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Recurrent stroke after low dose whole brain radiotherapy for brain metastases of breast cancer

Hanneke JM Meijer, Lucille DA Dorresteijn, Dominic AX Schinagl, Hanneke WM van Laarhoven

ABSTRACT

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Case Report: A 35-year-old woman diagnosed with breast cancer, developed pulmonary and cerebral metastases after initial treatment. After whole brain radiotherapy to a dose of 20 Gy in 4-Gy-fractions, followed by chemotherapy, she was in complete remission. After 20 years, she developed a stroke. Magnetic resonance imaging scan of the brain showed an ischemic lesion consistent with small vessel disease and also diffuse white matter injury. This is an atypical location for regular vascular disease, but it may be involved after cranial irradiation. Her hypertension was adequately treated. The patient lost weight and started with acetylsalicylic acid, dipyridamole and simvastatin. Despite these preventive measures, she had two more strokes within 18 months. Magnetic resonance imaging scan of the brain again showed ischemic lesions, consistent with small vessel disease. Her breast cancer remains in complete remission.

Conclusion: This case describes an extraordinary long survival in a patient with breast cancer and visceral metastases. It shows that low dose cranial irradiation may contribute to intracerebral vasculopathy. Lifestyle interventions and regular checkups for risk factors of cardiovascular disease might be in place for patients with a long survival after cranial irradiation.



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CASE REPORT

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Keywords: Recurrent stroke, Breast cancer, Whole brain radiotherapy (WBRT), Cerebrovascular disease, Stereotactic radiosurgery (SRS), Karnofsky performance score, Cranial irradiation

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INTRODUCTION

Breast cancer accounts for 10–20% of all cases of brain metastases [1]. Once brain metastases have developed, patients have a very limited prognosis and median survival is only 3–6 months, depending on age, Karnofsky performance score, extracranial disease status, number of brain metastases and administration of chemotherapy [1, 2].

Treatment options that alleviate neurological symptoms and prolong survival are surgical resection, stereotactic radiosurgery (SRS), whole brain radiotherapy (WBRT), corticosteroids or a combination of these approaches. Surgery is an option in case of single metastasis and is usually followed by WBRT. Patients with an irresectable single metastasis, or up to four metastases can be eligible for SRS. Surgery or SRS are considered when a patient's condition is good and the amount of extracranial disease is limited. For patients in a reasonable condition, WBRT alone is a good option. Corticosteroids can be used as a single treatment modality for patients in a poor condition, or in addition to other treatments [3].

After cranial irradiation coagulative necroses and demyelination of white matter have been observed [4, 5]. These histopathological changes can cause a spectrum of clinical syndromes long after cranial irradiation. Focal necrosis occurs between 6 months and 2 years after cranial irradiation and can be symptomatic [4, 5]. Diffuse white matter injury leads to symptoms like personality change and memory loss, with increasing severity of findings on magnetic resonance imaging (MRI) scan correlating with increasing severity of symptoms [5].

Cerebral blood vessel damage has been observed after cranial irradiation. In medium-sized and larger vessels intima thickening is the most prominent pathological change [6]. In large vessels myointimal proliferation has been found. In medium-sized vessels accumulation of foam cells in the intima and fibrosis of the adventitia have been observed. In smaller arteries, the main changes are subendothelial fibrosis, subendothelial foam cells, hyaline medial change and adventitial fibrosis and eventually obliteration of the arteriolar lumen [7].

Cerebrovascular disease after cranial irradiation has historically been described in children, primarily following parasellar radiotherapy [5]. It usually presents as progressive occlusion of the intracranial vessels, including Moyamoya syndrome, which can result in stroke. Moyamoya syndrome is characterized by abnormal collateral vascular networks, which arise adjacent to spontaneously occluded vessels of Willis' circle [8]. A recent review found 54 documented cases of Moyamoya syndrome after cranial irradiation [8]. Median age at initial radiotherapy was 3.8 years (range 0.4–47 years). Average dose was 55.2 Gy (range 22–120 Gy). The only four patients with Moyamoya syndrome after doses <30 Gy were <7 years old at the time of radiotherapy, suggesting a possible dose-response relationship and that younger children might be more sensitive. A review on cerebral occlusive disease after cranial irradiation found that 77% of the cases were <18 years old at the time of radiotherapy [9]. A chart review of 345 children treated with radiotherapy for a primary brain tumor reported Moyamoya syndrome in 12 children is 3.5% [10]. The onset of Moyamoya syndrome was more rapid for patients receiving >50 Gy (42 vs 67 months). Each 1-Gy increase in dose increased the rate of Moyamoya syndrome by 7%.

For adults, there are less reports of cerebrovascular disease after cranial irradiation. A recent chart review of patients treated with radiotherapy for pituitary adenomas described a cerebrovascular event in 78 of 385 patients (20.3%), 0.6–27.4 years after radiotherapy. Median age at the time of radiotherapy was 54 years (range 14–82 years) and median age at the time of stroke was 70 years. Risk of stroke was 1.45 times the expected rate for men and 2.22 for women [11]. In a similar study, a relative risk of cerebrovascular accidents of 4.1 was found, also in patients, mainly adults, treated with radiotherapy for pituitary adenoma. Usual dose was 40–50 Gy in 20–30 fractions. Again, relative risk was higher for women than for men [12].

Based on these studies, we can conclude that it is likely that there is a dose-response relationship for cerebrovascular disease. Adults who receive cranial irradiation are likely to be at higher risk for stroke than the general population, but they seem to be less sensitive for developing cerebrovascular disease after cranial irradiation than children.

