in a minority of people, could account for both language impairment and deficits in spatial orientation and memory. Although none of these correlations is sensitive or specific, Dr. Cho has presented some excellent insights into what can be discerned from the relatively nonfocal findings on the neurologic examination.

CT of the abdomen (Figure 2) shows marked hepatomegaly and mild splenomegaly.

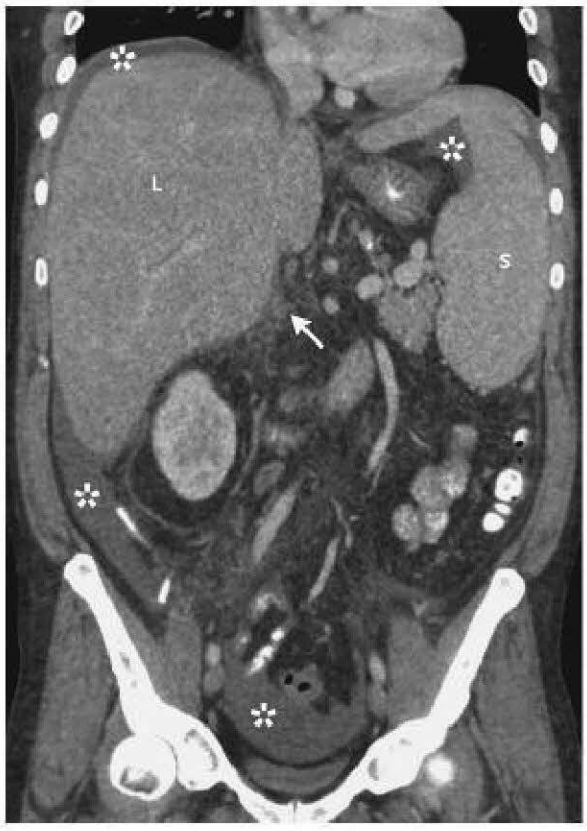


Figure 2:

CT Scan of the Abdomen and Pelvis.

A coronal image from a CT scan after the intravenous and oral administration of contrast material shows marked hepatomegaly (L), mild splenomegaly (S), a small amount of ascites (asterisks), and lymphadenopathy (arrow).

There is also mild portacaval, paraaortic, iliac, and mesenteric lymphadenopathy. A small amount of ascites surrounds the liver and extends into the pelvis. A CT scan of the chest showed subcentimeter pulmonary nodules in the right middle lobe, a very nonspecific finding.

Dr. Cho: Four major categories of disease could lead to the brain lesion identified on MRI. These are neoplastic, infectious, inflammatory, and vascular processes.1 The clinical presentation and additional radiographic sequences rule out inflammatory processes (e.g., tumefactive multiple sclerosis, acute disseminated encephalomyelitis, and sarcoidosis) and vascular processes (e.g., subacute ischemic stroke, hemorrhage, and thrombosed arteriovenous malformation).

Neoplastic Processes

The differential diagnosis of a peripherally enhancing brain lesion should always include the following neoplastic processes: metastatic tumors, primary glial tumors, and primary lymphoma of the central nervous system. Although tumor metastases may cause a solitary peripherally enhancing lesion, such lesions are more commonly multifocal, and this patient had no evidence of a systemic malignant condition. High-grade glioma may cause a solitary, rim-enhancing lesion as the relatively rapid tumor growth outstrips the blood supply, leading to central necrosis. However, both anaplastic astrocytoma and glioblastoma are more typically heterogeneously enhancing and often cross the midline. Primary lymphoma of the central nervous system, usually diffuse large B-cell lymphoma, may occur in otherwise healthy persons. Alternatively, it may occur as part of advanced infection with the human immunodeficiency virus (HIV), in which case it is characteristically associated with detectable EBV DNA in the cerebrospinal fluid. It is usually homogeneously enhancing, although cases involving patients who are HIV-positive may be heterogeneous or peripherally enhancing.2,3 The presence of peripheral low-level EBV viremia in this patient is nonspecific; this viremia may occur in systemic inflammatory states due to lysis of chronically infected B cells, and it is known to occur in immunosuppressed patients, without being predictive of lymphoma. Assessing this patient's cerebrospinal fluid for the presence of EBV would be more specific but is precluded by the risk of uncal herniation. The most important argument against a malignant condition is the rapid enlargement of the mass lesion, over a period of hours to days, which would be unusual for any of these neoplastic processes.

