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Central Nervous System Changes after Radiation Therapy and/or Chemotherapy: Correlation of CT and Autopsy Findings

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This is a retrospective correlative study of cranial computed tomography (CT) and autopsy findings in 50 patients after central nervous system radiation therapy and/or chemotherapy. Most patients had more than one posttherapy CT scan and all cases were autopsied. Twenty-six cases (52%) showed no posttherapy CT changes. In 18 cases (36%) enlargement of intracranial subarachnoid spaces and/or ventricles was seen on CT, but only two of these cases showed gross atrophy on postmortem examination; even in these, the cortex was histologically normal, suggesting that these CT changes may be reversible. In six cases a decrease in white-matter density was seen on CT. Two of these cases were histologically normal, two cases showed some white-matter rarefaction, one case contained multiple foci of white-matter and vessel wall necrosis, and one case had progressive multifocal leukoencephalopathy.

Adverse effects on the central nervous system (CNS) after CNS or cranial irradiation and various courses of chemotherapy for malignancy have been reported in the literature [1–7]. Dilatation of the ventricular system and sulci in patients who have received CNS radiation therapy and/or chemotherapy has been described [8–10]. White matter damage and delayed radiation necrosis have also been reported as complications of these modes of treatment [11–17]. In the following series of patients pre- and posttherapy computed tomography (CT) scans and autopsy reports were reviewed and correlated. Eighteen cases were reevaluated by additional histologic studies.

Materials and Methods

We reviewed the autopsy records from 1978 through 1981 at Brigham and Women's Hospital, Boston, for patients who underwent cranial irradiation and/or chemotherapy for neoplasia. All patients with available CT scans (50 cases) in this group are included in the retrospective study.

CT studies were performed on an EMI 1005 scanner at the Sidney Farber Cancer Institute and/or a Siemens Somatom II scanner at Brigham and Women's Hospital. Eighteen of the 50 autopsied cases were reevaluated by gross and microscopic examination of large histologic sections. The autopsy reports and original histologic sections of the other cases were reviewed without further sectioning.

The 50 cases were divided into three groups: (1) patients who

received CNS radiation therapy only (three cases); (2) patients who received chemotherapy only (25 cases); and (3) patients who received a combination of chemotherapy and CNS radiation therapy (22 cases). All but one of the 50 autopsy examinations were performed between 1 day and 10 months after the last CT scan; in one case in group 2, the interval between final scan and autopsy was 3 years 9 months.

The age range of the 50 patients (26 males, 24 females) was 10–80 years (mean age, 60 years). The distribution of types of neoplasia was as follows: metastasis, 30 cases; lymphoma, eight cases; leukemia, eight cases; glioblastoma multiforme, three cases; pituitary germ cell tumor, one case.

Results

CT examinations were negative or demonstrated changes not related to therapy in 26 cases. The CT findings in these 26 cases were: residual CNS tumors, 15 cases; negative CT scan, nine cases; aqueductal stenosis, one case; and acute subdural hematoma, one case. Twenty-four cases showed positive CT changes related to therapy. The correlation of these CT changes and the pathologic findings is summarized in table 1.

The most common CT presentation, seen in 13 cases, was compatible with cerebral atrophy (i.e., progressive enlargement of ventricles as well as subarachnoid spaces). Among these cases, the single case representing group 1 showed gross brain atrophy. However, abnormal histologic findings consistent with tissue loss or damage (e.g., neurofibrillary tangles, neuronal dropout) were absent. The only pathologic change in this case was a right frontal lobe metastasis. Of the four cases representing group 2, only one case had gross atrophy on postmortem examination, and there were no histologic abnormalities consistent with cortical atrophy in this or other cases from this group. Four of the eight brains representing group 3, including example case 1, showed various degrees of ventricular dilatation. None of these had histologic evidence of gross atrophy. The only microscopic abnormality was leptomeningeal infiltration by neoplastic cells in two of the four cases, which possibly led to communicating hydrocephalus. One case from group 3 that showed no gross atrophy or ventricular dilatation pathologically had multiple foci of white-matter necrosis, which had remained undetected by CT; the CT-autopsy interval was 1 month in this case.

