Fatal Foam Cell Arteritis of the Brain After Irradiation for Hodgkin's Disease: Angiography and Pathology

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Abstract: Fatal Foam Cell Arteritis of the Brain After Irradiation for Hodgkin's Disease: Angiography and Pathology

A case of foam cell arteritis of the brain following irradiation of the neighboring structures for Hodgkin's disease is described. A differential diagnosis of the unique angiographical findings is presented.

The etiology of foam cell arteritis restricted to the brain is considered. It is hoped that the experience of this case encourages a careful neuroradiological and neuropathological examination of the brain in all patients with Hodgkin's disease who present with the stroke syndrome.

ADDITIONAL KEY WORDS pregnancy hemiparesis lymph nodes laminar necrosis parenchymatous degeneration

Introduction

The use of radiation therapy to cure cancer involves irradiation of normal tissues. Often relatively large areas of normal brain tissue may be irradiated when cancer of the sinuses, nasopharynx, parotid, ear, scalp, orbit, and lymph nodes of the cervical region is treated by radiation. Documented cases of postirradiation encephalitis and cerebral necrosis have been reported.1-6

Foam cell arteritis of small arteries and arterioles has been incriminated as a relatively specific histological finding in human normal tissues irradiated with radium.6-7 Vascular lesions other than foam cell arteritis have also been found associated with irradiation.8,9

The following case is of some interest because of the very unusual angiographical findings associated with histopathological vascular changes possibly indicating irradiation injury.

Case Report (06-38-42)

This 20-year-old pregnant Caucasian was first seen by the Radiation Branch of the National Cancer Institute in October 1965, with a previous history of receiving irradiation to the cervical region for Hodgkin's disease in Ireland in 1961. Chest x-ray at that time was reported as normal.

Investigation at the National Cancer Institute showed enlarged lymph nodes in the hilar, paratracheal, and anterior cervical chains bilaterally. Because of pregnancy, retroperitoneal studies were not ordered. No symptoms of fever, sweats, or pruritus were documented. A history of penicillin allergy was recorded. Medication history was negative. Familial or personal history of any neuromuscular or collagen-vascular disease was denied.

The patient's neck, mediastinum, and hilum were irradiated by an anterior field from November 27, 1965, to January 15, 1966, with an excellent response. One month after the end of treatment, symptomatic pneumonitis developed secondary to the irradiation. The patient was placed on Prednisone, 40 mg per day. Seven weeks after irradiation, she had an acute respiratory infection with an exanthem. The clinical impression was a viral infection after cultures of the cutaneous lesions and the throat
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TABLE 1

<table>
<thead>
<tr>
<th>Date</th>
<th>Apparatus</th>
<th>Area</th>
<th>Dose/time</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/61</td>
<td>220 KV*</td>
<td>Bilateral cervical</td>
<td>2400R/3 weeks</td>
</tr>
<tr>
<td>7/61</td>
<td>220 KV</td>
<td>Bilateral supraclavicular</td>
<td>2000R/3 weeks</td>
</tr>
<tr>
<td>2/62</td>
<td>220 KV</td>
<td>Right supraclavicular</td>
<td>&quot;Limited amount of x-ray&quot;</td>
</tr>
<tr>
<td>11/65</td>
<td>Co60</td>
<td>Mediastinum and hilum</td>
<td>6100R/3 weeks</td>
</tr>
<tr>
<td>1/66</td>
<td>Co60</td>
<td>Bilateral cervical and axillary region</td>
<td>3900R/4 weeks</td>
</tr>
</tbody>
</table>

*220 IV, TSD 30, 0.5 mmCu filter. This information was obtained from Dr. M. J. Brady, FFR, City of Dublin Skin and Cancer Hospital, Hume Street, Dublin, Ireland.
†R means roentgens in air.

were negative. Electron microscopy of the cutaneous lesions was compatible with herpes zoster.

