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Radiologic-Pathologic Correlation
Cerebral Toxoplasmosis and Lymphoma in AIDS

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Clinical History

A 37-year-old human immunodeficiency virus (HIV)- positive man had a 6-month history of progressive left-sided weakness and sensory loss. Additional symptoms included a 15.75-kg weight loss, fatigue, and anorexia. He had been HIV-seropositive for 2½ years but had no previous acquired immunodeficiency syndrome (AIDS)-defining illnesses (Centers for Disease Control criteria, 1987). He had been on maintenance therapy with zidovudine and trimethoprim with sulfamethoxazole for approximately 1 year.

On admission, he was febrile at 38.6°C (101.5°F). Physical examination showed a lethargic and cachectic male who was oriented only to his name and "hospital." He had slow speech and comprehension with decreased attention but intact recent and remote memory. He also had left homonymous hemianopsia and left hemiparesis with increased tone and decreased bulk. Light touch, vibration, and position senses were all decreased in both distal lower extremities. Coordination appeared intact except for weakness in his left upper extremity. Deep tendon reflexes were brisk throughout with bilateral Babinski's signs present. Laboratory evaluations showed a mild leukopenia with CD4 count of 90. Serologies for toxoplasma IgG and IgM were both negative, whereas cytomegalovirus IgG was elevated at 179 AU/mL (normal, 0 to 17).

The patient was empirically treated with antitoxoplasmosis medications and dexamethasone. His mental status initially improved. However, on day 5 of treatment, he experienced two generalized tonicoclonic seizures and remained obtunded for 2 days. On awakening, he refused a brain biopsy and was discharged to a hospice on day 12 of hospitalization, where he received only dexamethasone for presumed cerebral lymphoma. He died 2 months later of hemorrhagic pancreatitis.

Neuroimaging and Proton Spectroscopic Studies

On the day of admission, computed tomography (CT) with contrast (not shown) showed a 3.5 × 4.5-cm right parietooccipital periventricular hypodense lesion with marked surrounding edema and ring enhancement. Additional enhancing lesions involved the margins of the right lateral ventricle and the

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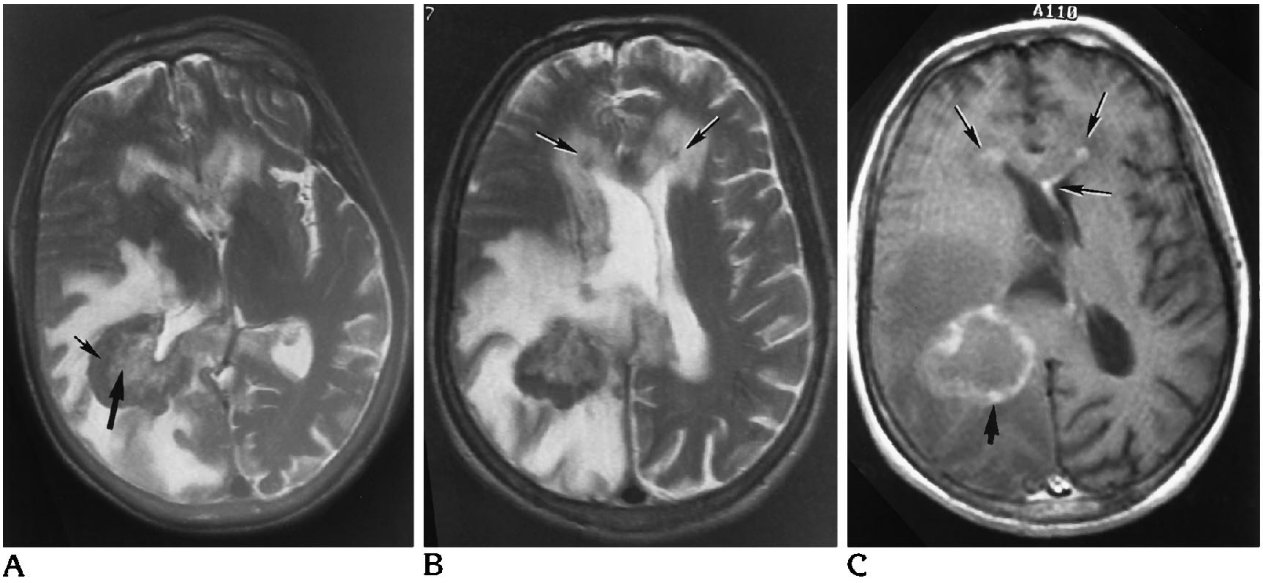

Fig 1. *A* and *B,* Axial T2-weighted MR images (3000/102 [repetition time/echo time]) show the periphery of the mass to be hypointense to the gray matter with a thick irregular wall (*short arrow*) and extensive surrounding edema. The central region of the mass (*long arrow*) is isointense, with some regions being slightly hypointense. There are additional hypointense small nodules along the borders of the frontal horns of the lateral ventricles (*arrows with white shadows*) and confluent increased T2 signal in a periventricular pattern.

