Multiple fusiform intracranial aneurysms following curative radiation therapy for suprasellar germinoma

Case report

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A 17-year-old girl died from the rupture of a large fusiform aneurysm of the terminal internal carotid artery. Autopsy revealed three other fusiform aneurysms originating from major cerebral arteries clearly within the ports of previously administered telecobalt radiation therapy. Five years prior to her death, a suprasellar germinoma was partially removed and the area was treated by radiation therapy via three ports. The original arteriograms showed a normal vascular tree. Repeat arteriograms, 3 years and 8 months before her death, demonstrated the aneurysms. The development of aneurysms following radiation damage of the arteries has been reported previously, but not in intracranial vessels.

KEY WORDS □ radiation damage □ vasculopathy □ fusiform aneurysm □ post-irradiation aneurysm □ germinoma

EVER since Thomas and Forbus' reported a case of arteriosclerosis after radiation therapy in 1959, numerous reports have appeared in the literature demonstrating that irradiation can indeed cause severe damage in all segments of the arterial tree, including the carotid arteries and the intracranial arteries. We report the case of a 17-year-old girl who developed four fusiform arteriosclerotic intracranial aneurysms following curative irradiation for a suprasellar germinoma.

Case Report

This 12-year-old girl first presented to this institution with panhypopituitarism and hydrocephalus on February 14, 1979.

First Admission. A skull x-ray film showed slight enlargement of the sella turcica. Coronal and axial computerized tomography (CT) scans revealed a large densely enhancing homogeneous mass within the suprasellar cistern extending into the third ventricle, with obstruction of the foramina of Monro. Arteriography of both the anterior and posterior cranial circulation demonstrated an extrinsic brain mass within the suprasellar cistern. All major cerebral arteries were well visualized and no aneurysm was identified (Fig. 1).

The patient underwent a right frontal craniotomy with subtotal removal of a suprasellar germinoma. Bilateral frontal ventriculoperitoneal shunts were placed. Postoperatively she developed diabetes insipidus which was controlled with Atromid-S (clofibrate) and Diuril (chlorothiazide).

Eight days following surgery, radiation therapy was started which lasted 6 weeks. She received a total of 4000 rads tumor dose to the whole brain in 22 fractions through right and left lateral parallel opposed ports, after which a cone-down further increment of 1220 rads in seven additional fractions was administered to the primary tumor. She also received a total of 3500 rads tumor dose to the entire spine through a single posterior port in 19 fractions. All treatments were delivered via cobalt-60 teletherapy. The only complication of irradiation was a transient pancytopenia which was resolved by withholding radiation therapy for a week. A CT scan repeated at the midpoint of the radiation therapy showed no evidence of tumor. Two days before discharge, the patient developed a urinary tract infection which was treated with Bactrim (trimethoprim and
FIG. 1. Angiograms obtained on February 16, 1979. Left: Right internal carotid arteriogram. The supraclinoid portion of the internal carotid artery is normal. Right: Left vertebral arteriogram. The vertebrobasilar system is well opacified with reflux into the right vertebral artery. No aneurysmal dilatation is identified.

sulfamethoxazole) for 2 weeks. Discharge medication included phenobarbital, Diuril, Atromid-S, Synthroid (levothyroxine), and cortisone acetate.

Second Admission. In June, 1980, 14 months after the operation, the patient was admitted for the second time. A CT scan revealed no evidence of tumor recurrence and resolution of the hydrocephalus. In retrospect, the CT scan did show some punctate contrast enhancement at the level of the suprasellar cistern in proximity to the right supraclinoid internal carotid artery (ICA) and the basilar artery. At this time, her medication for diabetes insipidus was switched to desmopressin acetate (DDAVP, 2.5 µg every 2 hours). It also was determined by insulin and arginine challenge tests that she had a growth hormone deficiency. She was placed on growth hormone, 0.67 IU intramuscularly three times a week.

Third Admission. On November 5, 1982, the patient was admitted for the third time to the hospital because of periodic vomiting. Shunt function was normal, and cerebrospinal fluid analysis was negative for tumor cells. The CT scan (taken on November 8, 1982) now clearly identified aneurysm formation on the right supraclinoid ICA and the basilar artery. Cerebral arteriography (Fig. 2) showed fusiform aneurysms of the basilar artery, the right ICA, and the right anterior cerebral artery. It was thought that surgical treatment was not indicated. The patient ceased vomiting, and she was discharged with her regular hormone replacement therapy.

