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REVERSIBLE OEDEMA AND NECROSIS AFTER IRRADIATION OF THE BRAIN

Diagnostic procedures and clinical manifestations

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Abstract

One hundred and twelve patients with primary brain tumour were followed every 3 months during and after brain irradiation and chemotherapy with brain scanning, EEG and neurological examination. Early delayed radiation reactions were seen in 6 patients. The symptoms developed 2–8 months after irradiation and lasted for 2–3 months. Two types of reactions were observed. One mild form appeared after 2–3 months and was characterized by low-attenuated expansive areas within the irradiated volume, without contrast enhancement on CT scan. Severe reactions appeared in some patients after 6 months, with exacerbation of earlier clinical signs and contrast enhancing lesions on CT. Regression of the CT finding was seen after 3 months. Recognition of this syndrome is important, as a new neurosurgical procedure might cause lasting neurological sequelae in patients who otherwise would recover without treatment.

Key words: Brain tumours, irradiation, radiation effects.

The treatment regimens for primary brain tumours often include extensive tumour resection with postoperative irradiation (1, 2). However, radiation-induced injury to normal brain tissue limits the dose that can be delivered to a brain tumour during conventional radiation therapy (3, 4).

The adverse radiation effects in the brain have been divided into 1) 'acute reactions', occurring during irradiation, 2) 'early delayed reactions' appearing from a few weeks to a few months after irradiation and 3) 'late delayed reactions', with onset several months to years later (5).

The early delayed reactions are usually transient. Clinically the patients complain of somnolence and lethargy, and frequently there is exacerbation of previous neurological signs and symptoms. CT scan may show changes indistinguishable from recurrent tumour (6, 7).

It is important to recognize the early delayed brain irradiation syndrome since it is generally transient, and further irradiation or chemotherapy may aggravate the symptoms and sometimes cause brain necrosis. Failure to recognize the syndrome may also lead to recraniotomy followed by neurological sequelae.

The present report describes our experiences with CT, EEG and neurological examination in transient adverse radiation reactions occurring 2–8 months after irradiation of the brain.

Material and Methods

One hundred and twelve patients with inoperable brain tumours were treated at the Norwegian Radium Hospital between April 1983 and October 1987. In all but 5 patients a stereotactic biopsy yielded the histologic diagnosis. There were 62 men and 50 women with an average age of 39 years (12–64). Forty-nine patients had malignant gliomas (anaplastic astrocytoma and glioblastoma multiforme) and 63 low-grade gliomas (grade I and grade II).

Treatment schedule. The treatment protocol included 4 cycles of combined intraarterial chemotherapy repeated every 4 weeks followed by irradiation 4 weeks after the last chemotherapeutic cycle. CT, EEG and neurological examination were performed before treatment and every 3 months during and after treatment. CT-examination was performed both with and without intravenous contrast injection. The slices had a thickness of 10 mm and a spacing (no unscanned interval) of 10 mm. The brain was scanned from the base to the top of the skull.

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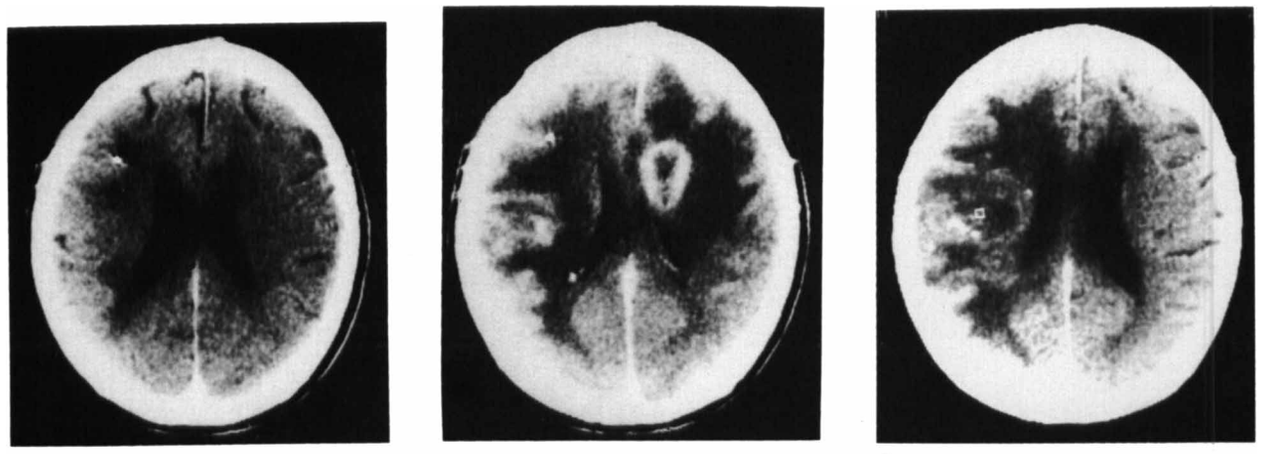

a) b) c)