C, Postgadolinium axial image (600/10) shows a nodular and irregular ring enhancement pattern (*short arrow*) in the periphery of the right parietooccipital periventricular mass. The additional small nodules along the borders of the frontal horns of the lateral ventricles and the septum pellucidum also enhanced (*arrows with white shadows*).

frontal horns bilaterally. There was a 1.5-cm midline shift to the left.

Both magnetic resonance (MR) imaging and MR spectroscopy were performed, 2 days after the CT, on a 1.5-T scanner. Figure 1A shows that the peripheral rim of the large mass was hypointense to gray matter on T2-weighted images, with a thick irregular wall and extensive surrounding edema. The central area of the lesion shows isointense to slightly hypointense signal intensity relative to gray matter. The periventricular region also appeared to have confluent increased signal on T2-weighted images (Figs 1A and B).

On T1-weighted images, there was postcontrast enhancement of the periphery of the mass, forming a nodular and irregular rim (Fig 1C). There were additional small enhancing nodules along the borders of the frontal horns of the lateral ventricles and the septum pellucidum. Differential diagnoses included lymphoma, cytomegalovirus, or toxoplasmosis.

Localized proton MR spectroscopy was performed both within the 4.5-cm mass lesion and in the contralateral hemisphere. Spectra acquired from 8-cm^3 ($2 \times 2 \times 2$-cm) voxels in both locations (Figs 2A and B) are compared with typical examples of a toxoplasmosis spectrum (from a lesion that later resolved after antitoxoplasma medication; toxoplasma IgG titer, 14 000 IU/mL [normal < 4 IU/mL]) and a biopsy-proved lymphoma spectrum (Figs 2C and D). This patient's MR spectroscopy exhibits characteristics of both toxoplasmosis (increased lipids and lactate) and lymphoma (higher level of choline than a pure toxoplasmosis lesion).

Postmortem MR (Fig 3A) was performed after realignment of macroscopic horizontal brain sections. There was less edema but no significant change in the size of the large parietooccipital lesion compared with the initial MR performed 2 months earlier.

Autopsy Findings/Radiologic-Pathologic Correlation

Macroscopic

The 1400-g brain appeared normal externally except that the right parietal and occipital lobes were enlarged with cortical softening.

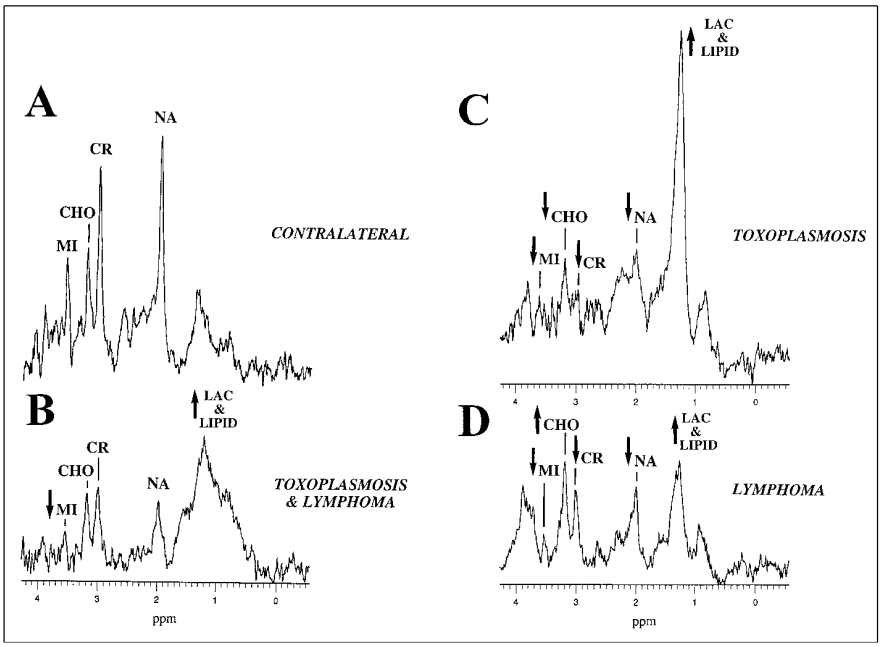

Fig 2. *A–D,* Proton MR spectroscopy studies were done using a stimulated echo sequence (43) (2000/30). Relative to the contralateral spectrum (*A*), the spectrum from the patient's lesion (*B*) shows marked elevation of lactate and lipids (*LAC & LIPID*, 0.9 to 1.5 ppm), decreased *N*-acetyl compounds (*NA*, 2.02 ppm), total creatine (*CR*, 3.0 ppm), and myoinositol (*MI*, 3.55 ppm) but a relatively preserved choline peak (*CHO*, 3.2 ppm). In comparison, the most striking abnormalities in the pure toxoplasma spectrum (*C*) are the markedly elevated lactate and lipids peak and decrease in all other metabolites; whereas the pure lymphoma spectrum (*D*) shows less increase in lactate and lipids but increase in the choline.