Infectious Causes

The radiographic appearance is classic for an abscess, but imaging studies cannot distinguish among pyogenic bacteria, fungi, mycobacteria, or parasites as the cause.

Pyogenic Bacterial Abscess

Solitary brain abscesses may occur in patients with otitis, sinusitis, or dental infection, typically by local extension of the infection to the temporal, frontal, or frontal and temporal regions, respectively. Abscesses due to hematogenous dissemination are most often multiple and distributed in the region of the middle cerebral artery at the junction of the gray matter and white matter. There are no findings on the patient's history, physical examination, or imaging studies to suggest risk factors for pyogenic abscess. However, the occurrence of cryptogenic pyogenic abscess may be independent of liver disease or advanced HIV infection; therefore, this diagnosis remains a possibility.4

Fungal Abscess

Aspergillosis may cause pulmonary infection in alcoholic persons in particular, leading to hemoptysis and nonspecific pulmonary infiltrates. The manifestations of aspergillosis vary with the status of the immune system.5 In patients who are moderately immunocompromised, invasive aspergillosis may cause a solitary rim-enhancing brain lesion (aspergilloma).6 Serum tests for galactomannan (specific for aspergillosis) and 1,3-β-D-glucan (a nonspecific fungal marker) might be useful to assess this possibility. The most common fungal pathogen in the central nervous system in immunocompromised patients is cryptococcus, which typically causes meningitis. However, cryptococcomas may occur in the Virchow-Robins perivascular subarachnoid spaces at the base of the brain as a result of direct extension from the meningitis.7 Serum cryptococcal antigen would be a sensitive test for active cryptococcal infection but would be nonspecific for the brain lesion.

Mycobacterium tuberculosis

Focal brain lesions due to Mycobacterium tuberculosis are uncommon in developed countries but may occur as part of a primary infection or reactivation. This patient's European origin (tuberculosis is endemic in Eastern Europe); his syndrome of subacute fatigue, cough, and hemoptysis; and the bilateral hilar lymphadenopathy with pulmonary nodules and effusions raise this possibility. Although this patient had a negative tuberculin skin test, the sensitivity of skin testing in a patient with central nervous system tuberculosis is low, ranging from 10 to 65%. Furthermore, sensitivity is reduced in an immunocompromised patient who has poor nutritional status.

Parasitic Infection

Brain abscess may be due to parasitic infection. Neurocysticercosis is endemic in parts of Eastern Europe and may cause a solitary peripherally enhancing brain lesion in the context of early cystic degeneration (colloidal stage). However, these lesions are usually smaller than the lesion in this patient, have only moderate surrounding edema, and are often accompanied by other foci of calcification. A serum assay for cysticercosis antibody is insensitive in a patient with a solitary lesion and would not be likely to add diagnostic value.8

Toxoplasma is a protozoon that rarely causes serious illness in normal hosts. In patients with advanced HIV infection, however, it is the most common cause of focal brain mass lesions.9 Patients with toxoplasma encephalitis typically present subacutely with headache, fever, changes in mental status, and focal neurologic deficits. Imaging studies of the brain reveal characteristic rim-enhancing lesions that are usually multifocal but may be solitary in up to 30% of cases. Lesions are typically less than 4 cm in diameter. Serologic testing for toxoplasma IgG would be helpful, since this test has high sensitivity for toxoplasma exposure. However, antibodies may be lost in patients with profound immunosuppression, and seroprevalence is higher in Europe than in the United States.10 These lesions characteristically improve rapidly with appropriate treatment.11 Therefore, if the clinical scenario allows observation, a trial of specific antimicrobial agents may be both therapeutic and diagnostic.

Diagnostic Considerations

Because of the focal brain lesion that is visible on the MRI scans, the presence of HIV infection would drastically change the differential diagnosis and should be tested for immediately. Already, the circumstantial evidence for advanced HIV infection includes macrocytic anemia without vitamin B12 or folate deficiency, thrombocytopenia with splenomegaly, lymphopenia, and elevated globulin levels. On the

basis of this patient's presumed immunocompromised state, the rapid progression of symptoms, and the MRI findings, the brain lesion is most likely an abscess.

