

CEREBRAL RADIATION NECROSIS — A CASE REPORT

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SYNOPSIS

Cerebral radiation necrosis has been a recognised hazard of high dose irradiation since 1930. It is important to be aware of this condition as it can and has frequently been mistaken for tumour progression or recurrence both radiographically and at operation.

The emphasis this case serves to illustrate is the inability of CT to distinguish between delayed radiation necrosis of the brain and recurrent tumour and that the radiation-induced changes seen are transient.

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CASE REPORT

A 27-year-old Chinese lady first presented to a Medical Unit at the Singapore General Hospital in September 1982 with a history of giddiness and 'unsteadiness' for a duration of 2 years. There was no history of seizure disorder or any other symptoms related to the central nervous system.

Physical examination then demonstrated nystagmus on looking to the extreme right and left. There was no neurological deficit.

A CT scan of the brain was done to investigate the cause of her vague symptoms. This showed an area of mixed increased and low attenuation situated high in the periphery of the left frontal lobe. The lesion showed no enhancement or mass effect (Fig 1). The nature of this abnormality was uncertain and an angiogram was suggested. She was referred to the Neurosurgical Unit of the Tan Tock Seng Hospital.

A left carotid angiogram was performed subsequently. This was interpreted as normal since no abnormal vasculature or displacement of vessels were seen. Following the injection of 10 cc Urografin into the left common carotid artery, the patient threw a right focal fit followed by generalised fit.

At this stage, a diagnosis of a left frontal infarct was made based on both the CT and angiographic findings. However, a tumour such as a glioma could not be excluded and close follow-up was necessary. The patient was put on Dilantin 10 mg tds following the episode of fits.

Two months later she was readmitted after an attack of generalised fits. She was discharged one day later.

In the subsequent 6 weeks, the patient experienced 3 more episodes of generalised fits. Not only did she not take her medication but she also absconded from her CT scan appointment. It was imperative that a cerebral tumour be excluded in view of the late onset of epilepsy.

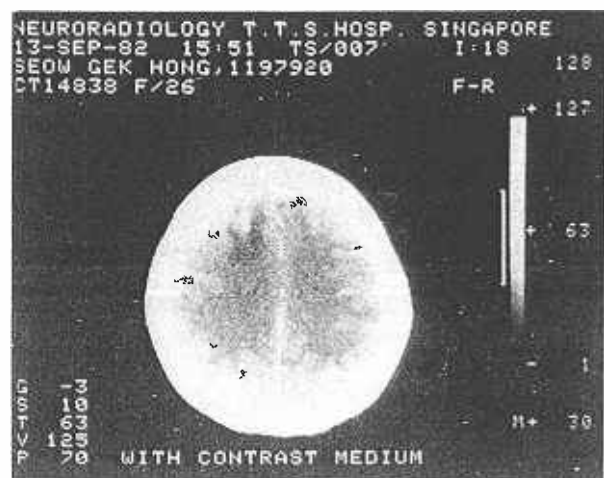


Fig 1: The first CT scan of the brain showed a small area of mixed high and low attenuation in the periphery of the left frontal lobe. No mass effect or enhancement was present.

The second CT scan was done in January 1983. Compared with the first scan, the hypodense lesion in the left frontal region had increased in size. The hypodensity appeared to follow that of the white matter. Some enhancement of the gyri was present. These features were highly suspicious of a neoplastic lesion and a repeat angiogram was suggested.

A third CT scan done 2 months later showed enlargement of the area of cerebral oedema. This time mass effect was present.

Subsequently, the bilateral carotid angiogram demonstrated a space-occupying lesion in the left frontal lobe displacing both the anterior cerebral arteries and the deep internal cerebral veins to the right. No definite evidence of vascularity was noted. This relative avascularity in the affected region was attributed to oedema. Nevertheless, the features suggested an infiltrative tumour.

At operation in March 1983, a firm grey tumour measuring 1.5 cm in diameter was found in the left frontal region. It was surrounded by firm white matter. This tumour was excised and analysed histologically.

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The histology was that of a low-grade astrocytoma. Two out of the six specimens taken from the margins of the excised lesion showed that the limits of the excision were not free of tumour.