CT scans in two cases showed marked dilatation of the fourth

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TABLE 1: CNS Changes after Radiation, Chemotherapy, or Both: CT and Pathologic Findings

CT Findings	No. of Cases (n = 24)*			Pathologic Findings
	Group No.†			
	1	2	3	
Progressive enlargement of ventricular system and intracranial SAS	1	4	8	Two cases gross atrophy (one each, groups 2 and 3); no histologic changes consistent with tissue loss or damage‡
Marked dilatation, fourth ventricle only	0	1	1	No gross changes
Disproportionate enlargement of intracranial SAS without significant ventricular dilatation	0	2	1	No gross atrophy; no histologic changes consistent with diffuse tissue loss or damage
Generalized decrease in density of cerebral white matter	0	1	2	Pallor and vacuolation of cerebral white matter in two cases from group 3; no large histologic sections available from group 2
Generalized decrease in density of the cerebellar white matter	0	1	0	No changes in cerebellar white matter; pontine metastases
Focal decrease in density of cerebral white matter with rim enhancement	0	0	1	Multiple foci of white-matter and blood-vessel necrosis
Focal progressive decrease in density of cerebral white matter without enhancement	0	1	0	Progressive multifocal leukoencephalopathy
Focal cerebral decreased densities consistent with infarct	0	4	0	Fungal infection (two cases); lacune (one case); embolic infarcts (one case)

Note.—CNS = central nervous system; SAS = subarachnoid spaces.

* Some cases are included in more than one category.

† Group 1 had CNS radiation therapy only; group 2 had chemotherapy only; group 3 had combined CNS radiation and chemotherapy.

‡ One case from group 3 had multiple foci of white-matter necrosis undetected by CT.

ventricle without evidence of third or lateral ventricular enlargement. No gross cerebellar atrophy was seen on autopsies. Histologic sections were not done in these two cases.

CT scans in three cases showed enlargement of the subarachnoid spaces without significant dilatation of the ventricles. Pathologically, these cases were normal on gross and microscopic examinations. The only abnormality was a leptomeningeal tumor in the single case representing group 3.

CT scans in five cases showed changes in the cerebral white matter. Three of these were diffuse and two focal. Of the three that showed diffuse changes, two had histologic abnormalities; one of these, representing group 3 (also the example case 2), showed pallor, vacuolation, perivascular hemosiderin-laden macrophages, and some fibrillary gliosis of the white matter. The other case, also from group 3, had pallor and vacuolation of the white matter without reactive changes. Of the two cases with focal decrease in white-matter density on CT scans, one showed rim enhancement. Pathologically, this reflected multiple foci of white-matter necrosis with blood vessel necrosis (example case 3). The white-matter necrosis in this case resembled that seen in the case that was not detected by CT, mentioned earlier. These histologic changes have been observed after irradiation and chemotherapy. The other case with focally decreased density on CT but without rim enhancement showed progressive multifocal leukoencephalopathy on autopsy (example case 4).

CT scans in four cases showed decreased densities consistent with infarcts. Pathologically, two of these cases had fungal infec-

tions with vasculitis, one case represented a lacune, and one case showed multiple small infarcts secondary to emboli.

Representative Case Reports

Case 1

A 51-year-old man had diffuse histiocytic lymphoma. The initial CT examination showed an enhancing low-density lesion in the right frontal lobe with surrounding edema (fig. 1A). Chemotherapy including vincristine, cyclophosphamide, adriamycin, prednisone, and intrathecal methotrexate was administered. A second CT examination 2 months after chemotherapy (fig. 1B) demonstrated resolution of the right frontal lobe lesion. A third CT study 2 months later (fig. 1C) showed a new enhancing lesion in the right occipital lobe and abnormal enhancement of the ependyma of the right lateral ventricle. At that time, radiation therapy consisting of 3,000 rad (30 Gy) was delivered to the brain. A fourth CT scan 5 months later and 4 days before the patient's death (fig. 1D) revealed resolution of these lesions and progressive enlargement of the ventricles and subarachnoid spaces. A new low-density lesion in the right frontal lobe was also evident. Autopsy showed mild dilatation of the right lateral ventricle and sylvian fissures and a gliotic lesion at the site of previous tumor infiltration in the right basal ganglia (fig. 1E). However, there was no evidence of generalized cortical atrophy and no microscopic evidence of neuronal dropout or other neuronal

