Radiation Necrosis of the Brain in Acromegaly*

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Radiation necrosis of the brain is a rare but serious complication of the treatment of acromegaly. This report describes 3 cases, each from a different institution, in which large doses of external irradiation produced significant delayed destructive lesions of cerebral tissue. In each case, craniotomy was necessary, in one bilaterally, for the removal of necrotic gliomatous masses. To our knowledge, no similar cases have been published, although reports of radiation damage and malignant changes in brain and spinal cord in other conditions5,9,11,17,18,21 have occasionally been recorded.

The large amounts of irradiation used probably do not reflect upon the institutions involved, but attest to the difficulty of control of acromegaly by non-surgical means in certain instances10,14,17,20,24,26 Until recently, 2 factors have prejudiced such control. 1. Satisfactory measurement of human growth hormone activity has been unavailable, and except for the serum phosphorus level, other laboratory data are unreliable. Furthermore, clinical evaluation of the patient, or estimation of acral volume, are inexact criteria of activity. 2. Beneficial effects of irradiation are difficult to assess since they are gradual, often transitory and incomplete, sometimes leading to repeated courses of treatment. At the present time, with modern radio-immuno-assay measurements of human growth hormone,3,6,8,11,16,25 and the remarkable safety and rapid effectiveness of total surgical hypophysectomy,22,23 the control of acromegaly can be more accurate. The serious complications of radiation therapy described in these 3 cases can be avoided.

Case Report

Case 1. A.B. A 58-year-old Italian-American man was admitted to the Long Island College Hospital in June, 1953, in a drowsy, non-cooperative state. In the previous 10 years he had shown an insidious change in behavior from a hard-driv-

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ing, dynamic personality, to a coarse-featured, gruff-voiced, indolent individual with increasing asthenia, excessive fluid intake, urinary frequency and drowsiness. In 1949, an active eosinophilic adenoma of the pituitary was diagnosed, and in June, 1950, a calculated dose of 3400 r was administered to the region of the sella using 4 portals (bitemporal, frontal and midline vertex) with a dose of 2000 r in air through each portal (250 KV with a 1 mm. copper filter).

For 5 months marked improvement, especially in the lethargy, was evident. Because of recurrent drowsiness, a 2nd dose calculated at 3350 r to the sella was administered in November, 1950, using a technique similar to the first. Moderate improvement of the acromegalic symptoms ensued and he was able to return to his work as a building contractor until June, 1952. At this point his former symptoms returned. A 3rd course of therapy was given (3025 r through 4 portals); this made a total dose of 9775 r.

Early in 1953 his lethargy became pronounced. In May he developed right-sided convulsions, progressive aphasia and a right-sided paresis. On admission to the hospital he was semi-stuporous, incontinent and markedly aphasic. He showed the typical features of advanced acromegaly. The blood pressure was normal. There was moderate right hemiparesis and hemianesthesia, papilledema on the right and evidence of glaucoma on the left. There was no field defect on confrontation. Skull films showed a mildly enlarged sella and a prognathic mandible.

Operation. On June 26, 1953, a left frontal craniotomy was performed by Dr. Jefferson Browder. The dura was not tense. There was a yellowish 2 cm. mass observed in the left superior mid-frontal cortex having the appearance of glioblastoma. A partial left frontal lobectomy, including the tumor, was performed. The pituitary region was inspected and slight prominence of the tuberculum sella noted but no suprasellar extension of the neoplasm was seen. There was some fibrosis of the leptomeninges about the infundibular region.

Postoperatively, the patient had a total right hemiplegia which partially cleared over a 3-week period. Two months later a mild adrenal crisis responded to cortisone. At discharge in November, he was able to walk with help and to carry on a simple conversation but showed marked blunting of intellect.
Pathological Findings. The specimen showed edematous gyri with a 2×5×4 cm. congested yellowish-brown area which on microscopic examination revealed large areas of necrosis and hemorrhage alternating with other areas where extensive neutrophilic infiltration intermingled with lymphocytes, macrophages and gitter cells. The small blood vessels were congested, their walls hyalinized and the site of fibrinoid degeneration. The Virchow-Robin spaces were filled with lymphocytes and neutrophiles. The pathological diagnosis was “localized necrosis of the cerebrum, cause undetermined.”