In patients with advanced HIV infection, the most common causes of focal brain lesions with mass effect are **toxoplasmosis**and lymphoma. Tuberculosis and neurocysticercosis should also be considered in patients who are from regions where these diseases are endemic. In this patient, the most likely causes of the brain lesion are **toxoplasmosis** or tuberculosis; lymphoma is less likely. Serum testing for toxoplasma and tuberculosis is not reliable in patients with advanced HIV infection. In this patient, lumbar puncture is precluded, given the anisocoria and the mass effect on the right midbrain. Glucocorticoids may temper the edema but might compromise the diagnostic potential of a brain biopsy, especially in the case of lymphoma. Most patients who receive empirical treatment for toxoplasma improve within 2 weeks and therefore can avoid undergoing a biopsy. However, if a patient is rapidly worsening or does not have a response to empirical treatment for toxoplasma, a brain biopsy is essential for accurate diagnosis, specimens for microbial culture and sensitivity, and therapeutic drainage.

Dr. Nancy Lee Harris (Pathology): Dr. Knox, would you tell us what the clinical thinking was at the time?

Dr. Knox: The team, which was led by Dr. Dan Hunt, arrived at a clinical diagnosis of acute liver failure due to alcoholic hepatitis and a brain abscess due to bacterial infection or**toxoplasmosis**, possibly associated with HIV infection.

Clinical Diagnoses

Acute liver failure due to chronic alcoholic liver disease.

Brain abscess due to either pyogenic bacteria or toxoplasma.

Possible HIV infection.

Dr. Tracey A. Cho's Diagnosis

Acute liver failure superimposed on chronic alcoholic liver disease.

Brain abscess due to toxoplasma.

Advanced HIV infection.

Pathological Discussion

Dr. Di Tian: The diagnostic procedure was a brain biopsy, which revealed a necrotizing inflammatory process with several large areas of necrosis. The areas of the biopsy specimen consisting of viable brain tissue (Figure 3A) showed scattered lymphocytes,

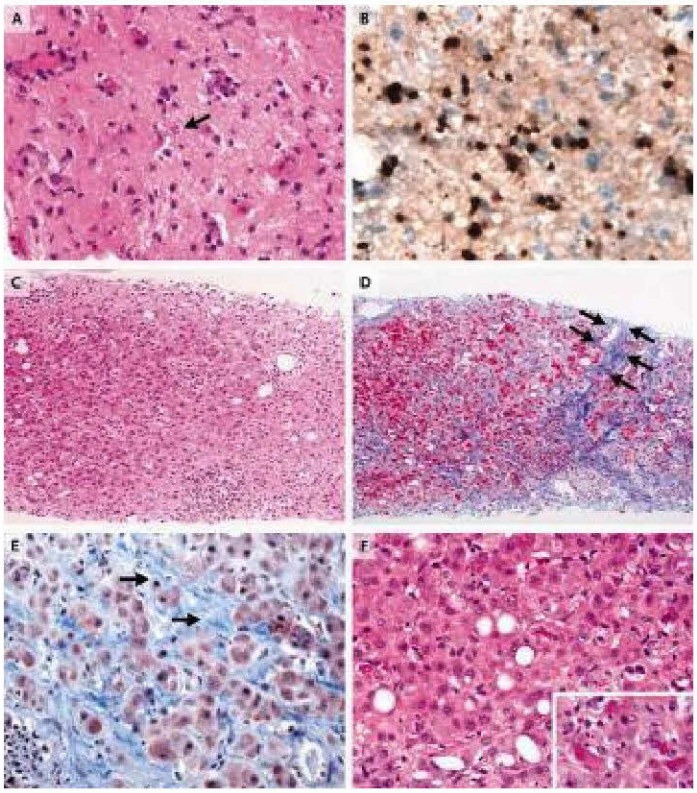
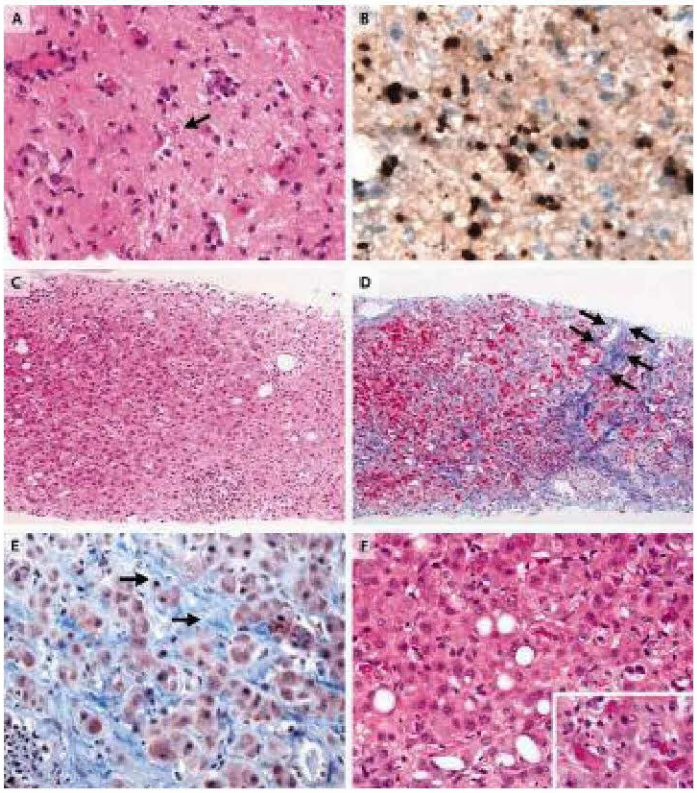