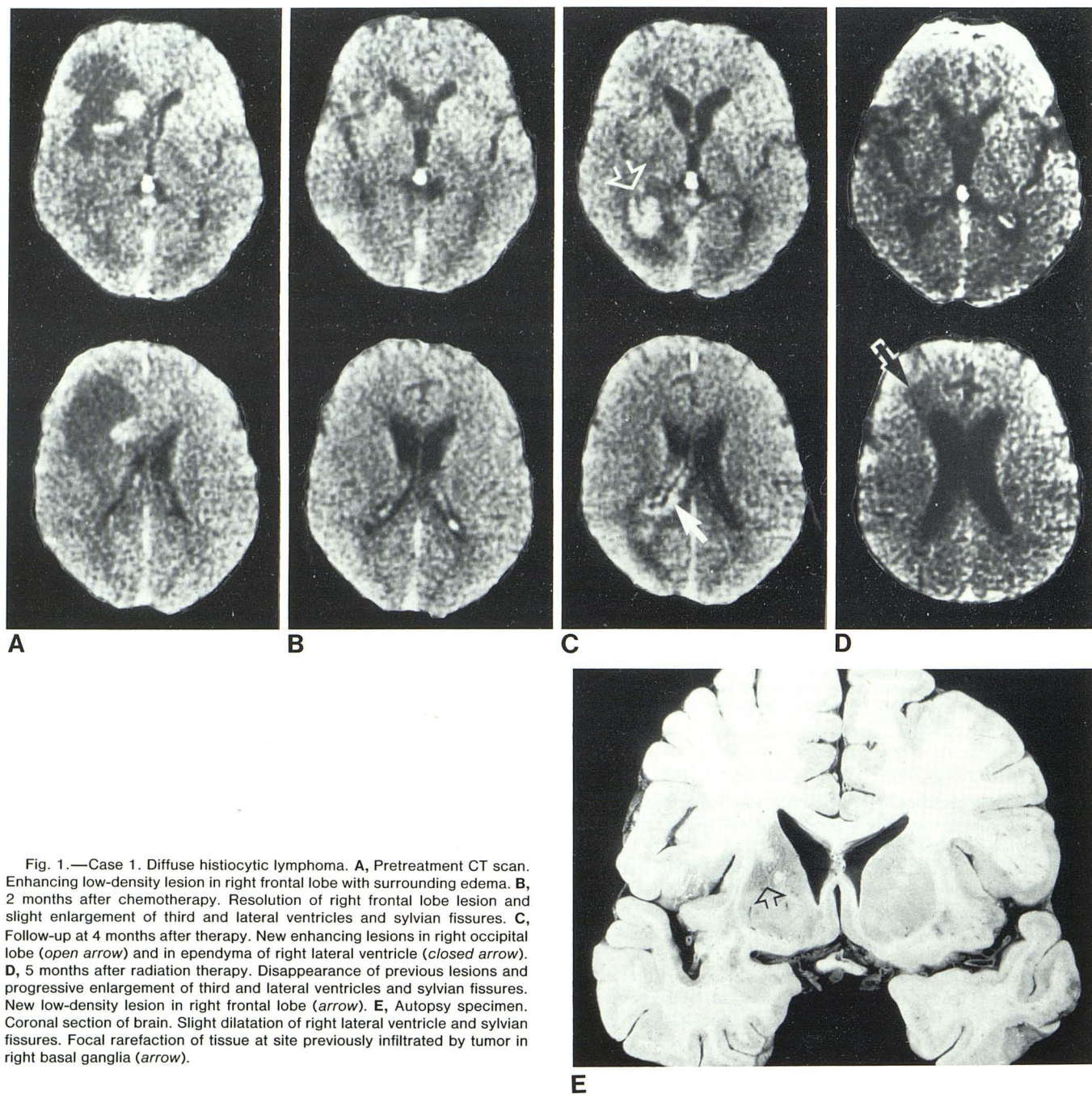


Fig. 1.—Case 1. Diffuse histiocytic lymphoma. **A**, Pretreatment CT scan. Enhancing low-density lesion in right frontal lobe with surrounding edema. **B**, 2 months after chemotherapy. Resolution of right frontal lobe lesion and slight enlargement of third and lateral ventricles and sylvian fissures. **C**, Follow-up at 4 months after therapy. New enhancing lesions in right occipital lobe (*open arrow*) and in ependyma of right lateral ventricle (*closed arrow*). **D**, 5 months after radiation therapy. Disappearance of previous lesions and progressive enlargement of third and lateral ventricles and sylvian fissures. New low-density lesion in right frontal lobe (*arrow*). **E**, Autopsy specimen. Coronal section of brain. Slight dilatation of right