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Hemorrhagic Vasculopathy after Treatment of Central Nervous System Neoplasia in Childhood: Diagnosis and Follow-up

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PURPOSE: To review the clinical data, imaging findings, and intermediate outcomes of a series of children with hemorrhagic vasculopathy after treatment for intracranial neoplasia. **METHODS:** We retrospectively analyzed the medical records and imaging examinations of 20 pediatric patients (ages 1 to 15 years) with intracranial neoplasia in whom delayed intracranial hemorrhage developed after cranial irradiation or radiation combined with systemic or intrathecal chemotherapy. Patients with intracranial hemorrhage from other identifiable causes were excluded. Histopathologic analysis was available in four patients. **RESULTS:** Twenty patients with delayed intracranial hemorrhage received cranial irradiation alone (n=9) or combined radiation and chemotherapy (n=11) for primary brain tumors (n=13), leukemia (n=6), or lymphoma (n=1). Imaging findings were consistent with hemorrhages of varying ages. The hemorrhages were not associated with tumor recurrence nor second tumors. Except for location of the hemorrhage, no significant relationship was established between outcome and original diagnosis, radiation dose (range, 1800 to 6000 centigray), chemotherapeutic agent or dosage, age at treatment, or interval between therapy and hemorrhage (mean, 8.1 years). Only brain stem hemorrhage was associated with a poor outcome. **CONCLUSION:** In children with central nervous system neoplasia who have undergone cranial irradiation, or radiation combined with chemotherapy, delayed intracranial hemorrhage may develop.

Index terms: Brain, effects of irradiation on; Brain neoplasms; Cerebral hemorrhage; Children, neoplasms

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Intracranial hemorrhage is a rare, late delayed effect of treatment for central nervous system tumors that has been described in a small number of children (1, 2) and adults (3, 4). Such an effect must be distinguished from recurrent tumor and from radiation-induced second tumors. The purpose of this study was to review the clinical aspects, imaging findings, and intermediate outcome in a larger series of

children with delayed intracranial hemorrhage after treatment for intracranial neoplasia, and to evaluate clinical and therapeutic factors that may predict it.

Methods

We retrospectively analyzed the medical records and imaging examinations of 20 pediatric patients in whom intracranial hemorrhage developed after cranial irradiation, or radiation plus chemotherapy, as identified by imaging during the period from November 1987 through October 1993, and who had no evidence of recurrent tumor nor other potential cause of central nervous system hemorrhage. The imaging studies included computed tomography (CT) in 1 patient, magnetic resonance (MR) in 10 patients, and both CT and MR in 9 patients. Axial 10-mm CT sections were obtained without contrast enhancement through the entire brain, usually with 5-mm axial sections through the posterior fossa. Contrast-enhanced CT was performed in 2 patients similarly after the intravenous injection of ioversol at a dosage of 2.22

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ml/kg (1 ml/lb). MR exams were performed using a 1.5-T General Electric (Boston, Mass) Signa system with imaging parameters of 5-mm section thickness, 2.5-mm gaps, 256 × 192 matrix, and 24-cm field of view for sagittal T1-weighted conventional spin-echo images (600/20/2 [repetition time/echo time/excitations]), and axial proton density (2000/17/1) and T2-weighted (3200/85/2) fast spin-echo images. Additional coronal T1, proton density, or T2 sequences were often performed. Contrast material was administered in 10 patients: gadopentetate dimeglumine (4) or gadoteridol (6) at a dosage of 0.1 mmol/kg intravenously. Follow-up imaging exams were available in

9 patients. The CT and MR parameters studied included size and number of lesions, location, density, intensity, and enhancement. Because the total sample size was 20, Fisher's Exact Test (5) was used for statistical analysis with regard to predictors of outcome.