Fig. 1. Case No. 1. Patient treated with intraarterial carmustine in right internal carotid artery followed by irradiation. a) CT 6 months after irradiation of the right hemisphere and the medial part of left frontal lobe: Postoperative changes after biopsy with clips on the right side. b) CT $8\frac{1}{2}$ months after irradiation. Marked bilateral oedema and ring-shaped enhancement paraventricularly on left side. c) CT 17 months after irradiation. Reduced oedema. The earlier enhancement is not visible. Small calcifications parietally on right side.

Chemotherapy protocol. The chemotherapy consisted of carmustine, (BCNU), vincristine and procarbazine. A preformed catheter was introduced into the femoral artery under local anaesthesia and the tip of the catheter placed in the internal carotid artery under fluoroscopy. Immediately prior to infusion 200 mg carmustine was dissolved in 1 ml 96% ethanol and added to 49 ml normal saline. The solution was then infused with a pressurized injector type Medrad, mark IV. Out of a total volume of 50 ml, 40 ml (= 160 mg carmustine) was given intraarterially at an infusion rate of 2 ml per min. The patient received 0.5 ml Leptanal as premedication. If orbital pain occurred during the infusion, 0.5–1 ml Diazemuls and 0.5 ml Leptanal was given intravenously. Immediately after the infusion, 1 ml Narcantee was given i.v. In patients with centrally located tumours or marked cerebral oedema 1 500 ml mannitol was given i.v. over 12 h. with start immediately after the BCNU infusion. Decadron 4 mg × 4 was given the day before treatment and then scaled down over 10 days. Vincristine 2 mg was infused intravenously the same day. The following day and for one week the patient received procarbazine 50 mg × 3 daily. The patients left the hospital the day after the carmustine infusion. All patients received anticonvulsant medication during the study.

Radiotherapy protocol. Radiation therapy started 4 weeks after chemotherapy. The treatment was given with 8 MV x-rays or cobalt-60. Low-grade astrocytomas were treated with 2 or 3 fields to a total dose of 54 Gy in 6 weeks, with daily fractions of 1.8 Gy and 5 treatments per week. Before treatment the tumour was localized by CT scan. The treatment fields included the tumour with generous margins and the dose was weighted to the side of the lesion. The whole tumour received a total dose of at least 54 Gy. The maximum dose was generally 5% higher in the centre of the tumour region. Patients with high-grade astrocytomas received whole brain irradiation from 2 opposed parallel lateral fields up to a total dose of 54 Gy given as daily fractions of 1.8 Gy and 5 fractions weekly.

Results

Six patients (2 women and 4 men) experienced clinical symptoms of early delayed radiation reactions.

Case 1. A 54-year-old man who finished external irradiation for a biopsy proven astrocytoma in February 1985. The tumour was located in the right frontal lobe. Eight months after irradiation he experienced impaired mentation, drowsiness and a slight left-sided hemiparesis. A CT scan showed large expansions in both cerebral hemispheres with ring shaped enhancement and marked bilateral oedema. Corticosteroid medication was initiated with symptomatic relief. CT scan 12 and 19 months after irradiation showed a gradual normalization of the pathological findings (Fig. 1).

Case 2. A 29-year-old man who finished external irradiation in June 1985 for an astrocytoma in the right temporal lobe. Follow-up CT scan 6 months after irradiation showed a large expansion in the right cerebral hemisphere with oedema and small areas of enhancement. His only subjective complaint was pronounced fatigue, although he was working full time as a school teacher. CT scan 12 months after irradiation showed normalization of the findings. Four months later, he developed a recurrent tumour. A tumour resection was performed and yielded the diagnosis of glioblastoma multiforme. He never recovered after the operation and died after 2 months (Fig. 2).