In May 1966, delivery of a healthy child occurred without incident. Prior to her final admission to the Medicine Branch of the National Cancer Institute in June 1966, the patient gave a history of several weeks of intermittent nonlocalized headaches and numbness in the right upper limb. One week before admission, right hemiparesis and aphasia were noted.

Physical examination on admission revealed aphasia, right hemiparesis, and poor ocular tracking. EEG showed diffuse irregular slow delta waves of high voltage over most of the left hemisphere. Multiple lumbar punctures, including viral and fungal cultures, were not diagnostic. A left carotid angiogram was distinctly abnormal and will be discussed under angiographical findings. Despite anticoagulation with heparin and large doses of steroids, left-sided pyramidal tract signs and decrease in the patient's state of consciousness developed, and she expired five weeks after admission, six months after Co60 teletherapy, and five years after her first course of orthovoltage irradiation. Table 1 lists all the irradiation data available.

Lithium fluoride dosimetric studies on the Rando phantom by Mr. Dwight Glenn, M.S., Physicist, Radiation Branch, National Cancer Institute, have indicated the following doses to structures within the brain which resulted from the Co60 teletherapy irradiation to the neck and mediastinum. This single anterior portal was treated with the patient supine and the neck hyperextended (table 2).

The doses listed in table 2 were given in four weeks. Unfortunately, we do not have available the exact portal arrangements for the orthovoltage irradiation, and thus do not know the definitive dose given to the base of the brain by the three courses of orthovoltage irradiation.

Assuming that the 1961 treatments were employed with lateral fields which were high enough to irradiate the posterior fossa, then 2100R (allowance for reduction of dose due to 3 cm of bone) in three weeks would have been the maximum contribution from orthovoltage. Although there should be no denial, the previous orthovoltage may have contributed some accumulated dose to the brain. The presence of mild telangiectasia before Co60 teletherapy, only in the lower half of the neck, and the absence of any skin changes in the upper half of the neck would favor our assumption that the major irradiation delivered to the brain was received during the course of Co60 teletherapy.

Angiographical Findings

Left common carotid arteriography was carried out. The visualized vessels in the neck were unremarkable. The endocranial internal carotid artery and its branches, on the other hand, showed significant changes. Specifically, there

TABLE 2

<table>
<thead>
<tr>
<th>Area</th>
<th>Dose in roentgens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td></td>
</tr>
<tr>
<td>At ear lobe</td>
<td>3,200</td>
</tr>
<tr>
<td>Submental</td>
<td>3,800</td>
</tr>
<tr>
<td>Midcervical</td>
<td>3,535</td>
</tr>
<tr>
<td>Cerebellum</td>
<td></td>
</tr>
<tr>
<td>Posterior cerebral artery region</td>
<td>1,435-1,625</td>
</tr>
<tr>
<td>Cortex-lateral occipital</td>
<td>360</td>
</tr>
<tr>
<td>Circle of Willis</td>
<td>340-440</td>
</tr>
<tr>
<td>1 cm above circle of Willis</td>
<td>285</td>
</tr>
<tr>
<td>Pericallosal artery at genu</td>
<td>210</td>
</tr>
<tr>
<td>Cortex</td>
<td></td>
</tr>
<tr>
<td>Lateral frontal</td>
<td>140</td>
</tr>
</tbody>
</table>
Narrowing and luminal irregularity of the supraclinoid portion of internal carotid artery. Beadlike appearance of pericallosal artery.

Angiographical narrowing and occlusion of the endocranial arteries are encountered in a wide variety of pathological conditions. These include subarachnoid bleedings, trauma, cerebral atherosclerosis, luetic arteritis, tuberculosis, and purulent meningitis, endangitis obliterans and periarteritis nodosa, fibromuscular hyperplasia, emboli, and thrombosis occurring after the use of oral contraceptives.

