CASE REPORT

Double trouble: a tale of two radio-treatments

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SUMMARY

In recent years, an increasing number of patients are treated with radiation. In the early era of radiotherapy, which began soon after X-rays were discovered by Roentgen in 1895, tumours were irradiated with high doses of X-rays in a single fraction. The major initial setback was the damage caused to normal tissues; however, in recent times the use of stereotactic radiosurgery, which delivers high doses of radiation precisely to abnormal tissue targets while sparing the surrounding normal brain tissue, and particularly for surgically inaccessible tumours, has taken centre stage. Prophylactic whole brain radiation (in conjunction with aggressive chemotherapy) for childhood acute lymphoblastic leukaemia has been shown to improve patient survival, however, this is associated with complications in survivors. We report an interesting case of one of the longest survivors who has had double complications from radiotherapy-based interventions.

BACKGROUND

Whole brain radiotherapy (WBRT) in childhood acute lymphoblastic leukaemia (ALL) has been shown to improve survival. However, this is associated with developmental side effects and formation of central nervous system tumours such as meningioma. In multiple or surgically inaccessible meningiomas, radiotherapy is a viable option of treatment. We report a case of one of Britain's longest survivors of ALL, who developed multiple intracranial meningiomas four decades after receiving WBRT and had to undergo stereotactic radiotherapy, from which she developed more complications (more like a merry-go-round thing).

CASE PRESENTATION

A 42-year-old woman presented to our unit 2 years ago with right sided weakness and facial droop of uncertain duration; her Glasgow Coma Scale was 15. MRI of the head revealed a left sphenoid wing homogeneously enhancing tumour (figure 1), which turned out to be a meningioma on histology following craniotomy and debulking of tumour. Eight months later, the patient underwent stereotactic radiosurgery (SRS). She had further SRS for nine other intracranial meningiomas. At her recent presentation following the last radiosurgery, she was found to be very unwell with headaches, poor concentration, drowsiness, self-neglect and poor speech articulation. MRI of the brain showed a large rim-enhancing lesion in the left frontal parafalcine region with significant surrounding oedema and mass effect (figure 2A, B). MRI spectroscopy showed a high lactate peak suggestive of necrosis possibly secondary to the radiosurgery rather

Figure 1 T1 postcontrast MRI of the brain showing a large left sphenoid wing meningioma and two other small meningiomas.

tumour progression (figure 3). She was managed on a high dose of dexamethasone and improved significantly prior to discharge.

Of note in this patient's medical history is that she underwent prophylactic whole brain irradiation for childhood ALL at 2 years of age. She has remained asymptomatic from the leukaemia, suggesting that the radical treatment that saved her life in childhood could be the cause of the enormous health challenges in adulthood.

DIFFERENTIAL DIAGNOSIS

- ▶ Tumour progression;
- ▶ Radiation-induced necrosis;
- ▶ High-grade glioma;
- ▶ Cerebral abscess.

DISCUSSION

Meningiomas represent the most common intracranial tumours and originate from the arachnoid cap cells of the arachnoid villi in the meningeal covering of the brain, accounting for 24–30% of primary intracranial tumours with an annual incidence rate of about 13:100 000.^{1 2} They are more common in women, particularly in middle age when there can be up to a threefold increase over men.³

Histologically, meningiomas are generally benign but about 30% are atypical and 1–2.8% are malignant.⁴ Current WHO classification of meningiomas

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Figure 2 (A) T1 postcontrast MRI of the brain showing a left frontal parafalcine-enhancing lesion resembling a high-grade tumour. (B) T2 MRI of the brain showing left frontal parafalcine tumour associated with significant surrounding oedema.

is into three: grade I, grade II and grade III (table 1).⁵ The 5-year overall survival is 92% for grade I, 78% for grade II and 47% for grade III meningiomas.^{6 7}

The pathogenesis of meningiomas remains uncertain, however, certain risk factors have been identified, common among which is exposure to ionising radiation. It has been demonstrated that patients who receive WBRT can develop radiation-induced intracranial lesions, which can include white matter necrosis, gliosis and demyelination leading to cerebral atrophy, as well as neoplasm formation (particularly meningioma) and vascular proliferative lesions.^{8 9} As it stands, radiation therapy to the head appears to be a significant risk factor for the development of meningiomas and is independent of the radiation dose administered, with tumours developing at an average of 20–35 years later.^{1 10 11} To our knowledge, our patient has one of the longest intervals (40 years) between cranial irradiation for childhood ALL and presentation of meningioma. Although radiation-induced-meningiomas (RIMs) are thought to be caused mostly by high-dose radiotherapy,^{12 13} low-dose irradiation used in the past for tinea capitis, or even doses of 1–2 Gy, are proven risk factors.¹⁴ Radiation therapy-induced meningiomas are the most common brain neoplasm known to be caused by ionising radiation; they are often

atypical or aggressive, with a high proliferation rate, and occur at multiple sites and generally in younger age groups than sporadic meningiomas.^{8 15 16}