Figure 3:

Brain-Biopsy and Liver-Biopsy Specimens.

A section of the brain-biopsy specimen stained with hematoxylin and eosin (Panel A) shows inflammation, reactive gliosis, and scattered oval organisms (arrow). Immunohistochemical staining for toxoplasma (Panel B) stained positive (brown) for many organisms. The liver-biopsy specimen shows hepatic parenchyma with disarray of hepatic cords, several hepatocytes with macrovesicular fat, and scattered inflammatory cells (Panel C, hematoxylin and eosin). In Panel D, at the same magnification, Masson's trichrome staining reveals prominent pericellular fibrosis throughout the hepatic lobules, with accentuation in the perivenular region (arrows), and bridging fibrosis. At higher magnification, there is prominent pericellular fibrosis within the lobules (Panel E, arrows; Masson's trichrome stain). In Panel F and the inset (hematoxylin and eosin), a view at high magnification shows several hepatocytes with macrovesicular fat in a patchy distribution and scattered hepatocytes containing amorphous, eosinophilic material, features consistent with Mallory's hyaline.

some polymorphonuclear leukocytes, activated elongated microglia, and reactive astrocytes. In addition, there were many isolated or clustered round-to-oval organisms throughout the brain parenchyma (Figure 3A, arrow);



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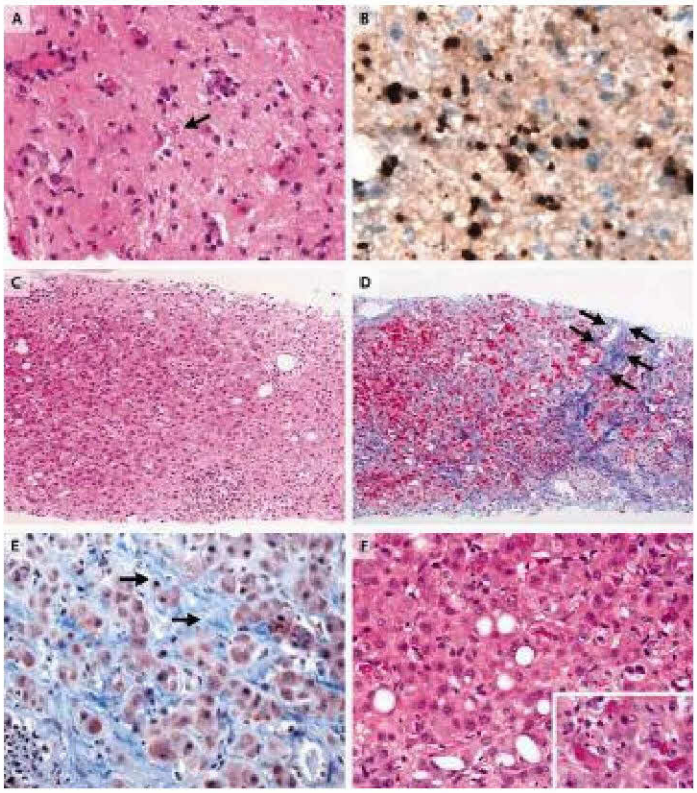
these organisms were strongly immunoreactive for a polyclonal antibody against toxoplasma (Figure 3B).