Results

Of the 20 patients identified (Table), 13 had primary brain tumors, 6 had leukemia, and 1 had lymphoma. There were 12 girls and 8 boys. All 20 patients underwent cranial irradiation,

Clinical and follow-up data: 20 children with irradiated intracranial neoplasms and delayed hemorrhagic vasculopathy

| Patient | Age at Hemorrhage, y/Sex | Initial Diagnosis | Radiation Dose, centigray | Clinical Presentation of Hemorrhage | Years After RT | Location | Follow-up since Hemorrhage, y | Outcome |
|---------|--------------------------|---------------------------------------|-------------------------------|--------------------------------------|----------------|---------------------------------------------------|-------------------------------|----------------------------------------------------------------------------------------|
| 1 | 16/M | ALL | 1800 WB | Seizures | 11 | Frontal and temporal | 1 | No recurrent seizures |
| 2 | 12/F | ALL | 2400 WB | Seizures | 8 | Temporal | 6 | Seizures controlled |
| 3 | 8/M | ALL | 2400 WB | Sensorineural hearing loss; L facial | 6 | Internal auditory canal; cerebellopontine angle | 6 | Resolution of facial palsy (1 mo); later recovery of sensorineural hearing loss (6 mo) |
| 4 | 15/F | ALL | Unknown WB | Headache | 9 | Thalamus | Unavailable | Resolution of symptoms |
| 5 | 15/F | ALL | 1800 WB | Dysesthesia L face, arm, leg | 10 | Thalamus | 1.5 | Resolution of symptoms |
| 6 | 4/F | Medulloblastoma | 3600 WB/CSI | Seizures | 1 | Frontal | 5 | Seizures controlled |
| 7 | 16/F | 3rd ventricle mass | 5350 LF | Gait ataxia | 13 | Vermis | 2.5 | Resolution of ataxia |
| 8 | 22/M | ALL | 2800 WB | R hemiparesis | 8 | Pons | 2 | Mild R hemiparesis |
| 9 | 17/F | Neurofibromatosis; optic nerve glioma | 5400 LF | Asymptomatic | 10 | Temporal | 1 | Asymptomatic from hemorrhage |
| 10 | 13/M | Medulloblastoma | 5520 CSI/CD PF | Asymptomatic | 5 | Parietal | 1 | Asymptomatic |
| 11 | 17/F | Tectal glioma | 5400 LF | L hemiparesis | 9 | Pons | 1 | Major deficit, L hemiparesis |
| 12 | 8/F | Medulloblastoma | 5390 3000 WB 2390 PF | Coma | 7 | Pons | Death | Death secondary to hemorrhage |
| 13 | 16/M | Pineal germinoma | 5400 LF | Asymptomatic | 2 | Cerebellar hemisphere; middle cerebellar peduncle | 2 | Asymptomatic |
| 14 | 22/M | Thalamic astrocytoma | 5400 LF | Asymptomatic | 7 | Parietal | 1 | Asymptomatic |
| 15 | 14/F | Cerebellar astrocytoma | 5400 LF; 1500 stereotactic | Nausea, vomiting, brain stem signs | 5 | Cerebellar hemisphere | 1.9 | No new deficit |
| 16 | 12/F | Malignant acoustic neuroma | 5824 LF | Asymptomatic | 10 | Temporal | .67 | Asymptomatic |
| 17 | 30/F | Thalamic glioma | 5000 LF | Asymptomatic | 19 | Midbrain | 1 | Asymptomatic |
| 18 | 14/F | Hypothalamic oligodendroglioma | 5400 LF | Asymptomatic | 4 | Frontal | .67 | Asymptomatic |
| 19 | 18/M | Frontal tumor | 6000 LF | Asymptomatic | 7 | Frontal | 4 | Asymptomatic |
| 20 | 20/M | Lymphoma of neck | 4750 2350 WB 2400 neck | L 3rd palsy and R hemiparesis | 9 | Midbrain | 4.5 | Resolved R hemiparesis; persistent L 3rd cranial nerve palsy |

Note.—ALL indicates acute lymphoblastic leukemia; WB, whole brain; LF, local field; CSI, craniospinal irradiation; CD, coned down; PF, posterior fossa; and RT, radiation therapy.

