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Radiologic-Pathologic Correlation

Gliomatosis Cerebri

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Clinical History

A 51-year-old white woman was well until approximately 3 years before death, when she complained of a new onset of chronic fatigue and urinary incontinence. She was thought to have atypical depression and was treated with antidepressants for 2 years with minimal success. Urologic evaluation revealed motor urge incontinence with detrusor instability. Her urologic symptoms temporarily improved with medication, but subsequently the incontinence progressively worsened. Family history was significant for depression and multiple sclerosis, but there was no brain neoplasia or neurodegenerative disease. Her general physical examination was normal. Mental status testing was normal except for mild flattening of affect. Neurologic examination was normal except for mild cogwheel rigidity in the wrists and ankles, greater on the left. Extensive blood tests were normal. Cerebrospinal fluid was normal, including negative oligoclonal bands and a normal IgG index. A magnetic resonance (MR) examination (Fig 1) and an 18-fluorodeoxyglucose positron emission tomography scan (Fig 2) were performed. A stereotactic biopsy

of the right thalamus was performed. Pathologic exam revealed normal brain with slight hypercellularity and was considered nondiagnostic.

The patient continued to have fatigue, and the urinary incontinence worsened. She became more apathetic and abulic and became progressively slower in her motor activity; concentration was poor. There was the new development of worsening in short-term memory. Repeat MR and positron emission tomography studies (6 months after the first studies) showed no progression of the lesion and no increase in the metabolic activity of the lesion. An extensive evaluation failed to identify a metabolic or infectious cause of her symptoms. Repeat stereotactic biopsy (9 months after first biopsy) was performed on the right thalamus. Pathologic exam revealed an infiltrating astrocytic neoplasm with nuclear hyperchromatism; a solitary mitosis was identified. The lesion could not be accurately graded because the specimen was small and the tumor cellularity relatively low. The patient was referred for radiation therapy and treated with 2340 cGy of a proposed 5400-cGy course. Symptoms were not improved with therapy, and she had suffered a sudden cardiac arrest while completing her radiation therapy course 3 years after symptom onset.

Autopsy revealed the lack of a focal mass lesion with mild enlargement of the thalami bilaterally; changes related to the patient's being on a respirator before death were iden-

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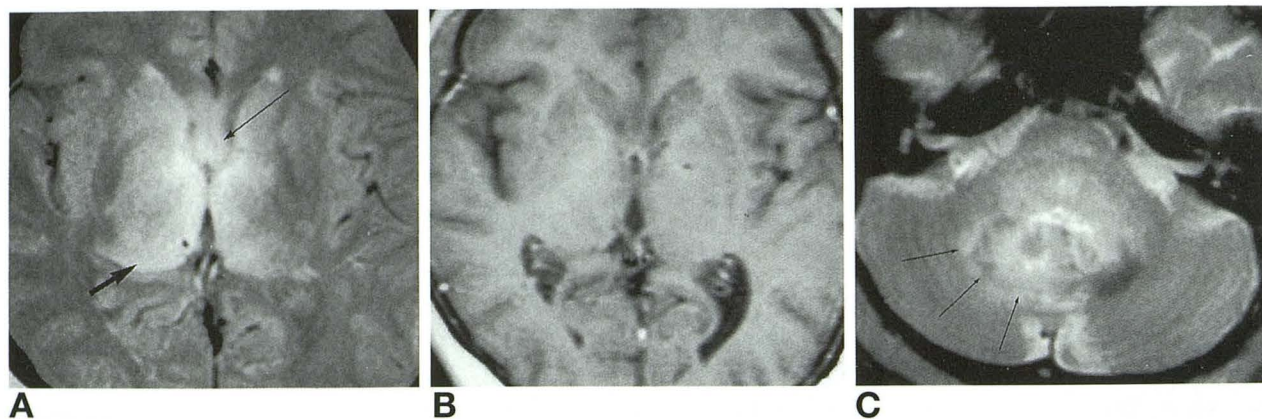


Fig 1. A, Axial proton density-weighted (2500/30 [repetition time/echo time]) MR image through the region of basal ganglia. Note heterogeneous abnormal hyperintensity predominantly involving the right thalamus (*arrow*) but also extending into the posterior limb of the right internal capsule and extending across midline structures (fornix, septum pellucidum, and anterior commissure; *long arrow*) into the left thalamus.

B, Axial T1-weighted (500/20) postcontrast MR image shows lack of pathologic enhancement in the thalami.