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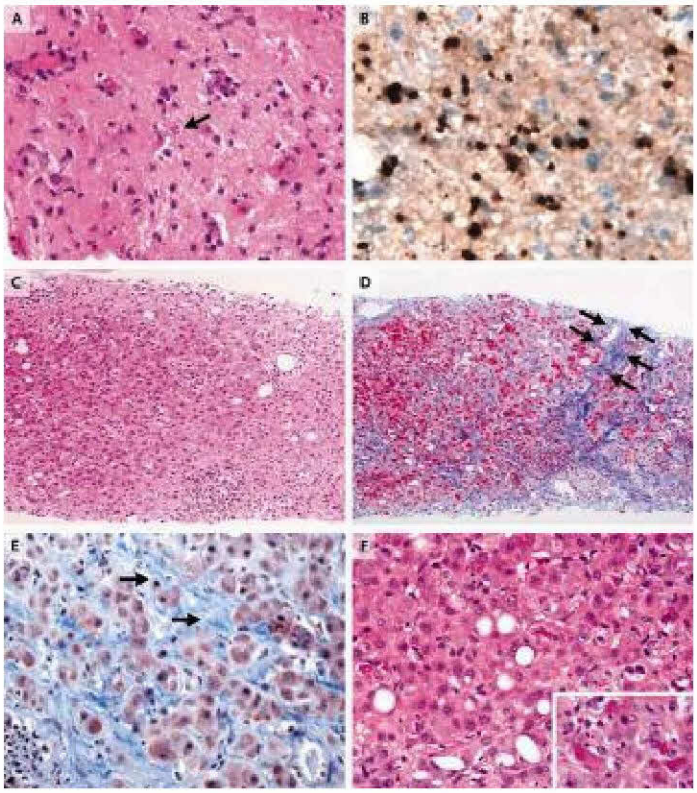
Special stains and immunohistochemical stains for other infectious organisms, such as bacteria, fungi, herpes simplex virus type 1 and type 2, and cytomegalovirus, were all negative. Cultures were also negative.

Dr. Mari Mino-Kenudson: A liver biopsy was also performed (Figure 3C through 3F).



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Examination of the specimen showed mild (<5%) steatosis; widespread hepatocyte ballooning, with prominent Mallory's hyaline and focal neutrophilic satellitosis; prominent lobular inflammation with lymphocytes and neutrophils; mild portal inflammation and ductular duplication; and stage 5 fibrosis (on a scale of 0 to 6, with 0 indicating normal and 6 cirrhosis)7 on trichrome stain. The overall features are consistent with a diagnosis of chronic toxic hepatitis, which in this patient is consistent with alcoholic hepatitis, with evolving cirrhosis. Changes indicative of acute hepatitis were not seen in the sampled tissue.

Management and Follow-up

Dr. Emily P. Hyle (Infectious Disease): The medicine team performed testing for HIV on hospital day 1. Standard HIV testing involves two steps. The initial test is enzyme-linked immunosorbent assay (ELISA), which is an extremely sensitive test for the antibody. If the test is positive, it is repeated. If the second test is also positive for the presence of antibody, then the more specific Western blot analysis is performed to confirm the diagnosis. It is important to perform both types of tests, because the ELISA has a high false positive rate.12,13 In this case, the ELISA for HIV antibody was positive, and the Western blotting confirmed the diagnosis. Analysis of the T-cell subsets showed that the absolute CD4 T-cell count was 78 per cubic millimeter (16.2%), which meets the definition of acquired immunodeficiency syndrome (AIDS) (i.e., a CD4 T-cell count of <200 per cubic millimeter). The HIV RNA level, also known as the viral load, was greater than 100,000 copies per milliliter. Together, these results were consistent with long-standing HIV infection. As a result, the patient was at extreme risk for not just one but several opportunistic infections.

The patient's mental status declined in tandem with worsening liver and renal failure. Although he was counseled extensively by the general medicine team regarding his HIV status, it was only after several days of discussion that he permitted disclosure to his wife.

As part of the initial workup for newly diagnosed HIV infection, the medicine team ordered serologic tests for hepatitis B and hepatitis C, a rapid plasma reagin test for syphilis, and a test for cryptococcal antigen, all of which were negative. An ophthalmologic examination was normal. In anticipation of antiretroviral therapy, HIV genotyping was performed to evaluate for drug resistance,14 and tissue typing for HLA B5701 was performed to determine whether the patient was at risk for hypersensitivity to abacavir.15,16

Serologic tests for **toxoplasmosis** were negative for IgM and positive for IgG, findings consistent with previous infection. Thus, the clinical presentation and findings in this case were consistent with a reactivation of **toxoplasmosis** in a patient with AIDS.