Case 2. E.Z. This man developed symptoms of acromegaly in 1948 at the age of 32 and the diagnosis was reliably established on clinical grounds in late 1950. The sella turcica was not enlarged and the visual fields were normal. In December, 1950, he received 2000 r low voltage therapy to the pituitary from 3 ports, right and left temporal and vertex. There was little symptomatic response and a 2nd course of 2100 r was administered through similar ports in March and April, 1952. There was some improvement in headache and acral enlargement following this treatment but the polyphagia, polydipsia and profuse malodorous perspiration and paresthesia continued.

The patient was first seen at the Memorial Hospital in New York in February, 1954. The active nature of the acromegalic process was indicated by the finding of a serum phosphorus of 5.0 mg.%. There was slight enlargement of the sella turcica by x-ray. Visual fields were normal and there was a normal glucose tolerance test. In March, 1954, a 3rd course of radiation was given over a period of 2 weeks through two 5 cm. temporal ports for a total of 3000 r. The x-ray beam of the 22.5 million electron volt betatron was used which gives a calculated dose to the brain, in line with the beam, approximately the same as delivered to the hypophysis. There was measurable clinical improvement but the headaches were worse and it was decided to give further therapy to tolerance. Accordingly the 4th course of pituitary irradiation was given in May, 1954, consisting of 3026 r with the betatron. After several months, jaw pain and headaches diminished considerably and the serum phosphorus fell to 3.4. There was measurable decrease in the size of his hands and feet.

The patient had now received a total of 10,126 r to the pituitary and was delighted with his good clinical response. However, in November, 1954, his headache recurred along with a measurable increase in the size of his hands and feet, loss of libido, increased weakness and a rise in serum phosphorus to 4.5 mg.%. Surgical hypophysectomy was advised and refused. In January, 1955, 8 months after the last course of x-ray, his headache greatly increased and papilledema was discovered. Several seizures occurred.

In May, 1955, he was re-admitted to the Memorial Hospital with marked impairment of recent memory, deterioration of abstract thinking, emotional lability and depression. There was a striking loss of ability to use his most recently learned language, English, although facility with Italian, German, Yugoslavian, and Jewish was preserved. Visual fields were normal. Papilledema was present. Radiation necrosis of the brain was suspected and the patient was transferred to the New York Hospital under the care of Dr. Bronson Ray.

Operation. A ventriculogram showed inadequate filling of the right frontal horn with a moderate shift to the left. A right frontotemporal craniotomy was carried out. The brain was found to be tense and the arachnoid gray and thickened. The temporal lobe convolutions were flattened and there was a yellowish-brown discoloration of the lobe. There was a general vascular suffusion over the brain and the small vessels were more prominent than usual. The middle and frontal portion of the temporal lobe was soft to palpation. The temporal lobe was resected from the middle cerebral artery to behind the vein of Labbé. The brain had a soft necrotic appearance and, in the sub-cortical area, could easily have passed for infiltrating glioma. The optic nerves were normal but the arachnoid about the chiasm was unusually thick. There was no evidence of a bulging of the diaphragma sellae.

Pathological Findings. The external surface of the temporal lobe appeared smooth and brown tinged. The internal surface was soft and spongy, and firm, apparently fibrotic nodules, were present. Microscopically, these nodules showed marked gliosis with small areas of necrosis and deposits of calcium. In other regions there were many diffusely scattered polymorphonuclear leukocytes and a marked increase in microglia. There was considerable thickening of the walls of the smaller blood vessels and a collection of lymphocytes surrounded them. The capillaries were so numerous that a few areas resembled granulation tissue. In these regions there were many macrophages filled with hemosiderin and numerous lymphocytes.