C, Axial T2-weighted (2500/80) MR image through the posterior fossa. Note heterogeneous abnormal hyperintensity throughout the pons surrounding the fourth ventricle and extending posteriorly into the region of the right dentate nucleus (*arrows*).

tified (Fig 3). Histologic examination after sectioning revealed extensive neoplastic infiltration of the brain, including the thalami, internal capsule on the right, brain stem, and cerebellum; a lesser degree of infiltrate was identified within the bilateral temporal and frontal lobes (Fig 4). A radiologic-pathologic diagnosis of gliomatosis cerebri was reached.

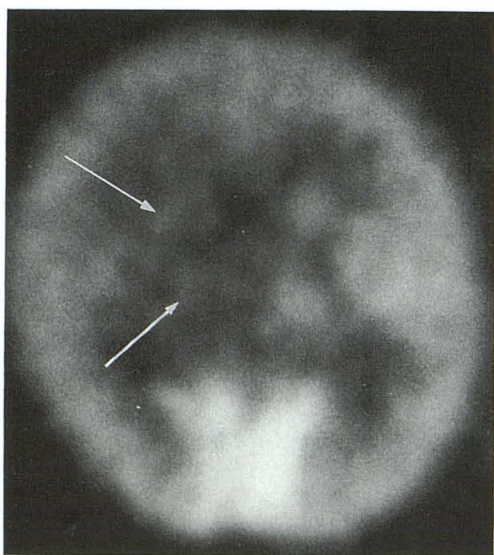
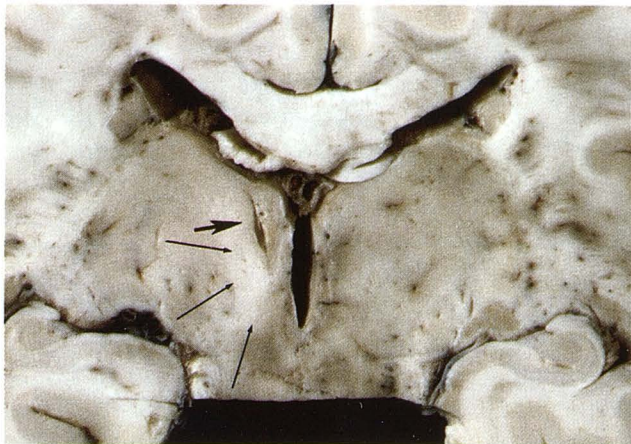


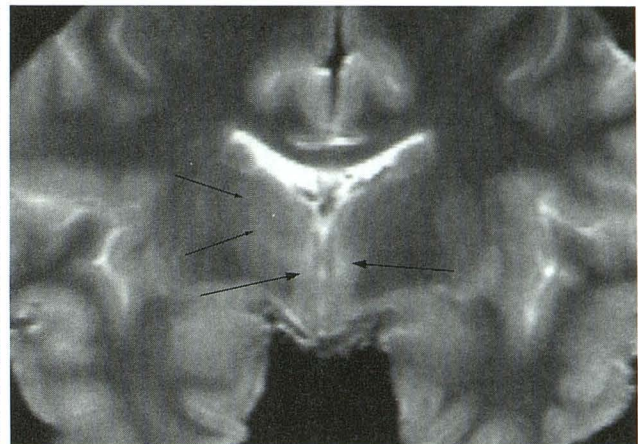
Fig 2. Axial 18-fluorodeoxyglucose positron emission tomography image shows hypometabolism involving the right thalamus and basal ganglionic structures (*arrows*).

Discussion

Gliomatosis cerebri is a rare neoplastic disease of the central nervous system with approximately 100 cases reported in the literature. The term was used by Nevin in 1938 to describe a highly infiltrative glial neoplasm with diffuse overgrowth of the brain and preservation of the underlying neural structures (1). However, similar lesions were reported earlier in the literature as "blastomatous type of diffuse sclerosis," "central diffuse schwannosis," "astrocytoma diffusum," and "gliomatous hypertrophy" (2). Nevin believed the diffuse nature of the lesion was caused by the development of tumor cells from multiple embryonic rests' "blastomatous malformation" with subsequent centrifugal infiltration (1). Other investigators have reported that gliomatosis cerebri is a neoplasm with multicentric transformation with dedifferentiation of astrocytes and subsequent centrifugal spread (2, 3). Still others have considered gliomatosis cerebri as one end of a broad spectrum of infiltrating gliomas but not a distinct entity (4, 5); if this criterion (eg, equating gliomatosis cerebri with diffuse astrocytoma) is used for the diagnosis, it is extremely likely that the incidence of gliomatosis cerebri is underreported. Whatever the pathogenesis, there is a diffuse overgrowth and gross



A



B



C

Fig 3. A, Coronal section of the fixed brain. There is minimal enlargement of the thalami without evidence of a discrete tumor mass. The normal and affected areas are not clearly demarcated. The slitlike biopsy defect in the right thalamus (short arrow) is surrounded by an ill-defined white indurated area (long thin arrows). Histologic sections confirmed the presence of tumor in this region.