and 11 had additional chemotherapy. The age at which treatment (radiation and/or chemotherapy) was administered ranged from 1 to 15 years (mean, 6.9). The 7 children with leukemia/lymphoma were irradiated prophylactically. Nine patients (leukemia/lymphoma, 7; medulloblastoma, 2) had whole-brain radiation doses ranging from 1800 to 3600 centigray (cGy) (median, 2400). Ten patients had local-field radiation doses ranging from 2400 to 6000 cGy (median, 5400), and 1 patient had craniospinal irradiation and coned-down radiation to the posterior fossa at a dosage of 5520 cGy. Six children with leukemia (patients 1 through 5 and patient 8) received some combination of vincristine, prednisone, doxorubicin hydrochloride, methotrexate, asparaginase, cytarabine, and mercaptopurine. Three children with medulloblastoma (patients 6, 10, and 12) and 1 with a pineal germinoma (patient 13) were administered vincristine and cisplatin. One of the patients with medulloblastoma (patient 12) also received the MOPP regimen (mechlorethamine, vincristine [Oncovin], prednisone, and procarbazine). The child with the mixed oligodendroglioma received procarbazine, lomustine, and vincristine.

The onset of hemorrhage occurred along an age range of 8 to 30 years (mean, 15.5). The interval between treatment and hemorrhage was 1 to 19 years (mean, 8.1). The radiation dose to the area in which the hemorrhage occurred ranged from 1800 to 6000 cGy, as established by comparing the radiation planning charts with CT and MR findings. The clinical

presentations for hemorrhage included brain stem signs in 5 patients, seizures in 3 patients, motor or sensory deficits in 2 patients, headache in 1 patient, and ataxia in 1 patient. Hemorrhage was demonstrated on routine surveillance or follow-up imaging in 8 patients. The clinical follow-up was 0 to 6 years (mean, 2.25; median, 1.5). Hemorrhages of varying ages were identified in all 20 patients (Table; Figs 1–4). Twenty-two lesions were seen, including a single lesion in 18 patients and multiple lesions in two. Lesion sites included the cerebral hemisphere (10), brain stem (5), thalamus (2), cerebellar hemisphere (2), cerebellar peduncle (1), cerebellar vermis (1), and cerebellopontine angle (1). In the patients with primary brain tumors, the majority of hemispheric lesions arose remote from the original tumor location (Figs 1–3), and not at a site of previous surgery. The lesion diameters ranged from 0.3 to 3.2 cm, with a mean diameter of 1.59 cm. In 10 of the patients undergoing CT, high attenuation was present in all lesions (Figs 2–4). On T1-weighted MR, 7 lesions were of mixed signal intensity, 7 were isointense to white matter, 6 were hyperintense to white matter, and 1 was hypointense to white matter (Figs 1, 3, 4). On proton density- and T2-weighted MR, 13 lesions had mixed signal intensities, 5 were hypointense, and 3 were hyperintense relative to white matter (Figs 1, 3, 4). Of the 2 patients who received intravenous contrast for CT, only slight enhancement was seen in both. Of the 10 patients who received intravenous contrast for MR, there was slight enhancement in 4. In 7 patients,