In the hope of achieving long term control of the glioma, the next course of management was radiation therapy. Because of the propensity for these lesions to have uncertain margins due to their infiltrative nature, the initial treatment was to the entire cranial contents through opposed right and left lateral fields. A midline dose of 1.8 Gy (180 rads) was delivered daily in 29 treatments over 42 days using Megavoltage radiation. After achieving a dose of 40 Gy (4000 rads), the field size was reduced. The estimated tumour dose at the end of treatment was 52.2 Gy (5220 rads).

For four months after the completion of radiation therapy, the patient was well. She was maintained on Phenobarbitone 300 mg tds. She then complained of headache, giddiness and vomiting for a duration of one week before admission again. On examination, there was no neurological deficit. A CT scan at this time (6 months post-op and 4 months after DXT) showed extensive hypodense area in the left cerebral hemisphere representing oedema. A ring-like enhancement was seen higher up. There was also significant midline shift and mass effect. These features were interpreted as recurrence of the tumour. An area of oedema was also noted in the right frontal lobe ? tumour (Figs 2 and 3).

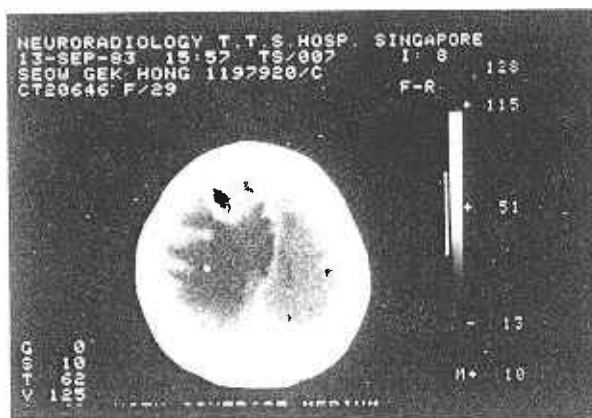
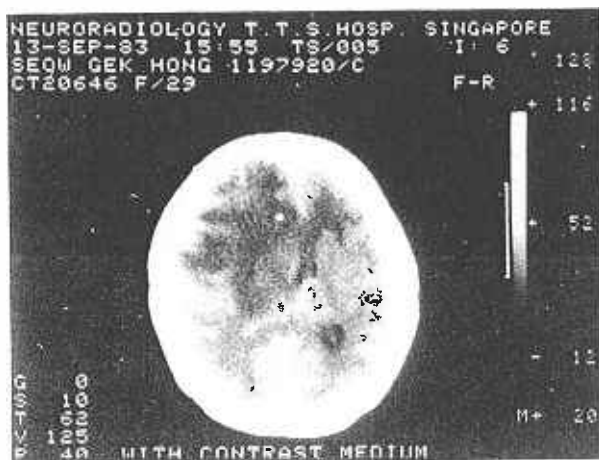


Fig 2 & 3: CT scan done 6 months after surgery and 4 months after completion of radiotherapy showed an extensive hypodense area in the left cerebral hemisphere. Ring-like enhancement was seen higher up. An area of oedema was also present in the right frontal lobe. The features suggested a recurrence of the left frontal glioma and a possible tumour in the right.

Another operation was scheduled in September 1983. At surgery, ? gliotic tissue was noted over the site of the previous tumour growth. This was excised. An area of ? tumour tissue (greyish) adjacent to the motor strip and other resilient and firm tissue around it were also excised.

The excised tissue were examined histologically. They were reported as: (A) areas of astrocytic proliferation with some pleomorphism and increased cellularity. Geminocytic cells were also seen scattered in between these areas. Vascular proliferations were noted occasionally. Areas of necrosis, infarction, calcification and gliosis as well as normal brain were seen. (B) The main piece showed a diffuse area of astrocytic proliferation with pleomorphism and increased cellularity. Vascular proliferation, haemorrhage and necrosis were seen. Some were abnormal astrocytes around the blood vessels and reactive glial tissue. In conclusion, the picture was consistent with astrocytoma Grade II to III.