First-line treatment for cerebral **toxoplasmosis** includes pyrimethamine and sulfadiazine,17 with folinic acid (leucovorin) to reduce the hematologic adverse effects from the antimicrobial agents. Sulfadiazine is often contraindicated in cases of renal failure, and this patient had an elevated creatinine level, at 2 mg per deciliter (177 µmol per liter). Nevertheless, the concern about the severity of his presentation prompted treatment with pyrimethamine, sulfadiazine, and folinic acid and close monitoring of his renal function. The administration of glucocorticoids was discontinued.

Unfortunately, the patient's renal function continued to worsen; therefore, sulfadiazine was discontinued on postoperative day 3. Second-line therapy was initiated, which involved the administration of clindamycin, pyrimethamine, and folinic acid. In the absence of sulfadiazine therapy, atovaquone was added for prophylaxis against Pneumocystis jiroveci pneumonia, since the patient's CD4 T-cell count was below 200 per cubic millimeter.

The patient was discharged home on postoperative day 9 to complete a 6-week course of clindamycin, pyrimethamine, and folinic acid for cerebral **toxoplasmosis**. Atovaquone was continued for prophylaxis against P. jiroveci pneumonia. Early initiation of antiretroviral therapy in patients with some opportunistic infections has been shown to improve outcomes18; therefore, this patient was to begin antiretroviral therapy on an outpatient basis when the results of the HIV genotyping and HLA-B5701 tissue typing were available and his renal function and liver function had stabilized.

After discharge, the patient spent 4 days at home, cared for by his wife. She grew concerned that he was becoming increasingly jaundiced and took him to his primary care physician. Laboratory investigations revealed advancing liver and renal failure, which prompted readmission to the first hospital.

Dr. Koushik Das (Medicine): On readmission, progressive liver, renal, and central nervous system failure developed. The total bilirubin level was 35.0 mg per deciliter (598 µmol per liter), the creatinine level 4.7 mg per deciliter (415µmol per liter), and the prothrombin time 15.9 seconds; encephalopathy persisted despite treatment with lactulose. The patient's Model for End-Stage Liver Disease score (which ranges from 6 to 40, with higher scores indicating more severe disease), adjusted for alcoholic hepatitis, was 37, corresponding to a 90-day mortality rate of 83%.19 The next day, renal function worsened, with the serum creatinine level increasing to 8.5 mg per deciliter (751 µmol per liter), an increase thought to be due to the hepatorenal syndrome. Through discussions with the patient's wife and family and in view of the patient's poor clinical prognosis and ineligibility for liver transplantation, it was decided that the goals of his care should be driven primarily by comfort. The patient died on hospital day 3, before he could be transferred to inpatient hospice.

Dr. Hasan Bazari (Medicine): What is the reservoir from which reactivation of **toxoplasmosis** occurs?

Dr. Eric S. Rosenberg (Pathology): There are two known reservoirs: the myocardium, which is why reactivation of**toxoplasmosis** is a problem in recipients of cardiac transplants, and the brain.

Dr. Cho, if this patient had a known diagnosis of HIV infection with a CD4 T-cell count of 78 per cubic millimeter and a rim-enhancing lesion, is it necessary to perform a biopsy, or could we try empirical therapy and see how he responds?

Dr. Cho: When the patient is relatively stable and not at immediate risk for permanent neurologic compromise, a trial of antitoxoplasmosis therapy can be useful, particularly when tests for toxoplasma IgG are positive, the lesion is in an inaccessible location, and there is no suggestion of other processes. There is a published algorithm for the diagnosis of focal mass lesions in patients with advanced HIV infection that incorporates factors such as whether the patient is already taking trimethoprim-sulfamethoxazole (reducing the likelihood of**toxoplasmosis**) or whether EBV is detected in the cerebrospinal fluid (raising the risk of lymphoma).9

Dr. Rajesh T. Gandhi (Infectious Disease): This case is a good reminder that of the 1.1 million U.S. residents who have HIV infection, 21% do not know they have it. Do we know whether this patient was ever tested for HIV before?

Dr. Hyle: He had not been tested previously for HIV and repeated that he did not know of any previous exposures to HIV.

A Physician: Was an explanation ever found for his respiratory symptoms, hemoptysis, and the findings on lung imaging?

Dr. Hyle: Unfortunately, he died so soon after the diagnosis was established that further investigation for other opportunistic infections or malignant conditions was not possible. An autopsy was not performed.

Anatomical Diagnoses

Alcoholic liver disease with fibrosis.

Brain abscess due to toxoplasma.

Advanced HIV infection.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

No potential conflict of interest relevant to this article was reported.

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