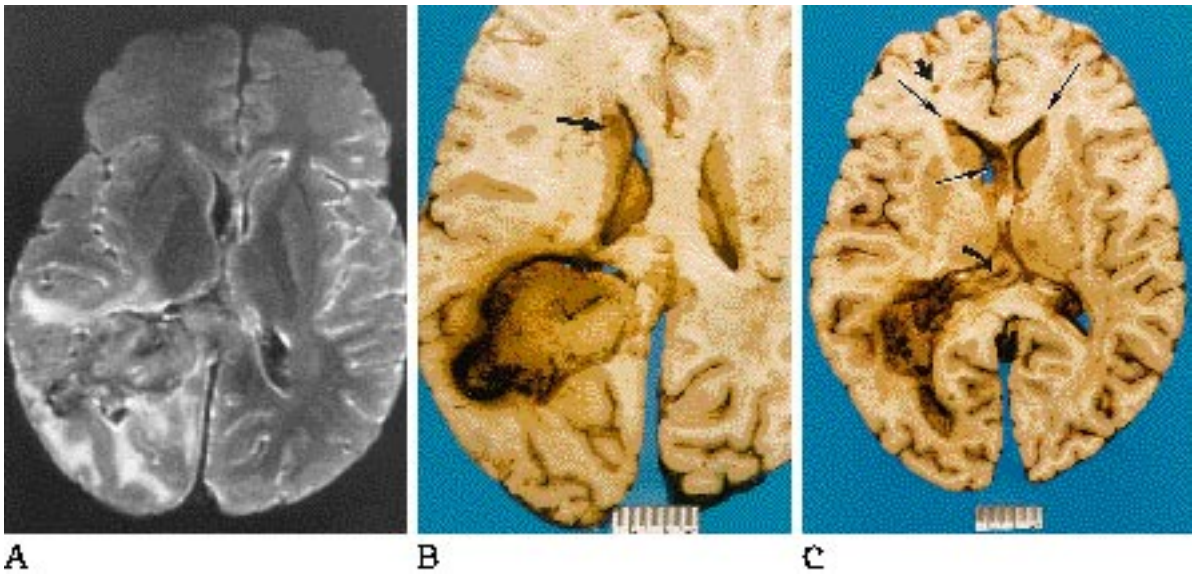

Fig 3. *A,* Postmortem MR performed 2 months after the initial MR shows less edema but no significant change in the size of the large parietooccipital lesion.

B, The lesions on MR corresponded to the gross pathologic findings showing a large 5.0 × 3.5-cm yellow-tan, sharply marginated, necrotizing mass, with a cellular rim and a necrotic center, lateral to the wall of the posterior horn of the right lateral ventricle, compressing the ventricular space, as well as multiple smaller combined lesions along the ventricle (*arrow* indicates a combined lesion in the right frontal horn).

C, Other smaller discrete lesions were identified, including a 0.6-cm lesion involving the right frontal white matter (*small thick arrow*), and minute subependymal foci along the angles of the frontal horns bilaterally and in the wall of the ventricle (*thin arrows*). Contiguous with the right parietal lesion, tissue necrosis extended in front of the splenium in the right ambient cistern (*curved arrow*) and along the wall of the right temporal horn and third ventricle with occlusion of the aqueduct at the level of the superior colliculus (not shown).

Horizontal 1-cm sections of the cerebral hemispheres revealed a 5.0 × 3.5-cm yellow-tan, sharply marginated, centrally necrotic mass lateral to the posterior horn of the right lateral ventricle (Fig 3B). The outer rim of the mass was hemorrhagic, whereas the center was necrotic (and appeared isointense to slightly hypointense on T2-weighted MR [Fig 1A and B]). Other smaller discrete lesions in the frontal horns (Fig 3C) showed no evidence of necrosis and appeared as small gadolinium-enhancing nodules on T1-weighted MR (Fig 1C), which was more sensitive than CT in detecting these lesions. Figure 4 shows a diagrammatic representation of the MR and postmortem brain section through the lesions and the locations of the microscopic specimens.