Case 3. A 54-year-old man who finished external irradiation in December 1984 for an astrocytoma located in the right frontoparietal region. Four months later he complained of impaired memory and fatigue. CT scan showed a large right-sided expansion with compression of the ventricular system without contrast enhancement. CT scan 8 and 10 months after irradiation showed gradual reduction of the expansion with a persisting cystic formation. The CT scan remained unchanged for 2 years. Then his neurological condition deteriorated with progressive left-sided

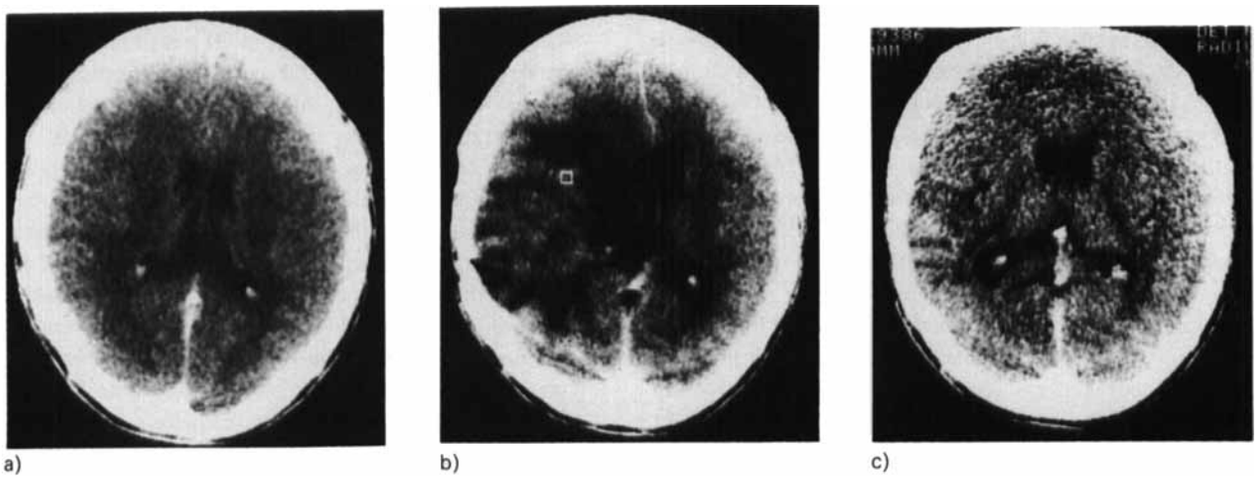

Fig. 2. Case No. 2. a) CT before start of intraarterial carmustine. Postoperative changes after right-sided craniotomy. Slight degree of right sided expansion. b) CT 6 months after radiation treatment. Marked right-sided expansion with oedema and small area of enhancement. c) CT 12 months after irradiation. Normalization of earlier oedema and expansion.

hemiparesis and CT scan showed recurrent local tumour growth with infiltration of the corpus callosum. He received 2 courses of combined systemic chemotherapy (vincristine i.v., lomustine and procarbazine orally) with transient improvement of the clinical condition. At the last observation (May 1988), he still had his paresis.

Case 4. A 41-year-old man who finished external irradiation in June 1984 for an astrocytoma in the right frontal lobe. CT scan 7 months after irradiation revealed a large expansion in the right cerebral hemisphere with contrast enhancement and reactive brain oedema. His only complaint was fatigue and impaired memory. Corticosteroid medication improved the neurological symptoms. Sequential CT scan performed every third month showed regression of the CT findings with only a persistent cyst. Forty-three months after irradiation he got focal epileptic fits and a slight left-sided hemiparesis. CT scan showed an expansion in the right fronto-parietal region. He then received 2 courses of systemic chemotherapy repeated after 6 weeks and is now improving.

Case 5. A 34-year-old woman who finished external irradiation in January 1987 for an astrocytoma located in the right fronto-parietal region. In April 1987 the CT scan was normalized. One month later she experienced increasing fatigue, impaired function of the left arm and a left-sided facial paresis. CT scan showed a large expansion in the right hemisphere with compression of the ventricular system without contrast enhancement. Corticosteroid medication improved the condition. CT scans 10 and 13 months after irradiation showed normalization of the CT findings. She is at time of writing (May 1989) working full time as a nurse without any neurological sequela.

Case 6. A 31-year-old woman who finished external irradiation in December 1984 for an astrocytoma in the right fronto-parietal region. Four months later she developed left-sided hemiparesis, and a marked expansion and ring-shaped contrast enhancement in the tumour region was seen on CT. Craniotomi was performed and yielded a radiation necrosis. After the operation the left-sided hemiparesis persisted. Twenty-five months after irradiation she developed a recurrent tumour interpreted as glioblastoma multiforme, located in the left fronto-parietal region, and died one month later.