The bizarre arteriographical findings of our case do not, however, quite match the angiographical changes reported in the abovementioned conditions. Although narrowing and irregularities of the arterial lumina of the large intracranial vessels—internal carotid, anterior, middle, and posterior cerebral arteries—are frequent findings, the extensive involvement of both the large and the smaller (pericallosal and other branches) vessels plus the lack of actual occlusion is much rarer. In other words, obstructive vascular disease is generally more segmental than in this case where widespread vascular involvement was present without...
Angiographically demonstrable complete "block of the flow." Although the radiographical changes observed in our patient are probably not unique or "specific," we lean toward the possibility that these changes are related to radiation arteritis of the brain.

**Autopsy Findings**

Sections of cervical lymph nodes taken just prior to the second course of irradiation showed complete effacement of the normal lymph node architecture. There were no discernible follicles and the sinusoids were obliterated. The cells were predominantly lymphocytes with large numbers of plasma cells and bizarre reticulum cells. A few eosinophils were present. The reticulum cells had large, vesicular nuclei with prominent nucleoli and Reed-Sternberg cells were seen. These lymph nodes were diagnosed as showing Hodgkin's disease.

The lymph nodes examined at autopsy were sclerotic and showed changes compatible with radiation effect.

The cervical and mediastinal lymph nodes were greatly enlarged, and the nodes of the pulmonary hila were bound together forming large masses which bound and compressed the adjacent pulmonary parenchyma. Upon microscopic examination, these nodes showed almost complete replacement by dense, fibrous connective tissue. No malignant cells were seen. There were fibrous pleural adhesions bilaterally. Multifocal lesions were seen microscopically in both lungs, compatible with radiation pneumonitis. The skin and subcutaneous tissue of the anterior neck were thickened and indurated. The small blood vessels in the neck...
FIGURE 3
Cerebellar artery—vessels showing obstructive changes. The internal and medial coats are relatively unchanged, whereas the tunica externa is quite thick. Note the absence of inflammatory infiltrate. 50x.

and mediastinal region showed changes compatible with late radiation injury. There was fibrosis of adventitia and media with hypertrophy of the endothelial lining. These changes were so marked that the vascular lumina were severely reduced. The internal elastic lamellae could be delineated and, indeed, the three histological layers of the blood vessels were fused.

The lesions of primary interest were in the brain and intracranial arteries (figs. 3 and 4).

Gross examination of the extracranial portion of the carotid vessels showed them to be patent. The parasellar portions of the carotid arteries were explored by removal of the petrous pyramids. Water injected into the cervical portion of the carotid vessels flowed freely out of the intracranial branches. The external appearance of the circle of Willis was normal. The cerebral vessels were stripped from the base of the brain out to the ends of the principal branches. Numerous nodular enlargements were seen in all the vessels and were most prominent in the middle cerebral branches. The lesions were firm, averaging 0.3 cm in diameter, and occurred at intervals of 1.0 to 1.5 cm. The larger vessels were lost before sectioning and consequently were not examined microscopically, but smaller branches containing similar lesions were available. These showed occlusion of the vascular lumen with partial recanalization.

The greater mass of the occluding material consisted of large cells with a small, dark nucleus, and abundant granular or "foamy" cytoplasm. The cytoplasm was well outlined and the cells resembled histiocytes. The internal elastic lamella and the tunica media were not involved. The tunica externa, however, was thickened and fibrotic. There was no significant inflammatory response associated with these lesions nor any degenerative changes in the tunica media. No hemosiderin granules were present in these lesions. A frozen section of a small vessel which showed a plaque or "foam cell arteritis" was prepared. The foam cells contained a lipid which stained positively with oil-red-O.

The brain weighed 1,500 grams. The cerebral hemispheres were grossly symmetrical. Examination after formalin fixation revealed that the major portions of the frontal, parietal, and occipital areas were spongy to palpation. The temporal lobes were not affected. Coronal sectioning demonstrated that the left motor area was markedly softened and discolored.