lateral ventricle and sylvian fissures. Focal rarefaction of tissue at site previously infiltrated by tumor in right basal ganglia (*arrow*).

change. Similar lesions were seen in the right hippocampal area and right occipital lobe.

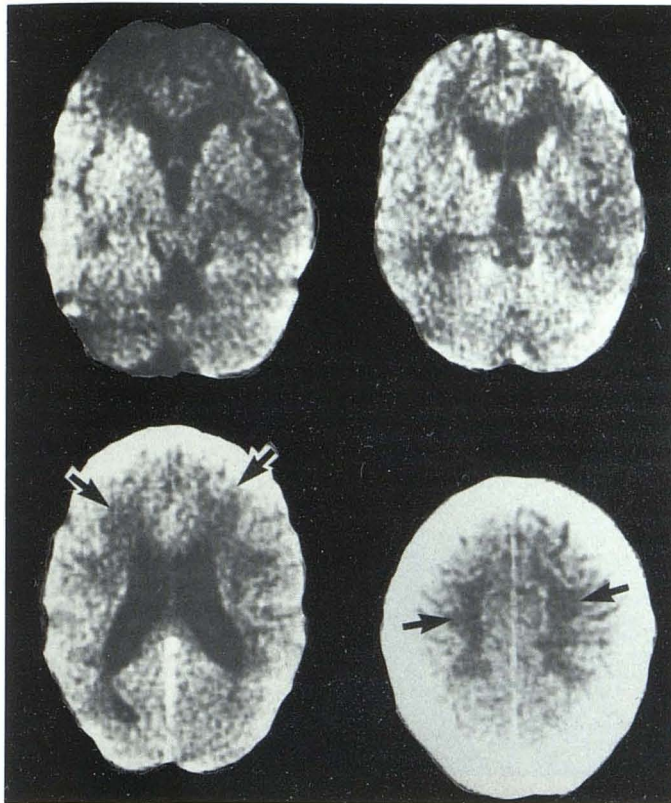
Case 2

A 29-year-old man had poorly differentiated lymphoma. The CT examination 6 months after combined CNS radiation therapy with 4,000 rad (40 Gy) to the brain and chemotherapy with methotrexate and intrathecal arabinosylcytosine (fig. 2A) showed diffuse low density in the cerebral white matter and generalized dilatation of the fourth, third and lateral ventricles. Autopsy 12 days after the last CT scan demonstrated mild generalized dilatation of the ventricles and pallor of the cerebral white matter on stained sections (fig.

