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replacement by a responsive tumor, rather than depression of marrow function by previous chemotherapy. This concept of therapy is commonplace in the treatment of hematologic malignancies and may also become commonplace for carcinoma as response rate and therapeutic indices for these tumors improve.^{15,16}

Summary

A 50-year-old man with oat cell carcinoma developed pancytopenia with severe thrombocytopenia while receiving localized radiation therapy. Smears of a bone marrow aspirate revealed complete replacement by "blast-like" cells resembling acute lymphoblastic leukemia. Bone marrow biopsy specimens resolved the diagnostic confusion, showing invasion of normal marrow by carcinoma. Prompt treatment with combination chemotherapy resulted in a complete bone marrow remission, documented with repeat biopsy and subsequently at postmortem examination. This case illustrates how metastatic carcinoma may occasionally mimic acute leukemia causing pancytopenia and replacement of marrow smears with abnormal cells. Pancytopenia in this instance should not be considered a contraindication to chemotherapy.

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Radiation-Induced Disease of the Carotid Artery

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A RARE BUT SERIOUS complication of radiation therapy to the neck is the development of radiation-induced disease of the carotid artery. We wish to (1) present an additional case of radiation-induced carotid artery disease and (2) review the clinical and angiographic findings of this unusual entity.

Report of a Case

A 72-year-old man had a three-year history of dizzy spells, occasionally accompanied by blurred or double vision and lasting two to three minutes. These were brought on by rising suddenly or turning his head rapidly. Nine years previously he had undergone excision of a moderately well differentiated squamous cell carcinoma of the left pyriform fossa together with a left radical neck resection. Postoperatively he received irradiation therapy utilizing a cobalt 60 apparatus to a single left neck portal (14 × 8 cm). The maximum left neck skin dose was 7,154 R with a calculated tumor dose at 4 cm of 6,045 R given in 42 fractions over 60 elapsed days. At completion of irradiation the residual tumor had disappeared, and the patient has been free of recurrent disease for the past nine years.

On admission the left carotid pulse was absent. A left subclavian bruit was present, and a blood pressure difference was noted between the two arms (right 130/70 mm of mercury; left 108 by palpation). Findings on physical examination were otherwise within normal limits. Angiographic studies showed that a 7-cm, smooth, 95

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percent stenosis involved the left common carotid artery from 5 cm above its origin from the aortic arch to 2 cm below the carotid bifurcation (Figure 1). The bifurcation showed no evidence of atherosclerotic disease. There was a 1-cm segment of severe narrowing of the left subclavian artery, 5 cm distal to the origin of this vessel from the aortic arch (Figure 2). There was a short, severely narrowed segment of the right internal carotid artery 2 cm above the bifurcation and a relatively long area of moderate narrowing in the common carotid artery (Figure 3). Minimal irregularity of the proximal portion of the right subclavian artery (Figure 3) was also noted.