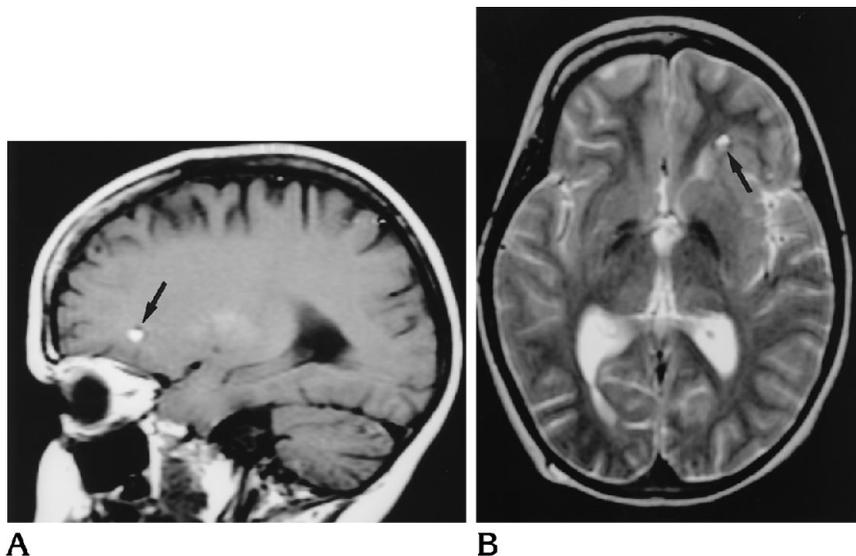


Fig 1. Fourteen-year-old girl (patient 18) with a history of hypothalamic mixed oligodendroglioma and seeding diagnosed at age 10 years, now stable 4 years after radiation therapy.

A, Sagittal T1-weighted MR shows a hyperintense focus in the left frontal lobe (arrow).

B, Axial T2-weighted MR shows a hyperintense focus in left frontal lobe consistent with a small subacute hemorrhage (arrow).



Fig 2. Eight-year-old girl (patient 12) with history of medulloblastoma diagnosed at age 17 months. After resection and radiation therapy, the patient was stable until 7 years later, when she presented with a seizure and obtundation. CT shows hemorrhage within the pons (asterisk) and extension into the third and fourth ventricles.

the lesions evolved to a chronic, stable stage. In 2 patients, hemorrhage recurred as recognized on follow-up imaging exams. One of these patients subsequently died and the other had surgical resection of the lesion. In 11 patients, no follow-up imaging was conducted because they had small subclinical lesions and have remained asymptomatic, or their minor symptoms quickly resolved and have not recurred. With the exception of the 3 patients who received surgery, in no instance did the occurrence of hemorrhage alter the treatment program for any patient.

Histopathologic analysis was available in four patients and showed no evidence of recurrent nor second tumor. In one patient, there was subacute hemorrhage with hemosiderin in the adjacent tissues and radiation-induced vascular change including large-vessel subintimal proliferation, vessel wall sclerosis, small-vessel proliferation, intramural fibrin, and mural necrosis. In two patients, there was microvascular proliferation and intramural fibrin. A fourth patient had acute hemorrhage and findings of gliosis, hemosiderin-laden macrophages, fibrin, and large dilated arborizing thin-walled endothelial-lined channels (Fig 5).

We divided patients into groups according to several variables to assess predictors of out-

come. Neither the original diagnosis, radiation dosage, chemotherapy, nor presence or absence of symptoms at the time of hemorrhage correlate significantly with outcome. When compared with patients with either cerebellar or cerebral hemorrhage, those with brain stem hemorrhage had a significantly worse prognosis, with new neurologic deficits in two and coma evolving to death in the third (Fisher's Exact Test; $P = .01$).

Discussion

The injurious effects of irradiation and chemotoxicity on the central nervous system are well documented (6–10). Radiation effects are classified as acute injury (1 to 6 weeks after irradiation), early delayed injury (3 weeks to several months after irradiation), and late delayed injury (months to years after irradiation). In acute injury, there is increased capillary permeability and vasodilation leading to vasogenic edema. Early delayed injury includes vasogenic edema and demyelination. The common late delayed effects of irradiation include white matter necrosis, focal or diffuse demyelination, reactive astrocytosis, dystrophic mineralization, gross atrophy, and radiation-induced vasculopathy. Vascular endothelial injury leads to disruption of the blood-brain barrier. Of these, focal or diffuse demyelination is most common in children. The well-known ischemic vascular sequelae include proliferation of small blood vessels, hyalinization and fibrinoid necrosis of blood vessel walls, and proliferation of the endothelial lining. As a result, there is narrowing of the vascular lumen with ischemia and infarction. Other uncommon sequelae of central nervous system irradiation include radiation-induced second tumors such as gliomas, meningiomas, or sarcomas.