Microscopic

A specimen from the lateral border of the large right parietooccipital lesion, which appeared as high density (on CT) and hypointense (on T2-weighted MR), showed a large necrotic center and an outer rim of viable lymphoma, separated from the brain parenchyma by a rim of hemorrhage (Fig 5A). The white matter region surrounding the lesion, which appeared hypodense or hypointense (on CT or MR) and hyperintense (on T2-weighted MR [Fig 1A and B]), consisted of marked astrogliosis and edema (Fig 5B). At higher power, sections of the brain from the medial edge of the lesion, with an appearance similar to that of the lateral rim on imaging, showed peripheral multifocal areas of atypical lymphocytic infiltration around vessels (Fig 5C). The atypical lymphocytes displayed large vesicular nuclei, with inconspicuous nucleoli and minimal population variation. Mitotic figures were easily identified. Abundant macrophages were seen surrounding the angiocentric lymphocytes (Fig 5C). Admixed within this peripheral zone of lipid-

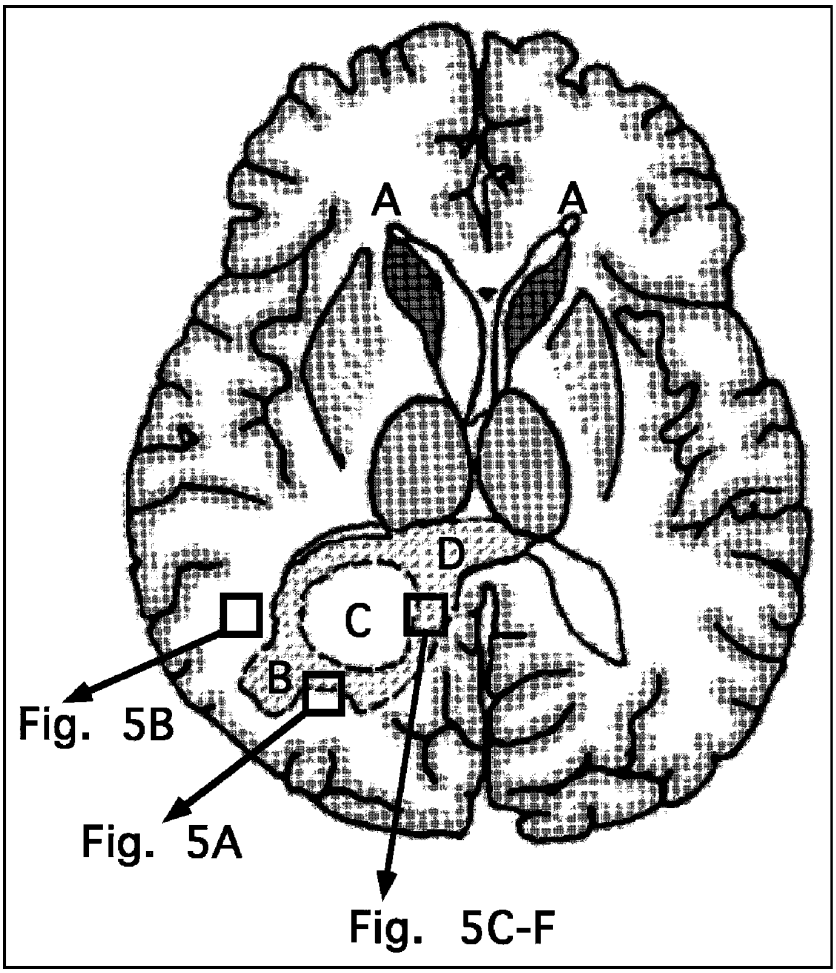

Fig 4. Diagrammatic representation of Figures 1 and 3 (composite of the different planes). See locations of microscopic specimens for Figure 5A through F. The present case illustrates good correlations of neuroimaging and pathologic characteristics of combined lesions of lymphoma and toxoplasmosis.

A, The small hypointense lesions with edema on T2-weighted scans correlated to the pathologic findings of foci of angiocentric atypical lymphocytes and abundant macrophages with toxoplasma cysts, but no confluent central necrosis or vascular thrombosis.

B, The high-density (CT) and hypointense-signal (T2-weighted MR) thick rim of the large right temporoparietal lesion was found to consist of atypical perivascular lymphocytic infiltrates and abundant lipid-containing macrophages with toxoplasma cysts (see Fig 5A through F). Marked astrogliosis and edema extend into the surrounding white matter (see Fig 5B).

C, The low density (CT) and isointense to slightly hyperintense signal (T2-weighted MR) in the central region are consistent with coagulation necrosis; no toxoplasma cysts or intact lymphocytes are found.

D, The lesion extends in front of the corpus callosum into the right ambien cistern.