B, Postmortem coronal T2-weighted (2500/80) MR image at a level slightly anterior to A shows abnormal hyperintensity infiltrating the right thalamus (small arrows) and extending inferiorly to involve the hypothalamic structures around the third ventricle (long arrows).

C, Transverse section of the fixed cerebellum and pons. There is dusky discoloration of the pons and cerebellum, compatible with total cerebral necrosis or "respirator brain." Note the absence of gross evidence of infiltrating tumor with preservation of the normal architecture of the pons and cerebellum.

enlargement of the central nervous system without significant focal mass effect, associated with a proliferation of neoplastic glial elements (5–8). Although there is some confusion in the literature, it is apparent that cases that are associated with focal tumor centers or masses, likely the origins of the lesions, are better termed *diffuse glioma* or *secondary gliomatosis cerebri* (5, 8, 9). In more recent discussion of gliomatosis cerebri, the working group of the World Health Organization has considered this form of glioma a distinct and separate clinicopathologic entity rather than a nonspecific pattern of glioma infiltration; criterion for diagnosis was considered to be involvement of at least two lobes of the brain by small elongated cells without a cellular, centrally necrotic center (10). Using this criterion, gliomatosis cerebri should be considered a distinct and unusual

form of glioma with characteristic microscopic findings and characteristic radiologic (or gross pathologic) demonstration of widespread invasion, quite different from the more common diffuse glioma. The pathologic diagnosis of gliomatosis cerebri therefore requires radiologic-pathologic correlation; otherwise, the entity may be underreported, because the widely infiltrative nature of the lesion will not be evident.

Personality and mental status changes are the most frequently seen symptoms, with hemiparesis, ataxia, headache, cranial nerve signs, and seizures noted less frequently (3, 11). Presentation with behavioral changes has been described as likely secondary to involvement of the temporal lobes and the diencephalon (12). The clinical signs are reportedly mild and out of proportion to the widespread extent of parenchymal involve-