Hemorrhage is a rare, late delayed focal radiation effect that does not have an established incidence. Of 11 cases reported in the literature (1–4), 6 included clinical and imaging data. In our series, the majority (65%) of hemorrhages occurred in the 13 patients who had received radiation (8), or radiation with chemotherapy (5), for primary brain tumors. Of the 6 patients in the literature, 5 had primary brain tumors and 1 had a nasopharyngeal carcinoma. These were reported in 4 children and 2 adults. In our series, the onset of hemorrhage after treatment occurred with a mean of 8.1 years, which com-

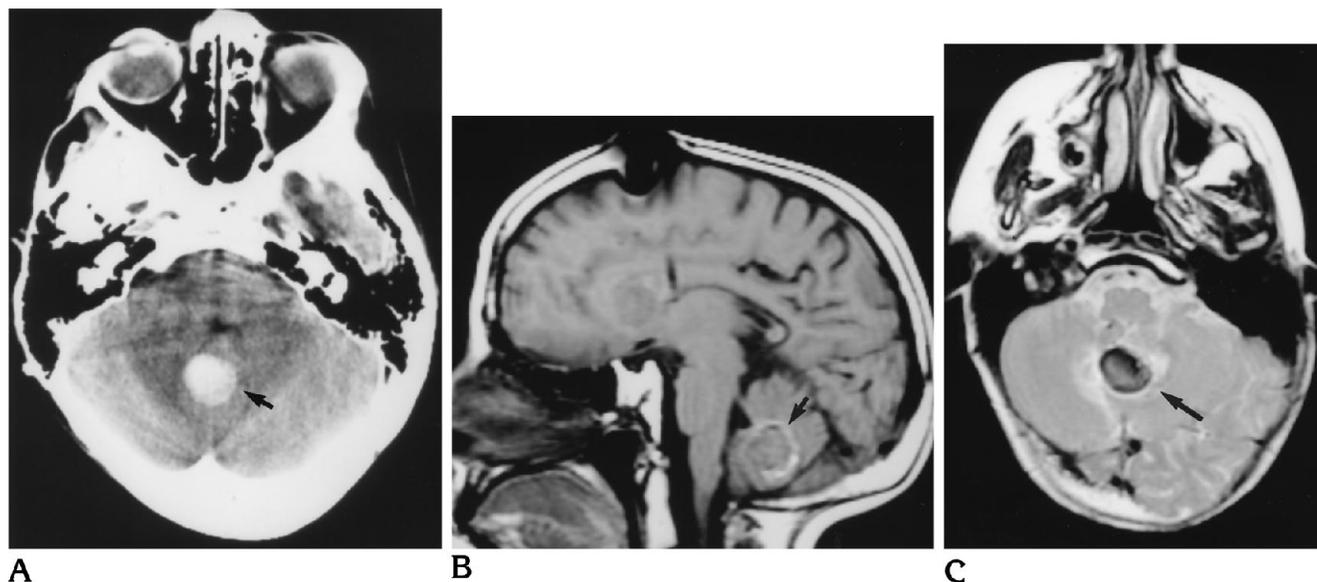


Fig 3. Sixteen-year-old girl (patient 7) with a history of an anterior third ventricular mass diagnosed at age 3 years without biopsy. The patient was stable until 13 years after radiation therapy, when she presented with gait ataxia.

A, Axial CT shows an acute hemorrhage in the inferior vermis (*arrow*).

B, Sagittal T1-weighted MR shows an isointense lesion with peripheral T1 hyperintensity (*arrow*).

C, Axial T2-weighted MR shows the lesion (*arrow*) with a hypointense rim and surrounding high-intensity edema.

compares with a mean of 7 years in the cases reported in the literature. Radiation dosage for cases in the literature for whole-brain or craniospinal irradiation ranged from 3600 to 5500 cGy, with local boost doses ranging from 600 to 1800 cGy. Only 1 patient of the 6 in the literature received chemotherapy, and was a patient with a germinoma who received cyclophosphamide. No significant relationship was found between intermediate outcome and radiation dose, chemotherapeutic agent or dosage, age at treatment, or interval between treatment and hemorrhage in our series or in the literature, although the numbers are small for the latter. Of the 6 patients in the literature, only 1 was asymptomatic, compared with eight in our series. The remaining 5 patients presented with neurologic symptoms including dysphagia, paraparesis, headache, and coma.