The postoperative course was satisfactory. There was an incomplete left upper homonymous quadrantic defect in the visual field. The patient was rather placid and childlike and showed a marked defect in memory. The papilledema disappeared in 4 months and about this same time a considerable improvement in mentality occurred. He became moderately well-oriented and was able to obey simple commands, and go about New York City alone. He was last heard from in 1964 when he sought help from the Welfare Department.
Case 3. B.M. In 1957, a 17-year-old girl developed bilateral frontal headaches. Three years later she noted that her hands and feet had increased in size. She developed amenorrhea, puffy lips, increased heat intolerance. She perspired heavily, her skin became oily and she gained 15 pounds in weight.

Examination. On admission to the Albany Medical Center Hospital in January, 1961, she was obviously acromegalic, with a prominent nose, jaw and tongue. She perspired heavily and had very oily skin. There was no organomegaly. The sella turcica measured 16×10 mm. Visual fields and neurological examination were intact. Multiple laboratory data, including serum phosphorus, were normal. She was treated with cobalt 60 teletherapy with a source surface distance of 60 cm. Within 3 days, the region of the sella turcica was treated through right and left lateral opposing 4×4 cm. fields, delivering a maximum dose of 3400 r at 0.5 cm. beneath the scalp, and achieving a dose within the neoplasm of 4150 r.

The patient’s headaches subsided and the acromegalic features diminished. Scanty menstruation occurred for several months. However, because of increasing headache, perspiration and soft-tissue puffiness, a 2nd course of cobalt teletherapy was given for a 28-day period in October, 1961. We used 3×3 cm. opposing ports to administer a calculated dose of 4000 r within the sella turcica making a combined total of 8150 r. Transitory diminution of symptoms followed, but by early March, 1962, the headaches were again significant and the soft tissue changes were progressing. Because of the relatively mild symptoms at this time, her age, and a great desire to bear children, hypophysectomy was deferred. Less than a year after the last course of radiation therapy, the headaches recurred and she began having sensations of numbness and tingling of the right side with progressive impairment of memory for both recent and distant events. The left optic disc became blurred and an electroencephalogram showed bitemporal slowing, mostly on the left.

Operation. A left carotid angiogram in October, 1962, outlined a temporal mass. The right side was normal. A left frontotemporal craniotomy in October, 1962, outlined a temporal mass. The right side was normal. A left frontotemporal craniotomy was performed. The left temporal lobe was replaced by what appeared to be a rather avascular glioma involving all 3 gyri and extending deeply into the uncal region and posteriorly to the vein of Labbé. All visible abnormal tissue was removed. The pituitary was inspected; the sella was large but its contents were not distending the diaphragm.

Pathological Findings. Microscopic examination

![Fig. 1. Case 3. Appearance of right temporal lobe at surgery showing widening of gyri, discoloration and hemorrhage.](image-url)
revealed extensive vascular changes with marked endothelial proliferation, reduplication, hyalinization of basement membranes, thrombosis, both recent and remote. In some foci there was a peculiar lymphocytic perivascular infiltrate, not unlike that seen in syphilis. There was atypical glial proliferation, thought to be non-neoplastic, but a response to cerebral necrosis of undetermined etiology, perhaps vascular in nature. The leptomeninges were moderately thickened.

Postoperative Course. For about 6 weeks the patient was free of symptoms but the sensory seizures recurred and further memory deficit was obvious. Despite anticonvulsants, the seizures became worse. In February, 1964, the patient's memory was so defective that she was unable to assume normal household responsibilities and was re-hospitalized. Angiograms revealed bilateral mass lesions, a left frontotemporal mass with depression of the left middle cerebral, shift of the anterior cerebral to the right and a right temporal mass. Spinal fluid pressure was 150. The protein was 116 mg.%. Her deterioration continued. She lost vision on the left to 10/50 and papilledema developed on the right. In July, 1964, the angiograms were repeated and revealed further evidence of an increasingly large right temporal lobe mass.