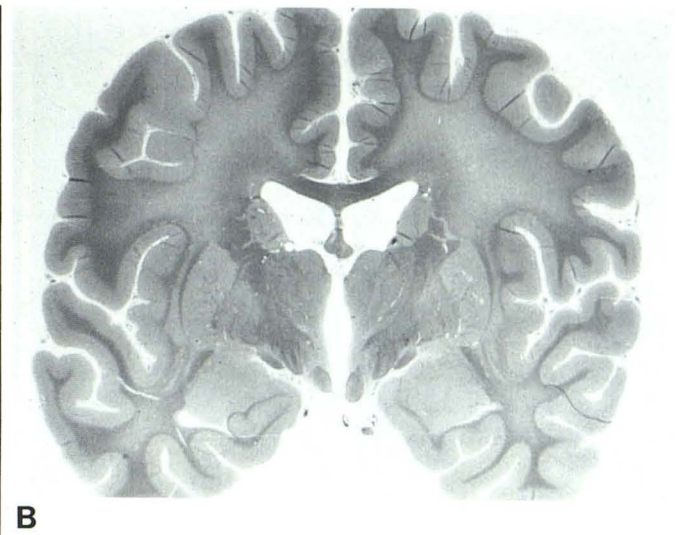
2B). Microscopically, diffuse vacuolization of the neuropile of the cerebral white matter was found with mild fibrillary gliosis and perivascular hemosiderin-laden macrophages.

Case 3

A 22-year-old man had a pituitary germ cell tumor. Radiation therapy of 4,500 rad (45 Gy) to the brain and an additional 1,000 rad (10 Gy) to the pituitary gland and chemotherapy including bleomycin, vinblastine, and cis-platinum were administered. The CT scan 4 months after combined therapy showed mild dilatation of the ventricles (fig. 3A). Multiple rim-enhanced lesions in the white matter associated with diffuse brain edema were found on the