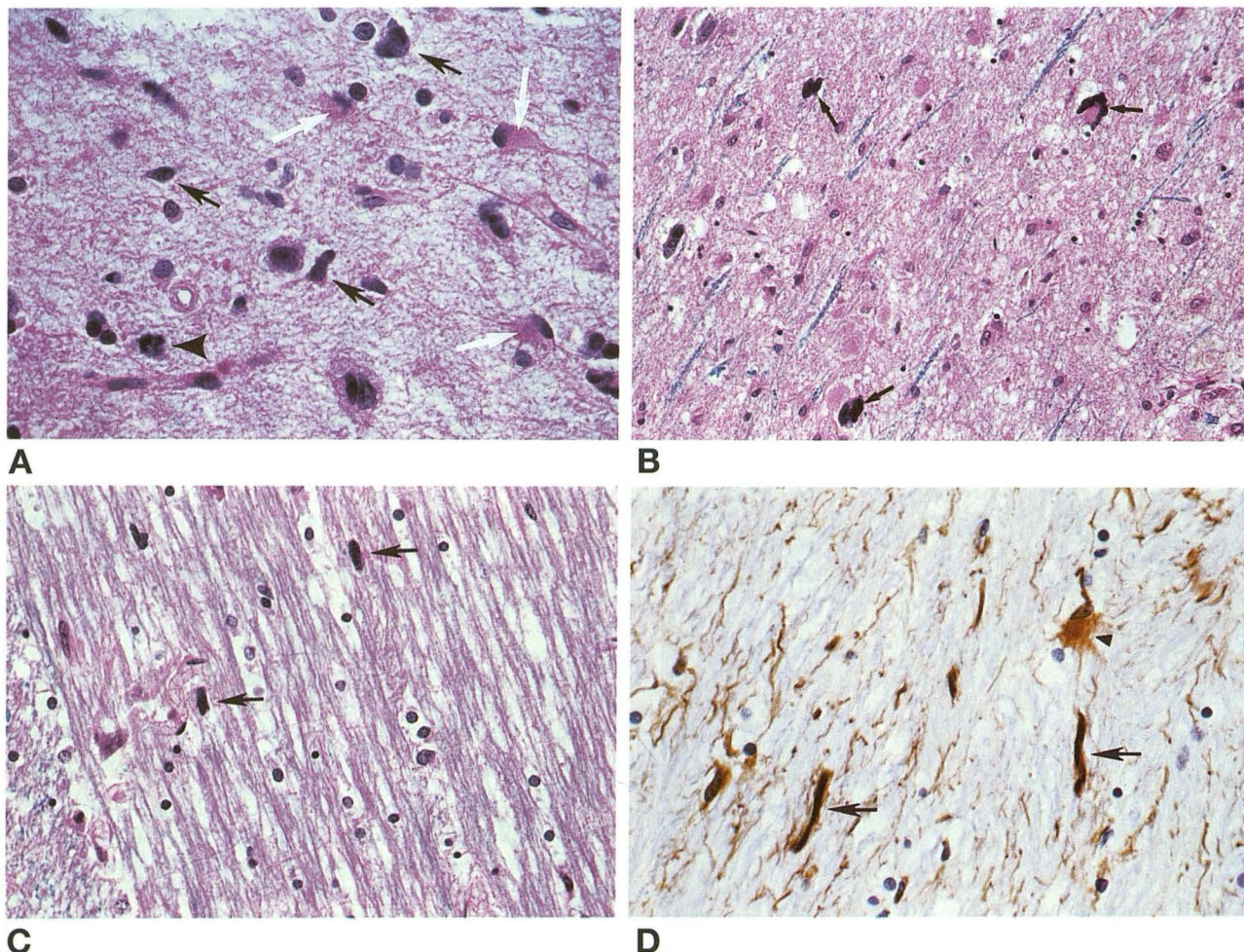


Fig 4. A, High-power photomicrograph of thalamic biopsy (hematoxylin-eosin stain). There is increased cellularity in the gray matter. Note the hyperchromatic, angulated neoplastic cells (*black arrows*). Scattered reactive astrocytes have abundant eosinophilic radiating processes (*white arrows*). A rare mitotic figure is seen (*arrowhead*).

B, Medium-power postmortem photomicrograph of a thalamic lesion (hematoxylin-eosin/luxol fast blue stain). In this field, the infiltrating neoplastic cells are bizarre with very elongated, hyperchromatic, and often multiple nuclei (*arrows*). Such anaplastic foci were seen scattered throughout the infiltrate in the thalamus and midbrain.

C, High-power postmortem photomicrograph of a pontine lesion (hematoxylin-eosin/luxol fast blue stain). Hyperchromatic, elongated neoplastic cells are interspersed in the transverse pontine fibers (*arrows*) without apparent tissue destruction.

D, High-power postmortem photomicrograph (glial fibrillary acidic protein immunostain). Two elongated neoplastic cells in this field are immunoreactive to glial fibrillary acidic protein (*arrows*). Note the reactive astrocyte with glial fibrillary acidic protein-positive glial processes (*arrowhead*).

ment (7), which may relate to the diffuse but generally nondestructive nature of the disease process. Focal neurologic signs may be seen late in the disease course (11, 13). The incidence of gliomatosis cerebri is greatest in the third through fifth decades (3, 13–15). An equal sex distribution is apparent from the reported cases (8, 14). The clinical duration can vary from weeks to years (3, 7), likely a

reflection of the variety of lesions previously subsumed under this diagnosis.

Laboratory studies have been helpful in excluding other focal disease processes; cerebrospinal fluid studies are usually unremarkable (3, 16). Small elevations of cerebrospinal fluid protein can be identified in 25% of cases (16). The electroencephalographic abnormality most commonly seen is diffuse

slow activity with focal slowing or occasional spikes (16). Early diagnosis is difficult given the variability of clinical presentations; definite diagnosis, however, can be made via multiple stereotactic biopsies or postmortem examination (14, 18). Antemortem diagnosis, via multiple stereotactic biopsies, is rarely possible because of the relatively low neoplastic cell density and associated reactive gliosis in early-stage disease (8, 11, 15). It is therefore not surprising that many published cases show a lack of correlation between the biopsies and the postmortem pathologic diagnoses (5). Nevertheless, awareness of the entity and correlation of clinical, radiologic, and pathologic findings may allow for antemortem diagnosis.