EEG-findings. Before treatment all six patients had focal changes on EEG which improved during chemotherapy. EEG after irradiation was recorded in four of the patients (cases 1, 3, 4 and 5), and showed a marked deterioration 4–7 months after cerebral irradiation in all four patients. There was an increase or recurrence of previous focal theta and delta activity in all patients, with focal sharp potentials in patient No. 4. Two of the patients (cases 4 and 5) also had generalized changes, with reduction of the alpha frequency and increased theta activity in the non-irradiated hemisphere. In three of the patients (cases 1, 4 and 5), the deterioration in the EEG appeared 2–3 months before changes were seen on CT, whereas the deterioration was detected simultaneously on EEG and CT in one patient (case 3).

Discussion

It is well known that radiation therapy for intra- or extracranial lesions can lead to brain injury. It may, however, pass undiagnosed since altered or new symptoms following brain irradiation are apt to be dismissed as tumour recurrence.

Neurooncologists are to an increasing extent relying on the CT scan for evaluation of the tumour response to radiotherapy. However, many patients have undergone surgical procedures a few weeks prior to irradiation, which can make it difficult to distinguish between postoperative changes and adverse radiation reactions on the CT scan (8–10). In our patients the diagnosis was obtained by a stereotactic biopsy and the problem with distinguishing between postoperative changes and radiation effects was therefore eliminated.

Since the period between irradiation and clinical onset of symtoms or changes on the CT scan correlates with the turnover of myelin, believed to be 5 weeks to 2 months, it is presumed that the early delayed adverse reaction to

irradiation is a result of demyelinisation secondary to transient depression of enzyme systems essential for the myelin production and maintenance (1, 7, 11–13).

A similar syndrome associated with irradiation is seen in the spinal cord. A few weeks to several months after irradiation of the spinal cord, transient tingling and paresthesias may appear. This has often been referred to as Lhermitte's sign, and the cause is thought to be temporary demyelinisation of sensory neurons (14, 15).

Since 1983 our patients have had routine CT scans, EEG and neurological examinations every third month after brain irradiation. We have thus been able to study changes in CT scans and EEG in patients with only slight neurological symptoms, and which otherwise would not have undergone these examinations. Hoffman et al. (16) in 1979 reported that transient changes in CT scans were seen in 51% of patients treated with chemotherapy in addition to irradiation. However, early delayed radiation reactions were observed in only 5% of our patients, who were irradiated after previous chemotherapy. The reason was probably that the intraarterial chemotherapy used (<200 mg carmustine, 2% ethanol in the solution and an infusion rate of 8 mg carmustine/min), was well tolerated by the normal brain tissue.

Three cases of eye-complications were seen. One patient had a haemorrhagic glaucoma with amaurosis, one had retinal branch artery occlusion with third nerve paresis and another had occulomotor paresis (17).

Our study indicates that early delayed radiation effects may be mild or severe. The mild form consists of pronounced cerebral oedema in the irradiated volume without any contrast enhancement on the CT scan. It appears 2–3 months after irradiation. In contrast to the pronounced alterations on the CT scan, the patient often has only slight clinical signs. The most common complaint is pronounced fatigue or somnolence. A CT scan performed 3 months later usually shows normalization, and the subjective symptoms have regressed.

The severe form appears 3–8 months after irradiation. There may be exacerbation of earlier clinical signs, and CT scan reveals pronounced cerebral oedema with contrast enhancement. In some cases the contrast enhancement can be defined as 'false contrast enhancement': Due to the diffuse oedema in the irradiated region, normal gyri express themselves as enhancement. A normalization follows after 3 months. In some cases a cyst or mineralisation persists within the irradiated area. It is known that a normally functioning blood brain barrier requires participation of the oligodendrocytes. Transitory dysfunction of these cells, caused by irradiation, may account for the contrast enhancement on CT scan seen in the severe form of early delayed reactions. Transient changes in white matter density and in contrast enhancement are often difficult to detect in high-grade gliomas. This may explain why all cases reported here were low-grade gliomas.

Many of the studies from the pre-CT era (2, 15, 17–19), which report pronounced avascular expansions during the first year after radiation, may represent early delayed radiation reactions similar to those seen in this study.

In conclusion, changes on the CT scan following brain irradiation should be viewed with caution if they occur within 2–8 months after irradiation. Rapid clinical deterioration and increasing EEG-pathology, followed by changes in the CT-scan within 2–8 months after irradiation, should not unequivocally be interpreted as tumour progression. This is particularly important in patients with low-grade gliomas and symptoms for more than 5 years. Care must be taken to rule out a transient adverse brain radiation effect, as a new surgical procedure in such cases may cause permanent neurological sequelae in patients who would otherwise recover spontaneously.

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