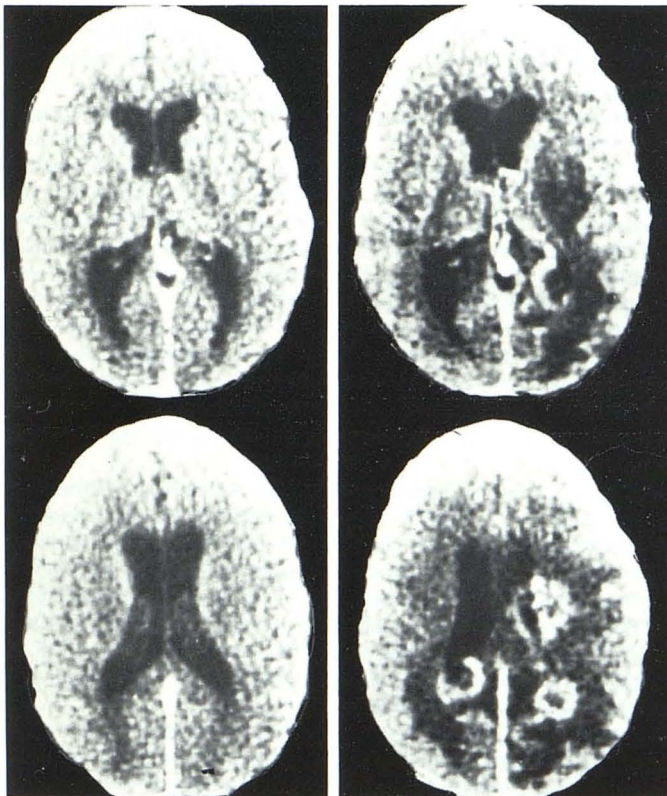


A

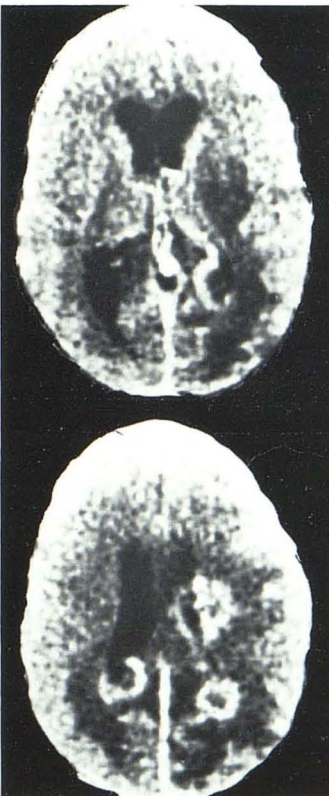


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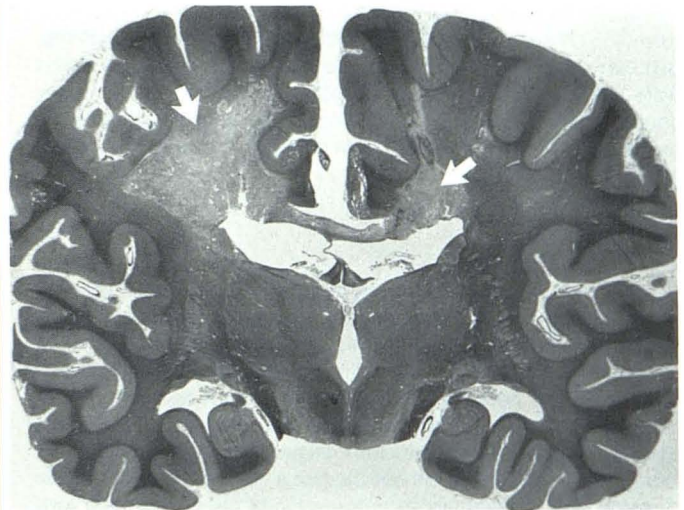
Fig. 2.—Case 2. Poorly differentiated lymphoma. A, CT scan 6 months after combined CNS radiation and chemotherapy. Moderate to marked dilatation of fourth, third, and lateral ventricles and diffuse low density in the cerebral white matter (arrows). B, Autopsy specimen 12 days later. Coronal section with myelin stain. Pallor of white matter and mild dilatation of third and lateral ventricles.



A



B



C

Fig. 3.—Case 3. Pituitary germ cell tumor. A, CT scan 4 months after combined CNS radiation and chemotherapy. Mild dilatation of lateral ventricles. B, Follow-up at 10 months after therapy. Multiple rim-enhanced lesions with surrounding edema. C, Autopsy specimen 3 months later. Coronal section. Bilateral necrotic lesions of white matter (arrows) and dilatation of third and lateral ventricles.