Pathologic Findings

Gross. Serial coronal sections demonstrated preserved symmetry of the right and left hemispheres and preserved anatomic landmarks without mass lesion. The thalami appeared slightly enlarged bilaterally, but no other focal lesions were apparent (Fig 3A). Changes consistent with respirator brain (Fig 3C) and secondary cerebellar tonsillar herniation were identified. The lack of a grossly distinct mass is typical of the reported cases in the pathologic literature (14, 15, 19) and satisfied the requirement for lack of a central necrotic center as suggested by the World Health Organization (10). Often diffuse enlargement of the cerebral hemispheres, cerebellum, and brain stem are apparent (14, 20); however, in the present case, this was restricted to the thalamic nuclei.

Microscopic. Stereotactic biopsy of the right thalamus revealed slightly hypercellular brain tissue with rare angulated, hyperchromatic nuclei, and rare mitotic figures, diagnostic of an infiltrating astrocytic neoplasm (Fig 4A). Postmortem examination showed classical histologic features of gliomatosis cerebri with a considerably more extensive and diffuse lesion than expected from gross examination. Microscopic sections of the thalamic nuclei, which was the region of maximal abnormal cell density, showed a moderately cellular infiltrate of variably differentiated neoplastic glial cells (Fig 4B). Cells had hyperchromatic, markedly elongated, fusi-

form to ovoid nuclei and little appreciable cytoplasm. Some cells were highly atypical, multilobulated, and multinucleated, and were extremely large, measuring up to 15 times the size of an oligodendrocyte. Scattered reactive astrocytes were identified within the infiltrate and predominated focally, as has been described previously (5, 7). Only rare mitotic figures were seen. As is typical of most cases described (14, 20), features generally associated with localized high-grade malignant gliomas, such as vascular proliferation and necrosis, were not identified. The lesion was widely disseminated with contiguous involvement of the posterior limb of the internal capsule and substantia nigra. The infiltrate was also noted in the left thalamus, pons, cerebellum, and rostral medulla (Fig 4C). A somewhat sparser infiltrate was seen in the gray matter and subcortical white matter of the bilateral frontal and temporal lobes. The degree of infiltration of both cerebral and cerebellar structures satisfied the diagnostic criteria of involvement of at least two lobes as suggested by the World Health Organization (10).

Overall, the lesion was associated with little tissue destruction; a central necrotic center could not be identified. Histologic sections stained with luxol fast blue showed minimal destruction of myelinated fibers, even in areas with moderate cellularity. This is typical of the reported cases (14). In general, axon cylinders and neurons are reported to be largely intact (14, 15, 19). The infiltrate tended to produce diffuse (or symmetric) enlargement of the most heavily affected region, in this case the thalamus, rather than a well-defined tumor mass. Immunoreactivity for glial fibrillary acidic protein was present focally in the population of elongated neoplastic cells (Fig 4D). Positive staining for glial fibrillary acidic protein is variable for this entity (5, 8, 14, 21).

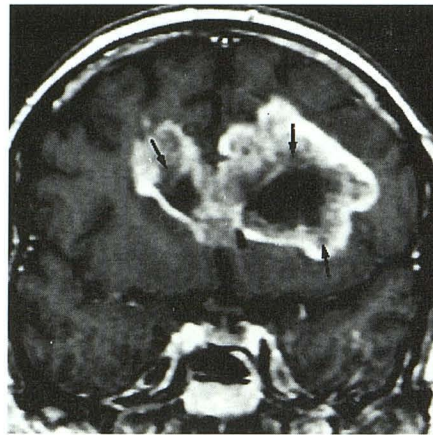
Differential Diagnosis. Astrocytic neoplasms are typically highly infiltrative lesions and may be composed of elongated neoplastic cells, similar to many cases of gliomatosis cerebri. The bizarre multinucleated cells seen in the present case, however, are out of the range of cellular atypia generally seen in a low-grade astrocytoma (20). Moreover, as-

Fig 5. Another patient, a 49-year-old man with glioblastoma multiforme.