In our series, the majority of the hemorrhages occurred in a supratentorial location. Of the six patients previously reported, the majority of lesions occurred in the cerebral hemispheres (4), one occurred in the spinal cord, and one occurred in the medulla. As in our series, these lesions were hemorrhages of varying ages (ie, acute, subacute, chronic), as diagnosed by MR, and in no case was there associated tumor recurrence or second tumor. In this study, patho-

logic analysis in four patients concurred with the findings in previous studies. Abnormal blood vessels, vascular proliferation, and a telangiectatic histologic pattern were identified in five of the six patients previously reported. In our series, as well as in the other reported cases, the imaging appearances and pathologic findings are often remarkably similar to those observed with cavernous angiomas.

The pathogenesis of these hemorrhages as related to radiation or chemotherapy is unclear. Ball et al recently summarized three theories to explain the pathophysiology of radiation injury (8). One theory suggests that ionizing radiation has an injurious effect on the endothelial cells, resulting in injury to the endothelial lining, with focal alterations in the fibrinolytic enzyme system leading to occlusion, thrombosis, and ischemia with infarction. A second theory hypothesizes direct injury to the parenchyma, and the third theory postulates an immunologic mechanism with an allergic hypersensitivity response. The development of hemorrhages is probably linked to disruption and alteration of capillary vascular integrity by irradiation. Microscopically, large irregular capillary telangiectasias with proliferation of small blood vessels have been described as a component of radia-