Fourth Admission. In February, 1984, 14 months after her previous admission, 5 years after the first admission, she was readmitted in coma to the neurosurgical service. She had been in her usual state of health until the previous evening, when she felt dizzy, said she could not see, and moments later collapsed. She was taken to the local emergency room and, after intubation, was transferred to the Indiana University Medical Center. A CT scan revealed rupture of a right ICA aneurysm, with massive intraventricular and subarachnoid hemorrhage. A chest x-ray film showed aspiration pneumonia. Just a few hours later the patient suffered a cardiac arrest and died.

Postmortem Examination. The general autopsy findings showed atrophy of the adrenal cortex, the thyroid gland, a small uterus, and poorly developed secondary sexual characteristics. There had been an arrest of growth; the body was only 138 cm in length. There were no changes in the blood vessels, either grossly or microscopically, in any organ or tissue, except the brain.

After fixation the brain weighed 1180 gm. There was massive subarachnoid and intraventricular hemorrhage. There was no evidence of transtentorial or transforaminal herniation. The frontal shunt catheters were in place within the lateral ventricles; they were patent and drained into the peritoneal cavity.

The circle of Willis was symmetrical with well developed anterior and posterior communicating arteries. Four aneurysms were found (Fig. 3). One was in the supraclinoid portion of the right ICA, measuring 15 mm in length and 15 mm in maximum diameter. A 4 x 4-mm rupture was present in the dome of this aneurysm, the only rupture found. The second, 13 mm in length and 10 mm in maximum diameter, was found in the upper third of the basilar artery. The third aneurysm was located in the right vertebral artery at its junction with the basilar artery; this measured 6 mm in length and 3 mm in maximum diameter. The fourth arose from the right anterior cerebral artery, at the level of the rostrum of the corpus callosum; it measured 5 mm in length by 3 mm in maximum diameter. All the aneurysms were basically slowly developing and subsiding widenings of the parent vessel, spindle-
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shaped, of the type usually referred to as fusiform. It is significant that two aneurysms were in or close to the suprasellar area and two were in the midline (those arising from the anterior cerebral and the vertebral arteries), and lay either at the point of intersection of the three radiation tracks, or along the track of the third beam. There were two lateral ports and one midline port. The rest of the larger arteries of the brain were thin and transparent. There was no evidence anywhere of atheromatous deposits or other intimal lesions.

Upon coronal sectioning there was slight enlargement of the lateral ventricles. No residual tumor was found. The pineal gland was in its normal position and showed no changes. The intracranial portion of both optic nerves and the chiasm were compressed by the aneurysm of the right ICA and were grossly softened. The pituitary stalk was not found. The superior aspect of the sella was covered by fibrous tissue. The sella turcica was removed en bloc and was coronally sectioned after fixation. After decalcification the slices were submitted for histological examination. The pituitary was quite atrophic, and was flattened against the floor of the sella.

Light and Electron Microscopic Observations. At the time of the autopsy, small segments of the ruptured aneurysm and segments from the left vertebral artery were immersed in 2.5% glutaraldehyde and processed in routine fashion for electron microscopic studies. The brain was then fixed in formalin for 10 days before it was cut. Histological examination was performed in 10-μ sections of paraffin-embedded material. The sections were stained with hematoxylin and eosin, Masson's trichrome, phosphotungstic acid hematoxylin, reticulum stain (Wilder), and elastic stain (Verhoeff).

No changes in the cerebral parenchyma were observed, and no residual tumor was found. The pineal gland was normal. The longitudinal sections of the involved arteries revealed that both the internal elastic and the muscularis laminae in the media ended abruptly. The wall of the aneurysmal dilatation appeared essentially to be formed by fibrous tissue. Ultrastructural observations of the ruptured aneurysm showed an incomplete and fragmented endothelial lining, resulting from focal losses of endothelial cells. Beneath the endothelium there was a poorly defined and fragmented basal lamina. There was no evidence of the elastic lamina. The entire thickness of the aneurysm wall was composed of bundles of collagen fibers oriented parallel to the main axis of the vessel. Between these bundles there were isolated spindle-shaped smooth-muscle cells containing numerous cytoplasmic lipid inclusions. Those cells were surrounded by a thick amorphous electron-dense coat. Fibroblasts were scant.