Microscopic examination of sections from frontal, parietal, temporal, occipital cortex, hippocampus, basal ganglia, thalamus, hypothalamus, mammillary bodies, midbrain, pons, medulla, cerebellum, and spinal cord were examined. The leptomeninges showed scattered reactive meningitis in the form of sparse

FIGURE 4
Cerebellar artery (higher magnification of fig. 3). The lumen shows recent obstruction with recanalization. The major portion of the obstructing mass consists of histiocytes with abundant, pink cytoplasm. 140x.
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collections of lymphocytes, increased amounts of connective tissue, and occasional reactive macrophages scattered throughout the subarachnoid space. These changes showed a predilection for perivascular locations. Occasional blood vessels showed adventitial thickening with lymphocytic infiltration.

Scattered throughout the cortex with a predominant localization at the depths of the sulci were areas of laminar necrosis and occasional areas of encephalomalacia involving all levels of the cortex. These were of varying age, some being characterized by acute coagulative necrosis with congestion and early capillary proliferation. Other older lesions showed absence of neurons and gliosis. These lesions showed no particular preponderance for any lobe and were distributed irregularly in the gray matter at the depth of adjacent sulci. In other areas the gray matter was unaffected.

There were sharply demarcated secondary lesions in the white matter characterized by demyelination, loss of axons, and an increase of reactive glial cells. Occasional lymphocytes were present in these lesions. There were no atypical astrocytes or any inclusion bodies. Lesions themselves were well demarcated and showed no reactive inflammatory changes with the exception of the lymphocytes mentioned previously. These lesions were scattered in the subcortical white matter, occasionally extending deep into the centrum semiovale. They were frequently linear and occasionally round with irregularly but sharply demarcated borders.

The interpretation of these lesions is as follows: There is laminar necrosis secondary to a decrease in perfusion pressure in an area of marginal circulation. The areas of demyelination in the white matter are interpreted as being secondary to neuronal loss in the cortex. They show none of the stigmata of progressive multifocal leukoencephalopathy which is a consideration in this case. The areas of secondary demyelination extend throughout all levels of the subcortical white matter into the centrum semiovale and have the same indiscriminate distribution as the areas of laminar necrosis. The areas of laminar necrosis are due to a drop in blood pressure and the severe stenosis of vessels is certainly a major predisposing factor to the appearance of such lesions. No fungal or inflammatory agents could be identified in the lesions and the absence of any acute or major chronic inflammatory response precludes the existence of an infectious etiology for these lesions.

Discussion

The cerebral postmortem findings are of three types: changes of the walls of arteries and arterioles, intraluminal thrombi, and parenchymatous degeneration.

The common thrombotic lesions are not generally associated with the degree of arterial wall changes found in this case. For this reason, we consider the intimal changes as primary. The parenchymatous cerebral findings, on the other hand, were not of the type encountered in direct irradiation injury to the brain but rather were consistent with injury secondary to occlusive arterial disease. The presence of foam cells occluding the arteries limits the number of conditions which might have been responsible. The thesis for the specificity of foam cell arteritis indicating irradiation injury has been discussed in relationship to the histological changes found in total hysterectomy specimens obtained six weeks to five months after radium therapy for squamous cell carcinoma of the cervix.4,8 Kirkpatrick27 has produced similar lesions by irradiating the ears of hyperlipemic rabbits. However, these lesions also occurred in hyperlipemic rabbits without irradiation.

In addition to the uniqueness of the pathological findings which hardly fit the common occlusive vascular conditions, the angiographical findings in vita were also most unusual. As stated above, these angiographical findings do not quite match the innumerable radiographical observations which have been made in the various arterial obstruction syndromes. The facts, however, point to a rather probable conclusion that the radiotherapy in this patient played an important role in the arterial wall changes which resulted in the unique morphological and angiographical findings.

Summary

A case of fatal foam cell arteritis of the brain following irradiation of the neighboring structures for Hodgkin's disease has been described. Angiographical and pathological details which followed have been presented. The etiological
influence of radiations is considered and discussed.

Acknowledgment
We wish to thank Drs. Louis B. Thomas and Marius P. Valsamis for their advice and encouragement.

References
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Stroke. 1971;2:232-238
doi: 10.1161/01.STR.2.3.232
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1971 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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