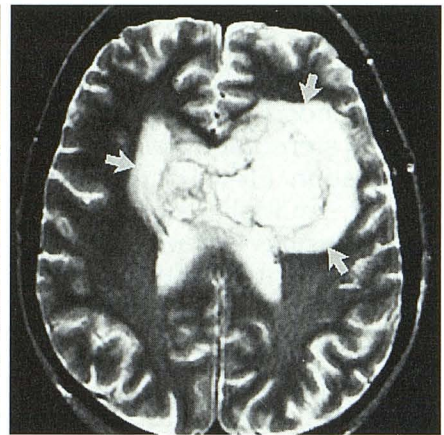
A, Coronal T1-weighted (500/20) postcontrast MR image. A focal lesion surrounds the frontal horns and is seen crossing the corpus callosum in a "butterfly" pattern. The tumor immediately surrounding the ventricular surface enhances slightly and is probably necrotic (arrows).

B, Axial T2-weighted (2500/80) MR image shows focal T2 signal hyperintensity consistent with edema and nonenhancing tumor (arrows). The focal findings and the suggestion of necrosis differs from the MR findings of gliomatosis cerebri.

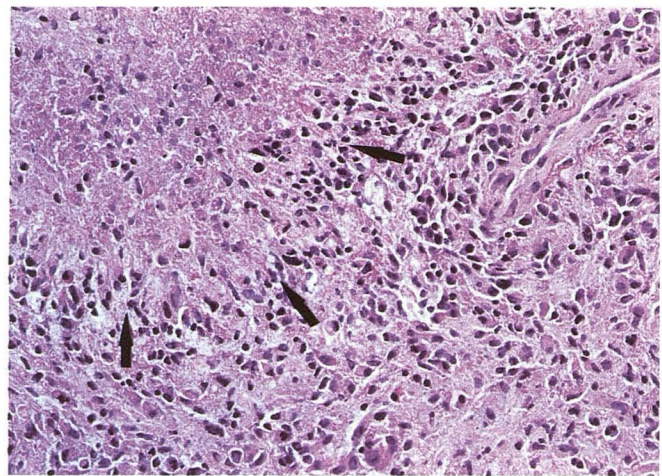
C, Medium-power postmortem photomicrograph of the enhancing portion of the lesion (hematoxylin-eosin stain). The palisading necrosis (arrows) and high tumor cellularity, corresponding to a mass lesion, distinguish the glioblastoma multiforme from the less-cellular nondestructive infiltrative growth of gliomatosis cerebri.



A



B



C

trocytomas are typically associated with a mass lesion, whereas gliomatosis cerebri manifests as infiltrative but not destructive growth (14, 19). Malignant astrocytic neoplasms generally contain foci of higher cell density than expected in gliomatosis cerebri and often contain vascular proliferation and/or necrosis, features rarely described in gliomatosis cerebri (14) (Fig 5). Furthermore, the degree of tumor cell dissemination seen with gliomatosis cerebri exceeds that of the infiltrating glioma.

Oligodendrogliomas are included in the differential diagnosis because they tend to infiltrate both gray and white matter, with the formation of so-called secondary structures of Scherer (20). The nuclei of oligodendrogliomas are characteristically round and are often associated with a halo. The neoplastic cells of gliomatosis cerebri may show oligodendroglial differentiation and hence may ap-

pear similar (22). However, a population of the more classical elongated, undifferentiated cells is likely to be present in gliomatosis cerebri, and a greater degree of dissemination is expected.

Multicentric gliomas are distinguished from gliomatosis cerebri by virtue of the distinct gross and microscopic appearance of the multiple lesions and the absence of dissemination by any of the known pathways in the former (23). It is possible that the diffuse infiltration of gliomatosis cerebri, however, may be confused at biopsy with multicentric well-differentiated glioma; that is, without extensive histologic examination a connection between the various foci of glioma may be missed. However, multicentricity is most frequently seen in glioblastoma multiforme, and it is exceptionally seen in well-differentiated astrocytomas or anaplastic astrocytomas (4).

Inflammatory and infectious conditions and other reactive processes may incite a proliferation of microglial "rod cells," considered endogenous tissue histiocytes, and may be mistaken for gliomatosis cerebri when microglia predominate. However, careful search will likely reveal features associated with inflammatory or infectious reactions, namely, perivascular lymphocytic inflammation, meningeal inflammation, and possible identification of a specific infectious agent.

Microgliomatosis, defined as a highly infiltrative population of neoplastic microglia, is more likely to be mistaken for gliomatosis cerebri. By light microscopy alone, the lesions may be indistinguishable (24). Both tend to enlarge an affected region without producing a defined tumor mass and, histologically, are widely infiltrative with morphologically similar cells. Immunohistochemistry with macrophage- and glial-specific markers should allow distinction. Microgliomatosis has been reported to be immunoreactive for macrophage markers and negative for glial fibrillary acidic protein, unlike gliomatosis cerebri (24). It is likely that some cases of gliomatosis cerebri and microgliomatosis reported in the literature before the availability of these markers were misdiagnosed.