Discussion

In this girl, the aneurysms developed within 3 years and 8 months following cranial irradiation. Arteriograms at first revealed a normal vascular tree and then strikingly illustrated the formation of aneurysms (compare Fig. 1 to Fig. 2). A retrospective study of a CT scan performed 16 months following irradiation showed that two of the aneurysms (of the ICA and basilar artery) were already present as well.

The morphology of these aneurysms, with lesions of the intima, elastica, and muscularis, corresponds with the classic pathology of fusiform arteriosclerotic aneurysms. There was no evidence of an active inflammatory process in the arterial walls. Only in the right vertebral artery aneurysm close to the point of transition between the aneurysm and the normal artery was there a focal mononuclear inflammatory cell infiltrate around the elastic lamina. This modest inflammatory...
type of change has been observed before in radiation-induced arteriosclerosis. Radiation injury of small blood vessels was recognized as early as 1899 by Gassmann, who saw it in radiodermatitis. In 1937, Windholz showed the intimal thickening of irradiated arteries accompanied by narrowing of their lumina. Experimentally induced arteriosclerosis has been reported by several investigators. Microscopically, the lesions are similar to those seen in human non-irradiated arteriosclerotic arteries.

McCreary, et al., studied a group of 20 patients with vascular lesions attributable to irradiation, and found two distinct patterns of vascular injury: 1) Arterial disruption: these lesions develop during the early post-irradiation period (1 to 20 weeks) and the patients usually die from massive hemorrhage. 2) Arterial stenosis or occlusion occurring 7 to 24 years after radiation therapy. Actual aneurysm formation has only rarely been associated with ionizing radiation therapy. Only one out of the 20 patients reported by McCreary, et al., developed an aneurysm, which arose from the right carotid artery approximately 3 months following irradiation of the neck region. Benson reported a 62-year-old woman who had received radiation therapy for carcinoma of the uterine cervix; 28 years later she developed bilateral fusiform iliac artery aneurysms.

The pathogenesis of radiation-induced arteriosclerosis is poorly understood. Fonksrud, et al., studied the effects of radiation in the femoral arteries of dogs. In the early stage (within 48 hours of the completion of irradiation), only endothelial changes developed. Only after a few weeks did the media show focal necrosis and loss of muscle cells. They postulated that these delayed changes may have been the result of damage to the vasa vasorum. As the intracranial arteries are mostly devoid of vasa vasorum, this mechanism cannot explain the lesions we have demonstrated. Further experimental data suggest that the radiation-induced damage involves several loci in the vessel wall, including endothelial cells, the ground substance, the elastic lamina, and the smooth muscle. These multiple injuries appear to alter the vessel wall permeability to circulating lipids, resulting in damage to the intima and fatty infiltration.

A well documented factor in the pathogenesis of radiation-induced arteriosclerosis is hyperlipidemia. In several animal models, doses of radiation insufficient in themselves to cause demonstrable vascular injury do produce significant atheromatous vascular lesions when combined with diet-induced hyperlipidemia. In 1978, Silverberg, et al., suggested a relationship between elevated cholesterol values and the occurrence of radiation-induced carotid disease. In our patient, we have no documented serum lipid values. She did suffer from hypopituitarism and was treated with Synthroid, but hypothyroidism was not specifically documented. Of four patients with radiation-related carotid arteriopathy, two had a history of therapeutic thyroid extract use for symptoms of hypothyroidism, and one patient had reduction in size of the thyroid gland, suggesting that hypothyroidism was possibly present. Another factor which perhaps contributed to the vascular lesions was the youthfulness of this patient. Experimentally it has been shown that radiation-induced arteriosclerosis readily develops in young animals, while older animals seem to be refractory.

Risk factors, such as hypothyroidism, hyperlipidemia, and early age, must be evaluated in patients receiving radiation therapy. It is possible that correction of some of these risk factors may minimize radiation-induced vascular damage.

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References

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