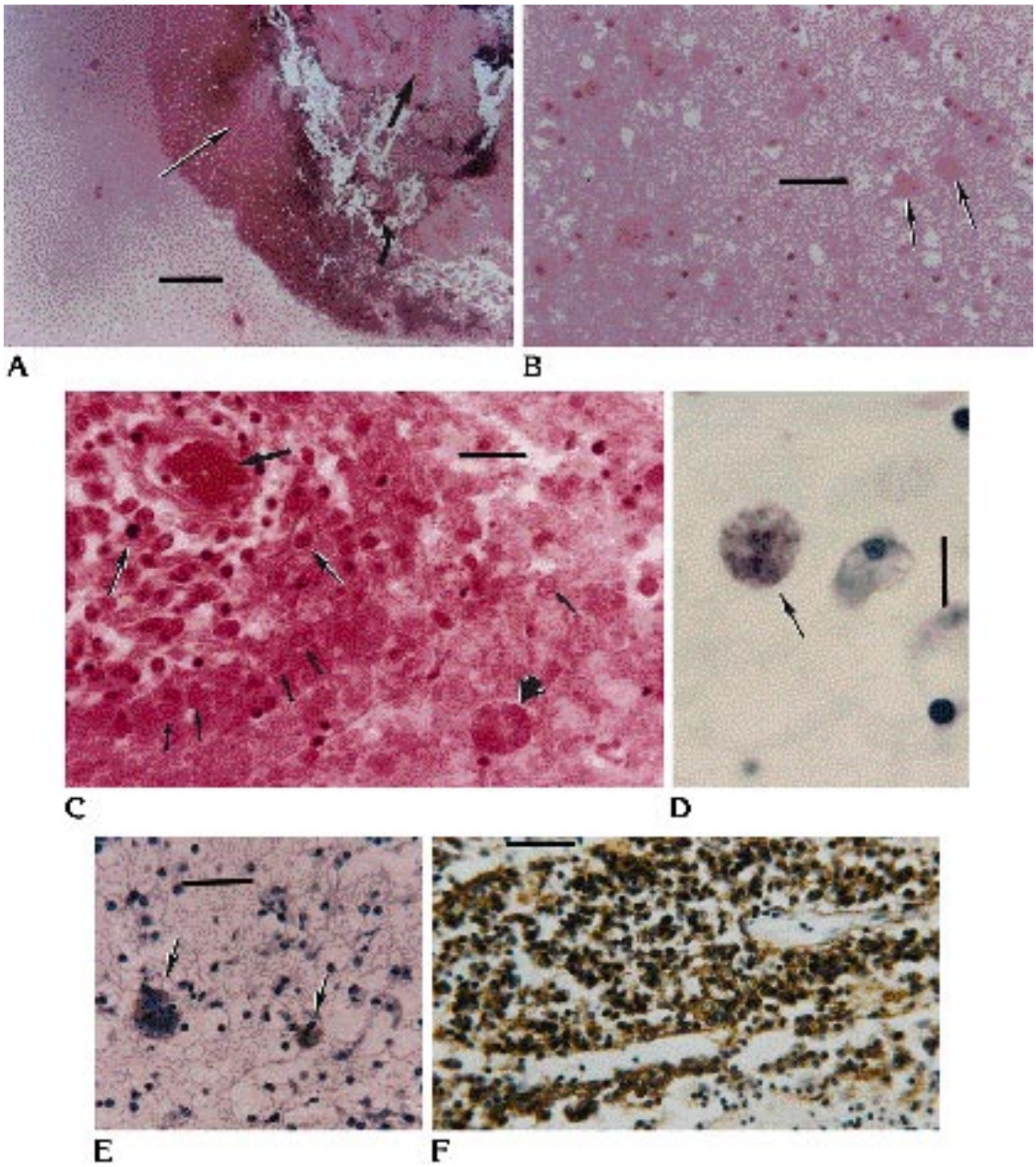

Fig 5. *A,* The lateral edge of the large right temporoparietal lesion illustrating a necrotic center with coagulation necrosis. A narrow rim of viable lymphoma (*curved arrow*) surrounds the central coagulative necrosis (*arrow*); an outer rim of hemorrhage (*arrow with white shadow*) extends into the surrounding parenchyma, which shows gliosis and edema. Magnification bar = 500 μ.

B, Reactive astrocytes (*arrows*) and edematous white matter in the peripheral zone around the large lesion in A. Magnification bar = 100 μ.

C, Section (hematoxylin and eosin) from the medial edge of the right parietooccipital lesion shows a peripheral area of atypical lymphocytic infiltration (*arrows with white shadows*) around a vessel (*arrow*) at the edge of the large area of central necrosis, and a toxoplasma cyst (*arrowhead with white shadow*); note abundant macrophages (*small arrows*). Magnification bar = 80 μ.

D, Giemsa stain shows multiple bradyzoites within a toxoplasma cyst (*arrow*) and the adjacent macrophage. Magnification bar = 60 μ.