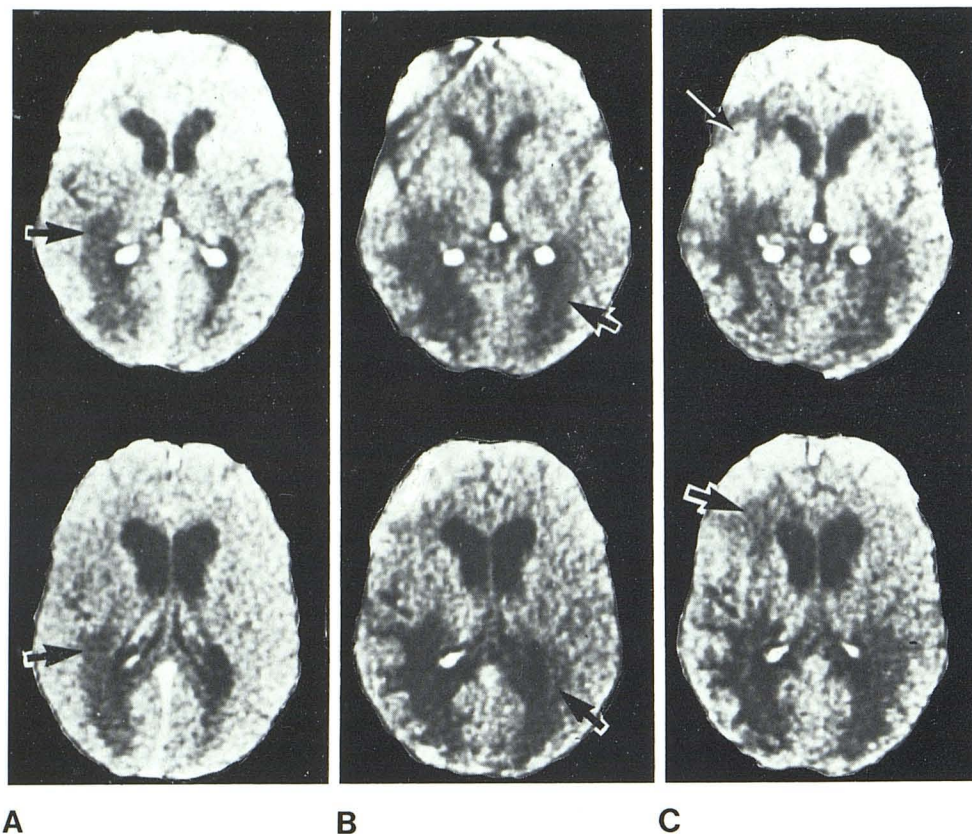


Fig. 4.—Case 4. Poorly differentiated lymphoma. A, CT scan 1 year after chemotherapy. Large low-density area in white matter of right occipital lobe (arrow) without abnormal enhancement. B, Follow-up scan 1 month later. Progression of low-density lesion in right occipital lobe. New lesion in left occipital lobe (arrow). C, CT scan 1 month later. Further progression of both occipital lesions. New lesion in right frontal lobe (arrow).

follow-up CT scan obtained 10 months after combined therapy (fig. 3B). Large and small necrotic lesions involving the white matter were found on autopsy 3 months later (fig. 3C). The lesions were characterized by calcified and noncalcified axonal spheroids as well as obliterative and necrotic changes in the walls of medium- and small-sized vessels.

Case 4

A 67-year-old woman had poorly differentiated lymphoma. CT examination 1 year after chemotherapy with prednisolone and chlorambucil (Leukeran) showed a low-density area without evidence of abnormal enhancement in the right occipital lobe (fig. 4A). At that time the patient had progressive loss of vision. A second CT scan 1 month later demonstrated progression of the white-matter low-density lesion in the right occipital lobe and development of another low-density lesion in the left occipital lobe (fig. 4B). A third CT scan 1 month later showed further progression of the white-matter low-density lesions in both occipital lobes and the presence of a third lesion in the right frontal lobe (fig. 4C). Autopsy 2 days after the last CT scan revealed extensive areas of loss of myelin with preservation of axons, bizarre astrocytes, and abnormally large oligodendrocytes, some of which contained intranuclear inclusion bodies. These are the diagnostic findings of progressive multifocal leukoencephalopathy.

Discussion

Of the 50 cases in our series, 30 (60%) were metastatic tumor, eight (16%) lymphoma, eight (16%) leukemia, three (6%) glioblas-

toma multiforme, and one case was pituitary germ cell tumor. The most striking finding in this study was the discrepancy between the incidence of brain atrophy on CT (18 cases; 36%) and gross pathologic atrophy on autopsy (only two cases). No histologic abnormality consistent with tissue loss or damage (e.g., neuronal dropout, neurofibrillary tangles) was seen in any of these 18 cases. This discrepancy raises the possibility that the observed CT changes may not be structurally fixed as, for example, in the case of Alzheimer disease or senile brain atrophy, but may be a dynamic or reversible alteration in the brain. Such reversible ventricular and subarachnoid space enlargement on CT has been reported after steroid treatment [18] or chemotherapy [9] and in alcoholism [19, 20], anorexia nervosa [21], and Cushing syndrome [22]. Variation in the water content of the tissue or increased protein catabolism has been suggested as the underlying mechanism in the observed CT changes [18], but the exact nature of the change is poorly understood.

In two of the three cases that exhibited diffuse white-matter low attenuation on CT, definite but nonspecific histologic changes were found (vacuolation of the white matter and, in one case, fibrillary gliosis and perivascular hemosiderin-laden macrophages). The nature of these changes is unclear. Two cases (one undetected by CT) showed postmortem multiple foci of white-matter necrosis. One of these showed fibrinoid necrosis of the vessel walls. These pathologic changes have previously been described in association with both radiation and chemotherapy [11].

The pathophysiologic mechanism of the enlargement of the subarachnoid spaces and ventricular system detected on CT remains unknown. The question of whether it is a reversible phenomenon and/or associated with neurologic deficits is a problem for future study, as are the pharmacodynamic effects of individual or com-

bined chemotherapeutic agents, administered with or without radiation therapy, in producing these CT findings.

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