CASE REPORT

In 1984, a 35-year-old woman was diagnosed with a pT2NoMo medullary carcinoma of the right breast, for which a modified radical mastectomy was performed. No additional treatments were given. Three years later, she started having difficulty with the coordination of her right hand and noticed a light paresis of the right arm. She had also coughed up blood recently. Cerebral computed tomography (CT) scan showed three metastases. A chest X-ray showed mediastinal enlargement and an intrapulmonary lesion. Sputum analysis revealed malignant cells of an adenocarcinoma, most likely originating from the earlier diagnosed breast cancer. She was treated with WBRT to a dose of 20 Gy in 4-Gy-fractions. This was followed by six courses of cyclophosphamide, methotrexate and 5-fluorouracyl. A new chest X-ray and cerebral CT scan showed a complete remission.

At the age of 58, the patient developed short-term memory loss, attention deficit, balance problems and an episode of dysarthria. Cerebral magnetic resonance imaging (MRI) scan showed an ischemic lesion in the right frontal lobe and diffuse white matter lesions (Figure 1). Intima thickening of both common carotid arteries was seen during duplex scanning as well as slight plaque build-up in the left internal carotid artery. The left vertebral artery had an abnormal flow, most likely due to hypoplasia. No significant stenoses were found. An electrocardiography (ECG) showed a sinus rhythm. Laboratory tests revealed normal glucose, cholesterol, folic acid, vitamin B1, B6 and B12 levels. Tests for antinuclear antibodies and antineutrophil cytoplasmic antibodies were negative. Hypertension was diagnosed, the patient was overweight, and she had never smoked. We concluded that this ischemic stroke had been

caused by small vessel disease. To prevent a second stroke, lisinopril, acetylsalicylic acid, dipyridamole and simvastatin were started. She was advised to lose weight.

Four months later, she had sudden complaints of paresis and coordination problems of the left hand and balance problems. Laboratory tests, an ECG, a cerebral CT scan and a new carotid and vertebral duplex scan showed no changes. Less than a year later she noticed sudden progression of her balance problems with paresis of the left leg and left sided ptosis and facial nerve paralysis. Her third acute ischemic stroke was diagnosed. A magnetic resonance angiography (MRA) showed three new ischemic lesions paraventricular, increase of white matter lesions and strongly diminished contrast filling of left vertebral artery due to stenosis or hypoplasia.

The complaints have improved with physiotherapy and speech therapy. Her breast cancer remains in complete remission.

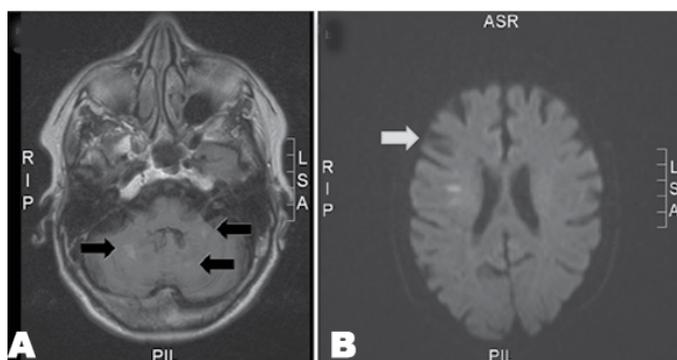


Figure 1: (A) T2-flair magnetic resonance imaging scan showing the white matter injury in the cerebellum, (B) Diffusion-weighted magnetic resonance imaging scan showing the ischemic lesion in the right frontal lobe.

DISCUSSION

This case shows an extraordinary long survival in a patient with cerebral and pulmonary metastases of breast cancer. Further, stroke after low dose radiotherapy is highly unusual in adults.

In our patient, intima thickening of the common carotid artery was seen at duplex scanning. The thickening was probably not caused by irradiation, as the common carotid arteries were outside the radiation fields. Further, common carotid artery occlusion cannot be linked to the location of the ischemic lesions in the brain. The observed left vertebral artery hypoplasia is not likely to be the cause of the stroke, as ischemic lesions seen on MRI scan were not in the blood supply region of this artery. Thus, since we observed no vascular lesions in large arteries consistent with the location of ischemia, we concluded the recurrent strokes were caused by small vessel disease, which should probably be attributed to the prior low dose radiotherapy. The diffuse white matter changes might

also be a late effect of radiotherapy, as there were also diffuse white matter changes in the cerebellum, which are atypical for white matter changes due to vascular problems. One might argue that a hypercoagulable state due to cancer may have played a role here. However, this seems unlikely, as this patient had been without evidence of disease for many years. She has two other risk factors for small vessel disease: she was overweight and had hypertension. These might have also caused the plaque build-up in the left internal carotid artery. Nevertheless, as small vessel vasculopathy is progressive in time after radiotherapy, it is likely that WBRT did contribute to the small vessel disease, even though a relatively low total dose was given.

CONCLUSION

This case shows an extraordinary long survival in a patient with pulmonary and brain metastases from breast cancer. It also shows that radiotherapy to the brain, even in a low dose, might contribute to intracerebral vasculopathy. Therefore, in patients with a long survival after cranial irradiation; even with low dose; lifestyle interventions such as regular check-up for risk factors of cardiovascular disease, might be essential to prevent stroke.

Author Contributions

Hanneke JM Meijer – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Lucille DA Dorresteyn – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Dominic AX Schinagl – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Hanneke WM van Laarhoven – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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