Operation. Because it was apparent that her life was now in jeopardy from increasing intracranial pressure, it was deemed necessary to remove the right temporal lobe, undoubtedly the site of additional gliosis. This was done on July 17, 1964. At the same time a total hypophysectomy was performed since there was clinical evidence of progressive acromegaly. At surgery, the right temporal lobe was yellowish-brown, and in places hemorrhagic (Fig. 1). Microscopic sections (Fig. 2) were similar to those of the left although somewhat more advanced. Following surgery, a significant loss of vision took place in both eyes. Although she became more alert for several months, her memory, intellectual ability and vision continued to fail and in early 1966, having been bedridden for many months, she died.

Comment. The composite picture of these 3 cases consists of resistant acromegaly, treated...
with multiple courses of ionizing radiation, totaling from 8000 to 10,000 r. Characteristic destructive lesions of the cerebrum subsequently developed after latent periods of from 7 to 12 months beyond the last exposure. Surgical resection of the necrotic gliomatous brain was only palliative, as the pathologic process was too extensive and progressive, but necessary because of the expanding nature of the lesion.

A 4th case, that of a chromophobe adenoma, treated by a single, rather rapid course of conventional rotational therapy provides another example of radiation necrosis.

Case 4. E.B. A 59-year-old woman was admitted to the Geisinger Medical Center in November, 1962, with marked loss of vision on the right and a right temporal hemianopsia. An intracapsular removal of a chromophobe adenoma was performed by Dr. Henry Hood with subsequent good recovery of vision. Postoperatively, the patient received 3650 r (280 KV, 3.5 mm, Cu) in 13 treatments over a period of 17 days using rotational therapy with a 4 cm. field size at the sella. One year later she became listless, confused and incontinent. A brain scan showed a large area of increased uptake in the right frontal lobe near the midline. At craniotomy, what appeared to be an infiltrative necrotic glioma was resected. This involved the posterior half of the inferior and media aspects of the right frontal lobe. The mass was yellowish, gritty, grey in color and relatively avascular. Microscopic studies showed a process characterized by vascular destruction and endothelial hyperplasia with vascular necrosis. In numerous areas, vessels had disappeared. The background of the nervous tissues showed complete necrosis; elsewhere, reactive astrocytes were increased. There was a proteinaceous exudate in many areas. Neurones were definitely reduced in some areas of the cortex and absent in others. A diagnosis of post-radiation necrosis was made.

At first, the patient improved but gradually deteriorated and died a year later.

Discussion

For many years the central nervous system was considered relatively resistant to radiation, but later clinical and experimental evidence indicated that a basic pattern of degeneration and repair occurs. The initial reaction a few hours or days after radiation is an acute inflammatory vasculitis, meningitis and choroid plexitis, with leucocytic infiltration. There are also characteristic alterations in certain neural tissues. The most notable changes seen by light microscopy are contraction and pyknosis of the nuclei of the granular cells of the cerebellum. Studies with the electron microscope of exposed granule cells, either in the intact animal or in tissue culture, show that rapid volumetric changes in the intracellular compartments take place with shrinkage of the nuclei, clumping of nuclear granules, folding and redundancy of the nuclear membranes and expansion of the cytoplasm.

These observations suggest that a marked hypertonicity of the cytoplasm takes place and that the acute effect of radiation is to interfere with basic cellular mechanisms with increased vascular permeability and development of edema. The changes in the granule cells may simply be a non-specific reaction to the presence of edema.

The cytologic changes are established within 2 hours of irradiation. They increase dramatically over 8 to 24 hours, then regress precipitously to disappear by 96 hours. In animals, an exposure of 2500 r (1000 r/min. Co 60) results in minimal reaction, whereas the use of 5000 to 10,000 r produces profound alterations, particularly in dogs.