Post-operatively, the patient was maintained on dexamethazone and phenobarbitone. No further radiation therapy was given as the patient had completed a full course of therapy during which the maximum dose was given.

About 3 weeks after the second surgery, she presented with one episode of generalised fits. The repeat CT scan showed irregular areas of diminished absorption — coefficient in both frontal lobes, more marked on the left. The rims of enhancement after contrast injection were also more marked than before. (This was about 5 months after DXT.)

There was no more seizure for the next 10 months. During this time, she was not on any anticonvulsants but only dexamethazone which appeared to be effective in controlling her headaches. There was one admission for Dilantine toxicity when Dilantin was prescribed after one episode of fits. The Dilantin level was 20.5 micrograms (normal 10-20 micrograms). The repeat CT scan was reported as recurrence of tumour in the RIGHT frontal region with extension into the temporal and parietal regions. At this point, surgery was advised but the relatives refused permission.

Nineteen months after completion of radiation therapy, she was admitted in September 1984 for frequent fits which occurred half-hourly. On examination, she was uncommunicative, ill and bedridden. There were a lot of bedsores. Another CT scan was repeated. Despite the deterioration of her clinical state, the mass effect compared to the previous CT scan was less. The oedema was still present in the right cerebral hemisphere (Fig 4). Her



Fig 4: CT scan taken about 1½ years after radiotherapy showed extensive hypodensity in the RIGHT cerebral hemisphere. Significant mass effect with shift of the midline structures to the LEFT was present.

fits were controlled with valium, dexamethazone and phenytoin. These seizures ceased one month after admission. She stayed a total of 14 months in the hospital during which she improved clinically with nursing care until her discharge in February 1986.

Presently she is conscious and able to obey commands and answer simple questions. The last two CT scans done 2 years and 8 months after radiation therapy showed a much smaller hypodense area in the left frontal region which does not enhance. All the ventricles appeared large, which were suggestive of post-irradiation therapy (Fig 5).

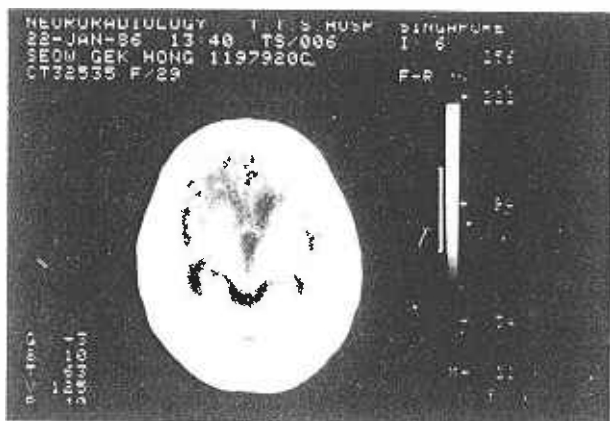


Fig 5: Final scan taken 2 years 8 months after radiotherapy showed only a small hypodense area adjacent to the left frontal horn. The oedema in the right hemisphere showed complete resolution. All the ventricles appear large. The features suggested post-irradiation atrophy.

SUMMARY

This is a 27-year-old Chinese lady presenting with vague symptoms of giddiness and unsteadiness who was diagnosed as having a left frontal low-grade astrocytoma 6 months after she was first seen. Post-operative irradiation of the brain was given.

Four months after radiotherapy, she presented with symptoms of raised intracranial pressure. The repeat CT scan showed features suggestive of a recurrence of the tumour which was excised.

However, the CT scans done a month later (5 months after completion of radiation therapy) and subsequently revealed changes suggestive of tumour progression although the patient was quite well symptomatically and clinically. It was 19 months after completion of radiation therapy that she deteriorated clinically. Unfortunately, no histologic confirmation of whether the features seen on CT were due to a recurrent tumour or brain radiation necrosis could be made as surgery was refused. Follow-up scans showed a regression of these changes thus favouring a final diagnosis of brain radiation necrosis.