E, Toxoplasma antibody localized the cyst content (brown coloration; *arrows*) and tachyzoitelike 1- to 2-μ objects at the lesion's periphery. Magnification bar = 100 μ.

F, Immunohistochemical localization with L-26 (B-cell) marker in a focus of angiocentric lymphoma in the viable zone of the large temporoparietal lesion. Magnification bar = 100 μ.

filled macrophages were several basophilic cysts 10 to 30 μm in diameter, containing multiple ovoid organisms (Fig 5C), which stained positive for Giemsa (Fig 5D) and immunohistochemically for toxoplasma antigen (DAKO, Carpenteria, Calif) (Fig 5E). The smaller periventricular lesions also contained foci of angiocentric atypical lymphocytes, with abundant macrophages and toxoplasma organisms, but no confluent central necrosis or vascular thrombosis.

The atypical angiocentric lymphocytes were immunohistochemically positive for B cells, with predominant IgG-κ clonality (Fig 5F). Specifically, these large lymphoid cells stained positively for CD20 and HLA-DR and negative for CDw75 and T-cell antigens, and some also expressed CD74 and vimentin. This pattern of staining is consistent with B-cell lymphoma. In contrast, a few small lymphocytes, admixed with the atypical B cells, were positive for CD43, CD45RO, and CD3 antigens by immunohistochemistry (indicating that they are T cells). Many neoplastic lymphocytes stained for Epstein-Barr virus latent membrane protein.

Focal microglial nodules, multinucleated giant cells with multiple small hyperchromatic nuclei and eosinophilic cytoplasm characteristic of HIV giant cells, and profound white matter astrogliosis and white matter edema typical of AIDS leukoencephalopathy also were found in the perihippocampal regions and in the right frontal white matter.

Diagnoses

1. Primary high-grade central nervous system (CNS) lymphoma, large B-cell type
2. Toxoplasmosis associated with the lymphoproliferative lesions

Discussion

Incidence and Etiology

In the AIDS population, cerebral toxoplasmosis is the most common cause of brain abscesses, and B-cell lymphoma is the most common cause of brain neoplasm. However, toxoplasmosis occurs 2 to 3 times more frequently than lymphoma in AIDS patients in many geographic areas (1,2). Toxoplasmosis is caused by opportunistic infection with the obligate intracellular protozoan *Toxoplasma gondii*; the incidence ranges between 13.4% and 33% of patients with central nervous system (CNS) complications of AIDS (3,4). Primary CNS lymphoma in AIDS is nearly always of high-grade B-cell type, and cells contain the Epstein-Barr virus (5,6). Therefore, it has been hypothesized that CNS lymphoma in AIDS may arise from Epstein-Barr virus–infected B cells (7). Primary brain lymphoma accounts for 2% to 10% of brain lesions in patients with AIDS (8,9).

Clinical Diagnosis and Imaging Studies

Differentiation of cerebral toxoplasmosis and lymphoma in AIDS patients can be a challenging clinical problem. As in the present case, the two diseases occasionally have been documented to coexist, which further complicates diagnosis (2,10–14). Either disease can present as a single brain mass lesion or as multifocal lesions, with similar neurologic symptoms and signs depending on the location(s) and size of the destructive lesion(s).

Toxoplasmosis. Approximately 70% of cerebral toxoplasmosis lesions are multifocal (15,16). Neurologic presentations include subacute headaches, fever, seizures, focal neurologic signs (12,13), and progressive dementia (17). Serology for toxoplasma frequently is positive, but specificity is low; only one third of cases show a rise in the titer of IgG antibody (18), and only 50% show intrathecal production of antibody to *T gondii* (19). Equally disappointing are the recent studies in polymerase chain reaction for *T gondii* in plasma and cerebrospinal fluid, which showed low sensitivity (20,21) and occasional false-positive results (22). Subsequent clinical response to antitoxoplasma therapy has been the main criterion for diagnosis.

Toxoplasmosis lesions are most commonly located in the cerebral hemispheric white matter and subcortical gray matter, such as thalamus and basal ganglia (13,23). CT characteristically shows multiple ring-enhancing lesions (13,23), although hypodense nonenhancing lesions have been reported

(15). MR demonstrates multiple discrete high-signal foci on T2-weighted images that are mostly heterogeneous, with well-circumscribed margins, and are hyperintense on postcontrast MR (24). Edema and hemorrhages commonly are associated with these lesions (25).

Lymphoma. Between 19% and 71% of primary brain lymphomas present as solitary lesions on neuroimaging studies (16,26). However, they often rapidly become multicentric; in fact, autopsy studies have shown primary brain lymphoma to be multifocal in 80% to 100% of AIDS patients (27). Typical clinical presentation consists of progressive neurologic deterioration with encephalopathy, focal signs, and seizures leading to death within 3 months (28). Cerebrospinal fluid cytology rarely is diagnostic, and brain biopsy generally is required for diagnosis (1).