Imaging Appearance

Computed Tomography (CT). CT studies in patients with gliomatosis cerebri most commonly show areas of structural enlargement, focal or diffuse, with pathologic hypodensity reflecting the widespread nature of the infiltrative process; a definable mass is not present (7, 8, 16, 25). Correlating with the subtle infiltrative spread identified in this type of neoplasia, CT examination has been normal in some cases, even after many years of symptoms (14, 16). Gliomatosis cerebri, in fact, should be suspected from the lack of significant radiographic abnormalities in light of clinically significant findings (3). Multifocal hypodense lesions have been described in the literature, which has suggested a multifocal cause of gliomatosis cerebri (25). It is likely, however, that in cases with definable masses, the final pathologic appearance may be in line with more conventional infiltrating

glial tumors and not gliomatosis cerebri (13). CT demonstration of ventricular compression (13) secondary to diffuse mass effect is more typical than ventricular enlargement, which can be seen because of enlargement of the white matter tracts and secondary obstruction at the level of the foramen of Monro (26). Contrast enhancement on CT study is usually minimal or absent, indicating an intact blood-brain barrier in this form of neoplasia (13). However, areas of enhancement have been correlated pathologically with areas of dense tumor infiltration (6, 25).

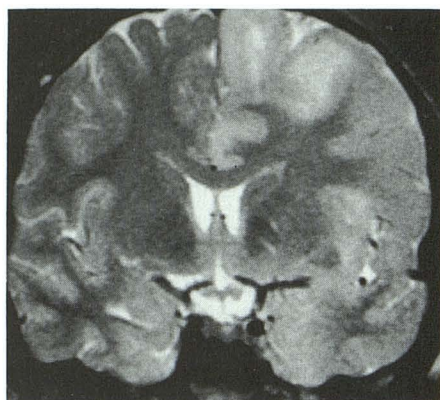
MR. Because of the greater sensitivity of MR examination, lesions that appear subtle or are not apparent on CT may be identified by MR (6, 27). In a process known to be extremely infiltrative, MR is clearly superior in defining the true extent of the lesion and in providing information necessary for biopsy (27). In our case, although a CT scan was not obtained, it is likely that the scan would have been interpreted as normal given the extreme lack of mass effect. MR studies in patients with gliomatosis cerebri commonly show diffuse and fairly symmetrical changes of midline structures; areas involved are usually of low signal on T1-weighted images and of uniformly high signal on T2-weighted images (7, 9, 13). As described in this patient, abnormalities of the basal ganglia, thalami, and hypothalamus (Figs 1A and B) are invariably observed on MR, but cerebral white matter involvement is variable (9). Brain stem, cerebellum, and spinal cord infiltration also have been documented on MR in patients with gliomatosis cerebri (9), as was identified in this case (Figs 1C, 6, and 7).

Hyperintensity on T2-weighted images observed in white matter tracts most likely reflects tumor spread but also may represent secondary destruction of myelin fibers (9). The superior ability of MR to define the gray-white matter junction makes identification of its loss fairly easy (Figs 6 and 7). MR depiction of enlargement of the cortical gyri can correlate with areas of neoplastic infiltration (6, 7, 13). Although MR is fairly sensitive to the pathologic changes in this disorder, when direct correlation is made with postmortem pathologic changes, MR studies underestimate the extent of the tumor, with areas of less-dense cellular proliferation and subtle in-

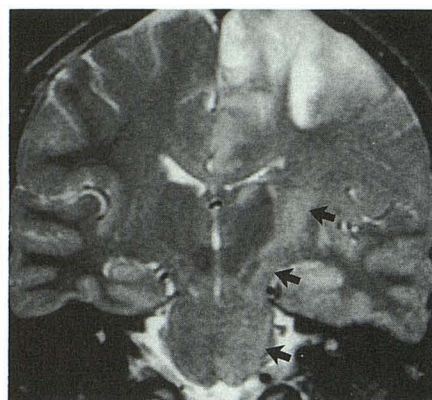
Fig 6. Another patient, a 16-year-old boy with gliomatosis cerebri.

A, Coronal T2-weighted spin-echo (2500/80) MR image. Note extensive diffuse infiltrative abnormality involving the majority of the left cerebral hemisphere causing enlargement of the affected structures and local effacement of the sulcal pattern but lacking a well-defined mass or midline shift.