DISCUSSION

INTRODUCTION

Radiation therapy is an effective and relatively safe treatment for some intracranial neoplasms particularly most gliomas which are primarily infiltrative. As a consequence, the transition between tumour and normal brain is indistinct. Histological analysis of the grossly normal brain obtained from beyond the apparent tumour edge commonly showed microscopic nests of neoplastic

cells. There are two groups of patients for whom radiotherapy is indicated: (i) where the tumours may have been only subtotally removed or showed recurrence; (ii) where the tumours must be considered inoperable because of location, invasive growth and a generally high operative-risk patient. However irradiation of the brain carries with it a small risk of disabling brain necrosis even with the use of standard therapeutic doses of radiation (1-2).

Fisher and Holtelder (3) first described a case of delayed radiation necrosis of the brain in man in 1930. Since then, many more cases have been documented (4-20). This condition is found to be a major complication of irradiation of the CNS (21).

EFFECTS OF RADIATION ON THE NERVOUS SYSTEM

There are 4 general categories of radiation effect on the CNS: (i) acute (ii) 'early delayed' (iii) leucoencephalopathy (iv) 'late delayed' necrosis.

'Early delayed' necrosis of the brain usually occurs within 2 months of irradiation. Rider (22) described a new syndrome occurring ten weeks after irradiation of the brain; this syndrome was characterised by an acute onset of neurological symptoms followed by complete recovery after a few weeks. Lampert and Davis (5) have emphasised that 'early delayed' effects may also follow brain irradiation although it is rare. It is suggested that these effects might represent an autoimmune reaction following sensitization by a necrobiotic process induced by the radiation.

'Late delayed' necrosis of the brain is quite different from the above (5). Clinically the onset is more insidious and occurs several months to many years after completion of radiotherapy.

INCIDENCE AND NATURAL HISTORY OF 'LATE DELAYED' NECROSIS

The true incidence and natural history of radiation necrosis of the brain are unknown. This late effect occurs most commonly at about 14 months after radiotherapy but has been reported to occur as early as 6 months and as late as 5 years after completing a course of treatment. Its incidence has been estimated at 5% in patients who have received greater than 45 Gy (4500 rads) in 2 Gy (200 rads) per day fractions (23). 25% of patients may suffer from radiation necrosis if the areas of the brain have received a total radiation dose of 60 Gy (6000 rads) or more (18).

WHAT ARE THE FACTORS RESPONSIBLE FOR THE INCREASING INCIDENCE?

These include (i) a more aggressive approach by the radiotherapist using higher doses; (ii) more frequent antemortem diagnosis and (iii) the period of survival after radiotherapy may be increasing, thus allowing more time for the effects to become apparent. Present evidence suggests the importance of at least 4 factors in causing radiation necrosis: (i) total dose (ii) overall time of administration (iii) size of each fraction of irradiation (iv) number of fractions per irradiated.

CLINICAL PRESENTATION

Delayed radiation necrosis may present as a mass lesion several months to years after irradiation. The brain parenchyma is actually replaced by an ill-defined space-occupying lesion. The mass can occur in or near the focus of previous surgery (21) or at a remote site (24).

Radiation necrosis of the brain should be included in the differential diagnosis of any neurological deficit that develops after therapeutic irradiation of the brain. However, presently, it is virtually impossible to differentiate from recurrent or progressive tumour without biopsy especially if the original tumour was a glioma, carcinoma or other aggressive neoplasm that usually recurs.

Both delayed radiation necrosis and intracranial tumour may present with papilloedema (13, 25), progressive loss of vision (12), hemiparesis (7, 25), dysphasia (4, 8), focal seizures (4, 8, 14), dementia (7) or hypothalamic insufficiency (12, 26).

PATHOGENESIS

The pathogenesis of delayed radiation necrosis of the brain remains speculative. Two theories have been proposed to explain the process. The first suggests that the basic mechanism is a direct effect of radiation on the parenchyma that is the neurons and glia (27) and that the vascular damage is of minor importance.

The second theory contends that vascular mechanisms play the principal role and that the chronic changes are secondary to ischaemic anoxia (4, 5, 7, 14, 28-30). Vascular changes are the most striking findings in autopsy studies of these patients. Pennybacker and Russel (4) suggested that irradiation initiated a progressive change in the smaller blood vessels which slowly diminished their lumen.