As time passes, a progressive, different and more extensive degenerative process becomes evident, as demonstrated in the cases presented. Marked damage to neurones occurs, with degeneration of the glia and a delayed reparative glial response, proliferation of collagenous tissue, late astrocytosis, and vascular changes consisting of endothelial proliferation, hyalinization of basement membranes and thrombosis. It is debatable whether the delayed necrosis is secondary to the vascular damage, or the result of a more direct effect on neural tissue. In tissue cultures, the early nuclear pyknosis and enlargement of the cytoplasm takes place without benefit of circulatory disturbance, whereas a latent period is necessary before vessels undergo morphologic changes in vivo. In the spinal cord, vascular lesions are always seen after a variable latent period before visible abnormalities appear in surrounding cord substance. It would seem reasonable that at least a fair portion of the delayed necrosis is of ischemic origin.

The relative radiosensitivity of the brain varies from one region to another. The cortex and immediate sub-cortical medullary region
are less sensitive than the deep-seated white matter. The sensitivity of the latter also appears to vary from region to region as suggested by the disseminated appearance of the lesions on uniform radiation of the entire brain. It has been calculated by Boden\textsuperscript{1} that the largest dose that the brain stem could tolerate is 4500 r/17 days (250 KV) for small and medium-sized fields, and 3500 r/17 days for large fields over 100 cm.\textsuperscript{2} Arnold et al.\textsuperscript{1} gave the brain stem and hypothalamic tolerance as 3000 r/28 days with 400 KV equipment and suggest a dose of 4500 r/30 days for centrally located tumors.

The degree of radionecrosis is proportional to the total size of the dose and the time factors in its administration. It becomes more pronounced as the time interval from irradiation is lengthened. Lindgren\textsuperscript{1,8} calculated time dose relationship curves for human brains on the basis of 13 cases adequately documented in the literature, plus 4 of his own drawn from previously irradiated autopsied gliomas. He stated that the minimal dose which produced necrosis on delivery of the rays through medium-sized fields was between 4500 and 5000 r in 30 days.

Radiation therapy of pituitary tumors remains an accepted mode of treatment,\textsuperscript{10,14,24,26} but experience suggests the need for careful attention to the subtleties of dosimetry. We propose a mid-plane tissue dose of 4000 r through stationary fields in 28 days, using 4×4 cm. portals at the surface. With Cobalt teletherapy, right and left opposing fields are used; with conventional voltage, right and left, frontal and vertical fields. There is little excuse for repeated courses of therapy.

While external irradiation by conventional methods can reduce tumor size and improve the clinical picture, it does not reduce growth hormone (HGH) levels in acromegaly.\textsuperscript{3,16,17} Implantation of yttrium\textsuperscript{9} or gold\textsuperscript{19} into the pituitary fossa also has failed to consistently reduce HGH levels.\textsuperscript{12,15} However, high energy alpha-particle irradiation produces an 8-fold reduction in plasma HGH,\textsuperscript{19} and similar reductions have been reported in surgically hypophysectomized patients who have acromegaly, diabetic retinopathy, or metastatic breast cancer.\textsuperscript{3,12} Thus, the ability to make accurate growth hormone determinations has shed a new light on the study and treatment of acromegaly, and made surgical hypophysectomy more reasonable. One must remember that if surgical hypophysectomy is employed, by whatever route, total removal of the contents of the sella is necessary for permanent control. Even small fragments of residual tumor, as in 2 of our cases, have led to the need for later treatment.

### Summary

Radiation of pituitary tumors can cause necrosis of the brain, particularly if a carefully considered schedule of dosimetry is exceeded. The error can be one of repeated courses of treatment or that of too rapid administration. The cerebral lesions develop after a latent period of months and are progressive and often fatal. Appropriate pituitary surgery is preferable to multiple treatments with radiation.

### References