B, Coronal T2-weighted spin-echo (2500/80) MR image. Note extension of subtle hyperintense signal inferiorly through the left corticospinal tract into the pons (arrows).



A



B

filtration appearing normal. In this case, areas of subtle tumor infiltration in both temporal and frontal lobes on microscopic examination appeared normal by imaging even in retrospect. Although a correct diagnosis by antemortem MR has been rare, the diagnosis may be suggested on MR when a lesion is seen associated with diffuse infiltration, diffuse mass effect, and hyperintense signal abnormality on T2-weighted images (5, 8, 9). Spread of signal abnormality along white matter tracts, such as the corticospinal tract, highly suggests this diagnosis (Figs 6 and 7). Stereotactic biopsy in conjunction with MR has been recommended as the diagnostic procedure in suspected cases of gliomatosis cerebri, although the diagnosis may be difficult to establish before death by focal biopsies in a diffuse process (5, 7, 8).

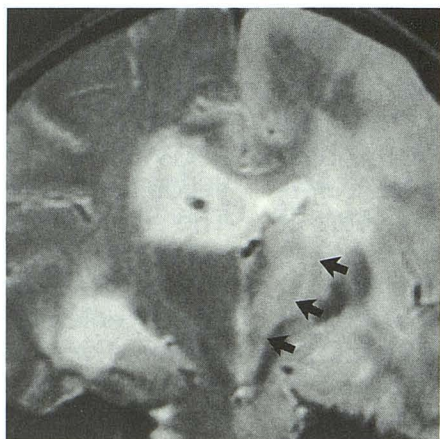
Reports of cerebral angiography in patients with gliomatosis cerebri state that this examination is frequently normal, or an avascular mass may be seen (13). Positron emission tomography with carbon-11-L-methionine has been reported in gliomatosis cerebri; activity has shown accurate correlation with areas of diffuse tumoral infiltration (28).

Differential Diagnosis. Findings on CT and MR in gliomatosis cerebri are relatively nonspecific and have been misinterpreted in the literature as leukoencephalopathy, multiple sclerosis, progressive multifocal leukoencephalopathy, or ischemic change (1, 15). Involvement of the deep or superficial gray matter should help exclude a leukoencephalopathy. Although plaques seen with multiple sclerosis can be large, there is usually a discrete or focal mass epicenter with focal mass

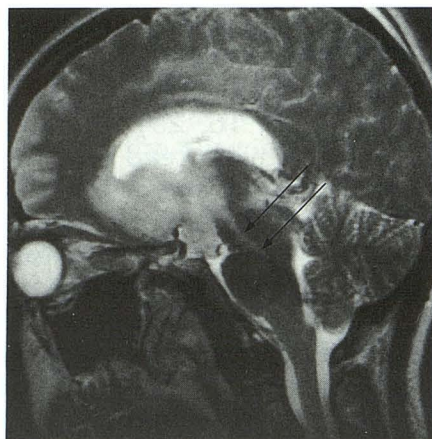
Fig 7. Another patient, a 24-year-old woman with gliomatosis cerebri.

A, Coronal T2-weighted spin-echo (2500/80) MR image. Note extensive, diffuse infiltrative hyperintensity involving the majority of the left cerebral hemisphere and medial portions of the right hemisphere. There is effacement of the sulci over the left convexity without midline shift. Extension of abnormal signal through the corticospinal tracts can be seen (arrows). Obstructive hydrocephalus of the right lateral ventricle results from tumor obstructing the foramen of Monro.

B, Sagittal T2-weighted fast spin-echo (4000/108) MR image. Note extension of signal abnormality involving the hypothalamic region inferiorly through the midbrain into the superior pons (arrows). There is an element of head rotation on this image, so that the right orbit and ventricle are seen with the middle to left brain stem.



A



B

effect. Other considerations should be given to an infiltrative conventional glioma and inflammatory or infectious processes including viral encephalitis. Clinical history and neurologic findings on examination are important in narrowing this differential.

Prognosis

Although there is a response to radiation therapy in some patients with gliomatosis cerebri, radiation therapy is of questionable benefit given the low-grade nature of some of the tumors (7, 8). Chemotherapy is of little benefit in these patients, although steroids may be useful in the short term (8). Treatment of patients with gliomatosis cerebri is also hampered by the difficulty of establishing an early diagnosis (11), as was demonstrated in this case. In the long term, no treatment has been proved effective, and the prognosis remains poor (8).

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