MICROSCOPIC FEATURES

Radiation necrosis predominantly affects the white matter since it contains fewer capillaries than the grey matter. The most characteristic finding is fibrinoid necrosis of blood vessel walls. Other typical features include proliferation of the vascular endothelium, hyaline thickening of blood vessel walls and coagulative necrosis.

COMPUTED TOMOGRAPHIC APPEARANCES OF RADIATION NECROSIS

CT has been established as a valuable method for monitoring brain tumours after radiotherapy. Although it was initially hoped that it would be helpful in differentiating radiation necrosis from recurrent tumour (31), the experience of later workers have not justified this hope (6, 18, 32). The CT appearances of radiation necrosis of the brain have been described by Mikhael (18).

The findings on CT are as follows: They are **oedema** characterised by diffuse hypodensity of the white matter extending into and compressing the overlying cortex; **necrosis** with enlarging focal areas of lucency; irregular, often extensive **contrast enhancement**; and **mass effect**, (18, 33). These are also the findings of tumour recurrence! However, CT is useful as it is non-invasive and can be repeated for follow-up to demonstrate regression of these changes which are transient.

Douglas A Graets et al (17) proposed some mechanisms that are responsible for these changes. The increase in size of the central lucency of the tumour suggests that increasing tumour necrosis is responsible for the tumour enlargement, and is presumably a direct effect of radiation. The subsequent decrease in size probably results from the gradual removal of dead cells. Additionally, the late decrease in tumour size may reflect delayed appearance of the direct effects of radiation as postulated by Hoffman et al (16).

The development of enhancement may suggest malignant transformation of the tumour. But if this phenomenon diminished with time, then this enhancement is more likely due to a transient effect of radiation upon vascular permeability with alteration of the blood-brain barrier (17).

TREATMENT

Therapy for delayed radiation necrosis of the brain often depends on whether or not a mass is responsible for the patient's symptoms.

Dexamethazone therapy often improves symptoms dramatically (7, 8). The efficacy of dexamethazone in treating radiation necrosis presumably derives from its anti-oedema action. Evidence has been presented indicating that its therapeutic activity may also depend upon its maintaining the integrity of excitable membranes and preventing loss of intracellular potassium. Doses as high as 40-60 mg/day are occasionally required to ameliorate post-irradiation symptoms and signs (16). Nevertheless, once neurological improvement has stabilised at a satisfactory level for 1-2 weeks, dexamethazone administration is reduced gradually to the smallest effective dose. Most patients can eventually be weaned from the drug (8).

Surgical excision of the necrotic swollen brain is necessary when there is intracranial spatial decompensation (7, 14, 34). This removes both the mass and the source of oedema and has resulted in permanent improvement of the patients (13, 34). On the other hand, patients with a large mass can resolve without surgery while others may continue to deteriorate despite surgery and dexamethazone (8).

It has been reported that dramatic improvement of two patients with proven radiation necrosis were observed while on **anticoagulant therapy** (9). Endogenous heparin is a very effective anti-inflammatory agent and modifies allergic reactions. It binds and inactivates many substances that injure vascular endothelium.

SUMMARY AND CONCLUSION

The diagnosis of delayed radiation necrosis of the brain is difficult to make without biopsy when it follows irradiation of a malignant neoplasm of the brain as illustrated by this case. An awareness and recognition of this occurrence mimicking tumour progression and of the transient nature of these changes seen on CT may prevent unnecessary patient concern or initiation of additional therapy such as surgery or radiotherapy especially in the 3 months following irradiation. Due to the extreme difficulty in differentiating clinically and on CT these 2 conditions, other modalities of investigation need to be looked into. Although **magnetic resonance** can depict radiation lesions of the brain with great sensitivity, it was found not to be helpful in differentiating between radiation necrosis and recurrent or residual brain tumour (10). Perhaps **positron emission tomography (PET) with glucose metabolism analysis** (35) will in future help to distinguish these conditions. One would predict glucose metabolism to be different in an area of necrosis than in an area of recurrent tumour.

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