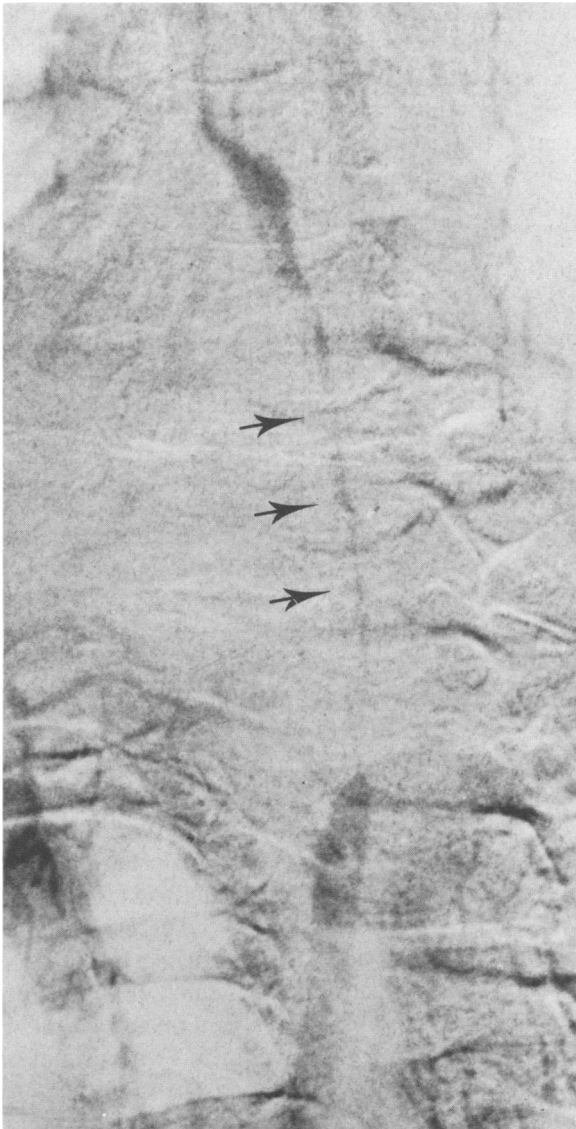


Figure 1.—Radiograph showing a long smooth stenosis (arrow) of the left common carotid artery.

At surgical operation, findings consistent with atherosclerotic disease were seen involving both the right common carotid and internal carotid arteries; transarterectomies were done in these areas. Since the patient's symptoms had decreased, and in view of the difficulty of operating on previously irradiated tissue,¹ decision was made not to operate on the left carotid artery.

Discussion

Ours is the sixth reported case of a patient with angiographic demonstration of radiation-induced disease of the extracranial carotid artery. Two general patterns of involvement have emerged. One is severe smooth narrowing of the carotid artery over a long segment that spares the carotid bifurcation (where atherosclerotic disease generally occurs) while involving areas not usually affected by atherosclerotic disease. In our patient, a 7-cm segment of the common carotid artery was severely narrowed; in the case reported by Levin-



Figure 2.—Radiograph showing short, severely narrowed segment of the left subclavian artery (white arrow). The severe stenosis of the proximal left common carotid artery is also shown (black arrow).

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son and co-workers,² a long segment of the internal carotid artery was similarly affected. In neither instance did the carotid bifurcation show atherosclerotic change. In Conomy and Keller-meyer's patient,³ thrombotic occlusion of the internal carotid was seen; in addition, a serpentine intraluminal defect was seen at the carotid bifurcation. The other manifestation of radiation-induced disease of the carotid artery is diffuse, irregular ulcerative lesions. The lesions may be associated with short stenoses² or with moderate dilatation⁴ of the carotid artery. As with the long smooth stenoses, the ulcerative lesions tend to occur at sites usually unaffected by atherosclerotic disease.

The changes in the right carotid artery seen at surgical operation in our patient were thought not to be directly attributable to irradiation disease. However, since these areas were in the region of the radiation port (though well removed from the level of maximum dosage) the possibility that irradiation accelerated atherosclerotic change must be considered.²⁻¹⁹

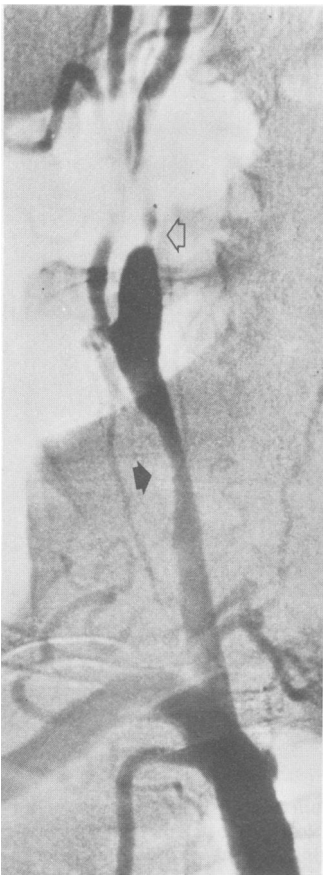


Figure 3.—Radiograph showing short, severely narrowed segment of the right internal carotid artery 2 cm above bifurcation (**white arrow**) and a large area of moderate narrowing of the right common carotid artery (**black arrow**). Minimal irregularity of the proximal portion of the right subclavian artery is also seen.

Radiation-induced disease has also been described in the subclavian artery after radiation therapy for carcinoma of the breast.^{5,6,15} Angiography in these cases revealed short segmental stenoses, similar to the appearance in our case. Radiation-induced disease involving aorta,^{14,20} iliac arteries,^{5,11} femoral arteries^{5,9,16,17} and coronary arteries,²¹ has also been described.