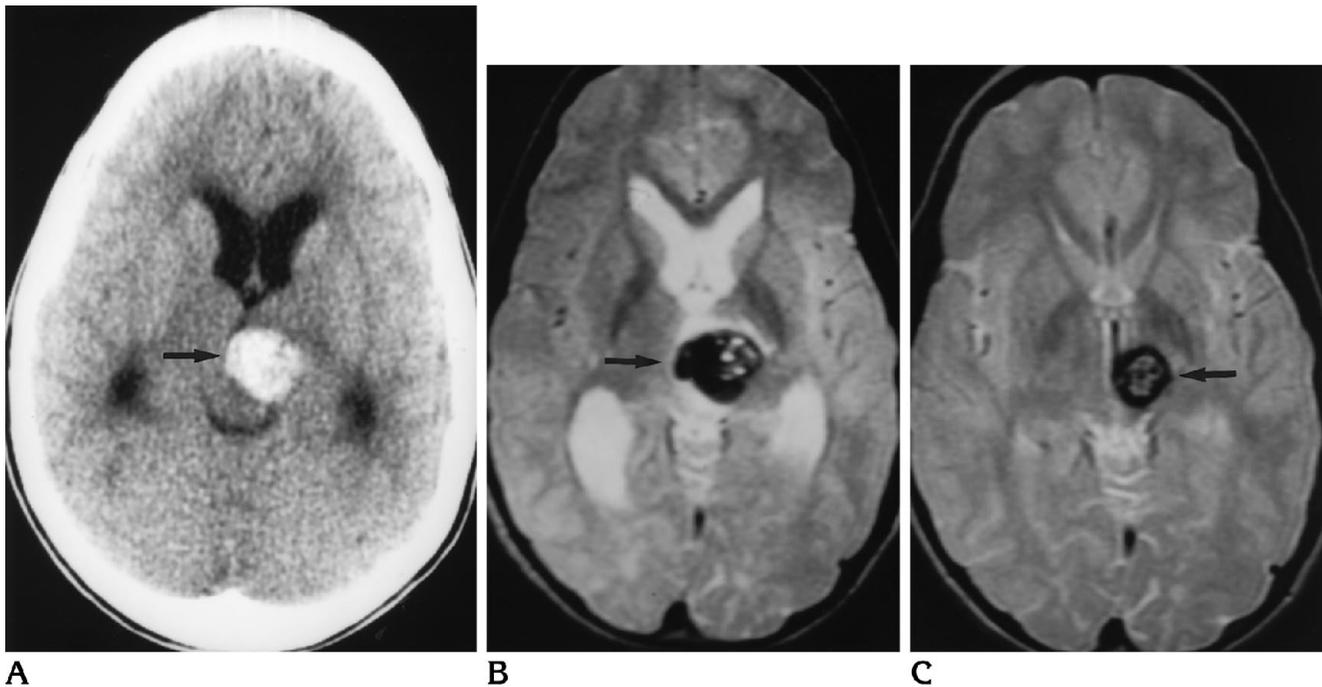


Fig 4. Fifteen-year-old girl (patient 4) diagnosed with acute lymphoblastic leukemia at age 6 years and treated with radiation therapy and chemotherapy. Nine years later she presented with headaches.

A, Axial CT shows an acute hemorrhage (*arrow*) in the left thalamus, and hydrocephalus.

B, Axial T2-weighted MR shows a hypointense lesion (*arrows*) with eccentric internal hyperintense foci and surrounding hyperintense edema.

C, T2-weighted axial MR shows resolution of hydrocephalus and further evolution of hemorrhage, with a decrease in size of the lesion (*arrow*), peripheral T2-weighted hypointensities, and areas of central hyperintensity.

tion injury (9). The latter may also provide the source for hemorrhage.

The influence or contribution of chemotoxicity is uncertain in the 11 patients undergoing additional chemotherapy in this series. Children with intracranial hemorrhage related to chemotoxicity, including thrombocytopenia from myelosuppression, and cerebral or dural venous thrombosis with hemorrhagic infarction from asparaginase, were excluded. Otherwise, intracranial hemorrhage as a late or delayed event

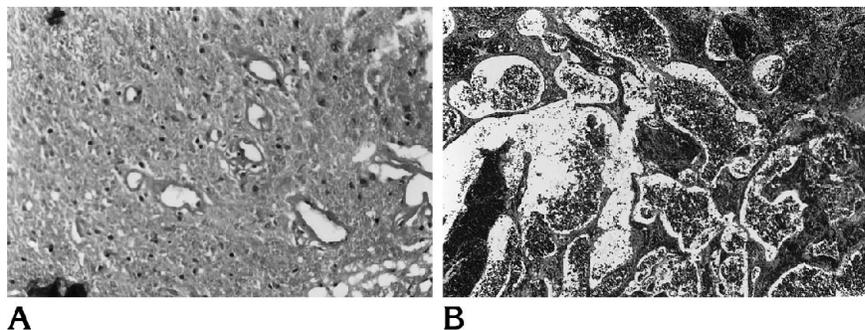
has not been linked specifically to chemotherapy toxicity nor to the effects of combined radiation and chemotherapy (10, 11).

In our series, brain stem hemorrhages were associated with persistent neurologic sequelae and death in one patient, whereas patients with cerebral and cerebellar hemorrhages had better outcomes. In the six patients reported in the literature in whom the majority of the lesions were cerebral, two deaths occurred in adults. Three of the remaining four patients were chil-

Fig 5. Histologic findings in patients with intracerebellar hemorrhage after radiation therapy.

A, Patient 7 (see also Figure 3). This biopsy shows an increased number of vascular channels in the white matter. The blood vessel walls are thickened and contain smooth eosinophilic material concentrically around the lumen (hematoxylin-eosin, 145 \times).

B, Patient 15. The resection shows dilated vascular channels, separated by thin walls without intervening neuropil. The channels are separated by red cells and collagenous stroma (hematoxylin-eosin, 36 \times).



dren who were stable after surgery, and one returned to prehemorrhage status (range, 5 months to 8 years).

In conclusion, delayed hemorrhage after radiation, or radiation combined with chemotherapy, is likely to be increasingly recognized as more patients survive for longer periods. These lesions should not be assumed to represent recurrent or second tumors. Even though a relatively benign outcome has been observed, except for brain stem hemorrhage, these patients should be followed closely over longer periods to establish a better understanding of the natural history and significance of this entity.

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