How radiotherapy increases the risk of development of meningioma is not completely understood, but it is known that arachnoid cells in childhood are very sensitive to radiation,¹⁷ and given that meningiomas arise from the cap cells of the arachnoid, cellular damage at this level induced by irradiation may not be unconnected with the development of meningiomas. It has also been shown that radiation induces hydroxyl-free radicals that cause strand breaks or base damage in DNA. While most radiation-induced damage to DNA is repaired by intracellular mechanisms, double-strand breaks are almost impossible to repair, and occasional misrepair can result in point mutations, chromosomal translocations and gene fusions, all of which have the potential for induction of cancer.¹⁸ In line with this, radiation induced cytogenic changes including aberrations of chromosome 1p, 6q and 22 as a consequence of irradiation has been proposed to be important factors in the development of RIM.^{19–23}

Surgical excision of RIM is the treatment of choice and radical excision with wide margins is advised where possible due to the aggressive nature and higher incidence of recurrence with these tumours.^{24–30} However, given the multiplicity of

Figure 3 MR spectroscopy showing high lactate peak suggestive of radiotherapy-induced necrosis rather than tumour progression.

Table 1 WHO histological grading of meningiomas⁵

WHO classification	Description	Recurrence rate (%)
Grade I	Meningiomas with low risk or recurrence and/or low risk of aggressive growth	7–25
Grade II	Atypical meningiomas with increased mitotic activity or three or more of the following features: increased cellularity, small cells with nucleus-to-cytoplasm ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, and foci of spontaneous or geographic necrosis	29–52
Grade III	Anaplastic meningiomas that exhibit frank histological features of malignancy far in excess of the abnormalities in atypical meningiomas. They invade surrounding structures and can metastasise outside the CNS	50–94

CNS, central nervous system.

Table 2 Radiation injury based on time frame

Radiation injury	Time frame	Characteristics
Acute injury	During or after completion of radiation	Reversible; characterised by oedema
Early delayed injury	Up to 12 weeks after radiation	Reversible; characterised by increased signal on fluid-attenuated inversion recovery abnormalities and T2
Late injury/necrosis	A few months to years	Irreversible; focal pattern characterised by circumscribed lesion; diffuse pattern characterised by periventricular white matter changes

Source: Adapted from Sheline GE, Wara WM, Smith V. Therapeutic irradiation and brain injury. *Int J Radiat Oncol Biol Phys* 1980;6:1215–28.

RIM, surgical excision may not be possible, and the preferable treatment modality is paradoxically radiotherapy by way of SRS.

SRS has been shown to be safe and effective in the treatment of RIM,^{31 32} but cases of SRS-induced cerebral oedema and radionecrosis (RN; table 2) with attendant clinical consequences (as in the case with our patient) have been reported and date back as far as 1930; the trend continues to increase with increased use of SRS.^{33–35} How SRS causes such necrosis and cerebral oedema is currently not completely understood, but available information suggests damage to the vascular endothelial cells, which results in fibrinoid necrosis of the small arterial vessels. This leads to focal coagulative necrosis and oligodendrocyte damage and demyelination.³⁵ It has also been demonstrated that vascular endothelial growth factor (VEGF) could play a role in the development of radiation-induced necrosis and oedema as studies have shown increased VEGF in necrotic tissue following radiation.^{36 37}

RN can resemble tumour recurrence on neuroimaging (figure 2A, B), thus accurate diagnosis of RN, although a challenge, is important as it determines the treatment modality: that is, whether the patient undergoes complex craniotomy for tumour excision or conservative management. Possible methods of differentiating between RN and tumour recurrence include assessment of relative cerebral blood volume,³⁸ lesion/oedema volume ratio,³⁹ fluorodeoxyglucose positron emission tomography^{40 41} and MRI spectroscopy.⁴² However, apart from the histological investigation there is no imaging method that will differentiate between RN and tumour recurrence in 100% of the cases.

Learning points

- Radiation-induced-meningioma should be considered in the differential diagnosis of irradiated patients presenting many years after treatment.
- Extra care should be taken to avoid unnecessary surgical intervention for what might seem like tumour progression, but is actually radiotherapy-induced necrosis, which is amenable to conservative management.
- Given that patients with acute lymphoblastic leukaemia can survive long into adulthood, other effective central nervous system prophylactic measures with less developmental side effects should be considered other than radiotherapy.

Standard treatment for RN includes steroids and surgery; however, in asymptomatic patients, watchful waiting can be an option.⁴³ Other treatment modalities include the use of anticoagulants such as heparin and warfarin,⁴⁴ vitamin E and pentoxifylline,⁴⁵ and hyperbaric oxygen.^{46 47} Another important aspect is the use of bevacizumab, an anti-VEGF (VEGF is implicated in the pathogenesis of RN).^{48 49} In refractory cases, laser-interstitial thermal therapy has been used successfully.⁵⁰

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