Radiation-induced damage to the carotid artery secondary to radiation therapy to the neck can cause the clinical manifestations of cerebrovascular insufficiency. Of the six cases with adequate clinical data previously reported, three had sudden hemiparesis.^{2,5,7} In one of these,⁷ there had been a single previous episode of hemispheric ischemia which cleared in three days; in the other patients,^{2,3} no history of previous transient ischemic attack could be elicited. Two patients^{2,4} had transient ischemic attacks only. In one patient,⁴ the ischemic attacks were hemispheric, consisting of unilateral hand and leg weakness but no visual symptoms. In the other,² there were daily attacks of blindness for six months with no motor symptoms. One patient had a single sudden "drop attack" attributed to generalized cerebrovascular insufficiency due to combined carotid and vertebral lesions.² In our patient, the overriding symptom was generalized cerebral insufficiency with decreased perfusion due to stenoses of both common carotid arteries, the right internal carotid artery and the left subclavian artery proximal to the origin of the left vertebral artery. The visual symptoms were attributable to the carotid lesions alone.

Several mechanisms account for the variable symptomatology in patients with radiation-induced disease of the carotid arteries.² Reduced retinal perfusion produces transient visual disturbances; reduced cortical perfusion produces transient hemispheric ischemic attacks. Emboli from ulcerated lesions in the carotid artery can evoke sudden hemiparesis as well as hemispheric ischemic attacks and transient visual disturbances. When decreased blood flow in the carotid system is combined with decreased perfusion in the vertebrobasilar system (for example, vertebral or subclavian artery stenoses), generalized cerebral ischemia leading to "drop attacks" and dizziness can occur.

Pathological examination of specimens from patients with radiation-induced disease of large elastic arteries has shown findings consistent with

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premature atherosclerosis and perivascular fibrosis.* There is marked thickening of the arterial wall which may lead to partial or total obstruction of arterial blood flow. This thickening involves all portions of the arterial wall, but primarily the adventitia. A narrow band of fibrin covering the intima has been described, and necrosis of the intima with intense subintimal edema has been noted. Thinning and fragmentation of elastic fibers is common. Polymorphonuclear neutrophilic infiltration is widespread in areas of intimal and subintimal necrosis. Fat-laden macrophages and radiation fibroblasts are often seen.

Similar pathologic findings of accelerated atherosclerosis have been experimentally demonstrated to occur following irradiation of large elastic arteries in animals. Smith and Lowenthal²² showed that irradiation in mice produced an increase of ground substance and fraying of the elastic membrane comparable with physiological aging. Gold⁸ produced intimal proliferation with medial degeneration and fibrosis by radiating hypercholesterolemic rats; Lamberts and DeBoer¹² produced similar effects in hypercholesterolemic rabbits. Sams¹⁹ described similar changes in the vessel walls in irradiated mice and stressed the severe degree of periarterial fibrosis, which he believed constricted the artery. Lindsay and associates¹³ created similar atherosclerotic changes by irradiating segments of the aorta in normal dogs. Marcial-Rojas and Castro¹⁴ studied radiation injury to elastic arteries in patients treated for neoplastic disease and described rupture of major blood vessels with fatal hemorrhage.

The exact pathogenesis of radiation-induced disease is unclear. Rubin and Casarett¹⁸ described occlusive changes in the vasa vasorum of large arteries after irradiation. These occlusive changes could lead to ischemia of the arterial wall with subsequent generalized necrosis. Marcial-Rojas and Castro¹⁴ suggested that the initial damage is caused by a local tissue effect, enhanced by the subsequent obliterative vascular changes in the nutrient arteries.

In view of the large numbers of patients whose necks are radiated to high levels for upper airway neoplasm and mediastinal adenopathy, the occurrence of radiation-induced disease of the carotid arteries appears to be rare. However, it must be considered in any patient with transient

hemispheric or visual ischemic attacks, sudden hemiparesis, or generalized cerebrovascular insufficiency who has previously undergone radiation therapy to the neck. Angiography may demonstrate the characteristic findings of either a long smooth narrowed segment or a diffuse ulcerated segment, both in areas that usually are not affected by atherosclerotic disease.

Summary

Radiation-induced disease of the carotid artery is a rare but serious complication of radiation therapy to the neck. Clinical manifestations include transient hemispheric and visual ischemia, sudden hemiparesis and generalized cerebrovascular insufficiency. Angiographic studies may show severe smooth narrowing of the carotid artery over a long segment or diffuse irregular ulcerative lesions. These tend to occur at sites usually unaffected by atherosclerotic disease.

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