In the non-AIDS population, primary brain lymphoma shows a solid pattern of contrast enhancement on CT and MR, and subependymal spread of lymphoma encasing the ventricles is highly characteristic when present (16). The solid hypercellular peripheries of lymphoma lesions are much wider than the inflammatory zones around toxoplasmosis lesions (16,29). These lesions on average are larger and fewer than toxoplasma lesions. However, in the setting of AIDS, lymphoma often is multicentric and can grow rapidly, more than doubling in size within 2 weeks (9,30). This accelerated outward growth of the tumor may divert the vascular supply to the growing edge of the tumor. Central areas of necrosis may result from thrombosis and deterioration of the vessels in the oldest parts the lesions (9,30). Therefore, on MR, lymphoma is hypointense on T1-weighted images, isointense to hyperintense on T2-weighted images, and often ring enhancing (16,30). In this patient, the lesion showed a hypointense central region on T2-weighted images, with a relatively wide margin of hypointense (not isointense or hyperintense) rim, which enhanced with contrast. Pathologically, the central region, corresponding to the hypointense region, consisted of confluent coagulation necrosis and vascular thrombosis (Fig 5A). The outer rim, however, showed a viable zone of angiocentric lymphoma as well as abundant lipid-ladened macrophages, toxoplasma cysts, and reactive astrocytosis (Fig 5B and C). This combination of B-cell lymphocytes, macrophages, and reactive astrocytosis may account for the hypointensity rather than the typical isointensity to hyperintensity observed in primary cerebral lymphoma. Furthermore, the rim of the lesion appeared thicker than the typical toxoplasma abscess on T2-weighted MR. Spontaneous hemorrhage is uncommon but may occur after therapy with steroids or radiation (16,30). In this case, the lesion showed a rim of hemorrhage in the outer periphery of the lesion only on the postmortem MR (Fig 3A) and postmortem brain sections (Fig 3B); this hemorrhage may have resulted from the dexamethasone treatment before the patient's death.

Pathology

Focal lesions of toxoplasmosis can be divided into three morphological types: necrotizing abscess, organizing abscess, and chronic abscess (11,13). The earliest stage of infection includes necrotizing lesions with a variable amount of inflammation and vascular reaction. In patients who are untreated or treated for less than 1 week, cysts and free-living tachyzoites generally are abundant and typically are located in the periphery of the expanding necrotizing lesions. On imaging studies, the periphery usually enhances with contrast agents, probably because of interruption of the blood-brain barrier by the macrophages, as was observed in this case (Fig 1C). Subsequent organization occurs 2 to 4 weeks later when the abscess becomes cystic, without the development of a fibrous capsule. In a chronic abscess, areas of necrosis with numerous free tachyzoites suggest ongoing infection, as was seen in our case. *T gondii* organisms are inconspicuous on routine stains; immunohistochemistry usually is needed for definitive diagnosis in the absence of cysts. In addition, disseminated toxoplasma cysts can be seen with diffuse mild inflammation only or even without a parenchymal reaction in the CNS with AIDS (11). In these cases, contrast enhancement may be absent on imaging studies. Toxoplasmosis

also can cause vessel adventitial proliferation and perivascular lymphocytic infiltration mimicking angiocentric lymphoma (31). Therefore, immunohistochemical studies, as were performed in this case, are needed to differentiate lymphoma from toxoplasmosis. This staining will show markers for B cells, as in this case.

Histopathologically, most of these lymphomas show a high mitotic rate with variable amounts of central necrotic tissue, consistent with high-grade B-cell lymphoma, although T-cell lymphoma has been reported (14). Immunohistochemical marker studies are customarily used to differentiate the cell types. The presence of Epstein-Barr virus–latent membrane protein in the neoplastic B cells in some patients, as in our case, further implies that Epstein-Barr virus may play a role in the pathogenesis of diffuse large B-cell lymphoma in AIDS patients.

Differential Diagnosis

In addition to toxoplasmosis and lymphoma, differential diagnoses of focal brain lesions in AIDS include progressive multifocal leukoencephalopathy, cryptococcoma, tuberculoma, syphilitic gumma, bacterial abscesses, lymphomatoid granulomatosis (32), and focal encephalitic lesions of cytomegalovirus (see the Table). Combined lesions of lymphoma with toxoplasmosis, as in the present case, or with progressive multifocal leukoencephalopathy, cytomegalovirus, or candida have been reported in AIDS (11,13).

There is preliminary evidence that MR spectroscopy is helpful in differentiating toxoplasmosis from lymphoma (34–36). MR spectroscopy provides an in vivo chemical assessment of the lesions. In a toxoplasmosis lesion, lactate and lipids are markedly elevated, whereas all other normal brain metabolites are virtually absent, which is consistent with the anaerobic acellular environment of an abscess. In contrast, lymphoproliferative lesions show mild to moderate increase in lactate and lipids, with preservation of some normal metabolites, but markedly elevated choline, probably because of the increased cellularity. In this patient, the characteristics of both diseases were present in the spectra, which suggested a combined lesion. Some investigators have tried to differentiate lymphoma from nonmalignant CNS lesions using positron emission tomography and found high fludeoxyglucose F 18 uptake correlated with a malignant process (37). However, MR spectroscopy is noninvasive and without radiation, and may become more readily available than positron emission tomography, because it can be performed on clinical MR scanners.

Prognosis and Treatments

Accurate and early diagnosis is important because the treatment and prognosis for these diseases are so different. Tissue biopsy should be done in all suspected cases of brain lymphoma with or without toxoplasmosis to determine appropriate therapy. Cerebral toxoplasmosis can respond dramatically to antitoxoplasma medications, usually within 7 to 10 days, but lifelong therapy in AIDS patients usually is required to prevent relapse (38). These medications include pyrimethamine, sulfadiazine, and clindamycin. In patients who were allergic to these drugs, recent reports showed efficacy with azithromycin (39,40). Cerebral edema in both diseases can be treated with steroids. With lymphoma, regression and tumor lysis can occur with steroid treatment, and this response has been considered to be diagnostic (41). Lymphoma, however, requires whole-brain radiation plus a boost dose to the tumor site (28,42). Most patients show improvement in neurologic symptoms after treatment. Survival usually is less than 1 year despite therapy.

Summary

Cerebral toxoplasmosis and lymphoma are the most common focal destructive brain lesions in AIDS. They can occur in isolation or simultaneously. Previous neuroimaging studies found toxoplasmosis to be indistinguishable from lymphoma. However, more recent studies showed that focal enhancing mass(es) with subependymal spread on CT or MR can be more characteristic of primary CNS lymphoma. The cooccurrence of toxo-

Differential diagnosis of focal brain lesions in AIDS

Disease	Clinical/Pathologic	CT	MR			Proton MR Spectroscopy
			T1-weighted	T2-weighted	Contrast Enhancement	
Toxoplasmosis (13,15,16,23, 26,35)	Infarctlike lesions, peripheral cysts, chronic inflammation, ± toxoplasma titer	Hypodense mass(es), ring or nodular enhancement	Hypointense lesions unless hemorrhagic	Discrete high-signal foci, moderate edema or hemorrhagic	Moderate to intense ring enhancement	Markedly elevated lactate and lipids; depletion of normal metabolites
Lymphoma (9,14,16, 30,35)	Mass lesion, central necrosis, uniform neoplastic B-lymphocytes; signs of increased intracranial pressure	Hyperdense lesions, solid or ring enhancement	Hypointense	Isointense to hyperintense mass(es), moderate edema and mass effect	Homogeneous or ring enhancing	Elevated choline; mildly to moderately elevated lactate and lipids
Progressive multifocal leukoencephalopathy (1,23,26,35, 44,45)	Concentric demyelinating lesions, viral inclusions in oligodendrocytes, perivascular lymphocytes; JC virus DNA in cerebrospinal fluid	Isodense to hypodense lesion(s) minimal to no enhancement, no mass effect	Hypointense	Hyperintense lesion(s) without mass effect, primarily white matter location	Minimal if any	Elevated choline and myoinositol; occasional increased lactate
Cryptococcoma (1,46)	Multiple small mass lesions in expanded perivascular spaces, no inflammation; history of meningitis India ink positive in cerebrospinal fluid	Hypodense discrete, with or without contrast enhancement	Hypointense discrete	Hyperintense "soap bubbles," well-circumscribed without edema, located in Virchow-Robin spaces (eg, basal ganglia)	Nonenhancing	Elevated lipids >> lactate; depletion of normal metabolites
Tuberculoma (47,48)	Centrally necrotic granuloma with acid fast bacilli and multinucleated giant cells; ± acid fast bacilli in cerebrospinal fluid	Hyperdense discrete, homogeneous enhancement	Hypointense discrete	Hypointense well-circumscribed, moderate edema	Thin ring or nodular enhancement	Markedly elevated lactate >> lipids; depletion of normal metabolites

plasmosis and lymphoma should be suspected in all cases that resemble lymphoma on imaging. The present case illustrates that the combined lesion of toxoplasmosis and lymphoma may appear as a hypointense lesion, rather than isointense or hyperintense as in typical lymphoma, with a ring-enhancing pattern, and the rim of the lesion may be wider than the typical toxoplasma abscess on T2-weighted images. MR spectroscopy appears to be a helpful adjunct to imaging for improving the diagnostic accuracy.

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