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Case report

Secondary malignancy following radiotherapy for thyroid eye disease

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ABSTRACT

Aim: To describe the first case of a secondary meningioma in a patient after radiation treatment for thyroid eye disease (TED). Secondarily to identify any additional cases of secondary malignancy resulting from radiotherapy for thyroid eye disease from our institutional experience.

Background: Thyroid eye disease (TED) is a self-limiting auto-immune disorder causing expansion of orbital soft tissue from deposition of glycosaminoglycans and collagen, leading to significant cosmetic and functional morbidity. Established management options for TED include: glucocorticosteroids, orbital radiotherapy, and surgical orbital decompression. Two large series on radiotherapy for TED have been reported without any cases of secondary malignancy.

Materials and methods: The case of a patient with visual failure, found to have a sphenoid wing meningioma after previous TED radiotherapy is described. We then reviewed 575 patients with at least 3-year follow-up receiving radiotherapy for TED at British Columbia Cancer Agency to identify other possible secondary malignancies.

Results: The patient had postoperative improvement in her vision without any identified complications. Three additional cases of hematologic malignancy were identified. The calculated risk in our population of developing a radiation-induced meningioma after TED with at least 3 years of follow-up of is 0.17% (1/575); with hematopoetic malignancies the risk for secondary malignancy is 0.7% (4/575).

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Conclusions: Our calculated risk for secondary malignancy (0.17%, 0.7%) is similar to the reported theoretical risk published in the literature (0.3–1.2%). There is real risk for the development of a secondary malignancy after radiotherapy treatment of TED and treatment options should include consideration for this potential.

1. Introduction

Thyroid eye disease (TED) is a self-limiting auto-immune disorder causing expansion of orbital fat and muscle from deposition of glycosaminoglycans and collagen, leading to a significant cosmetic and functional morbidity.[1] Established management options for TED are: oral or intravenous glucocorticosteroids, orbital radiotherapy, and surgical orbital decompression. The role of radiotherapy for TED remains controversial but has been used for over 60 years.[1]

Two large retrospective series on the safety of radiotherapy for TED have been performed by Wakelkamp et al.[2] and Marcocci et al.[3] These studies contain 363 patients with a minimum follow-up of 10 years and did not identify any single patient who developed malignancy within the irradiated field.[1] The calculated cumulative theoretical risk of developing secondary malignancy over a lifetime by Snijders-Keilholz et al.[4] is 1.2%.

The 1920s provided the first reports of post-radiation sarcomas in patients, demonstrating evidence of the carcinogenic effects of radiation.[5,6] Following these reports, Cahan subsequently developed the original criteria for the diagnosis of a post-radiation malignancy (specifically sarcoma). This has most recently been revised by Al-Mefty et al.[7] specifically for use with meningiomas and summarized in their manuscript as Table 1 (reproduced here):

1. Tumor must arise within the irradiated field
2. Histological feature must differ from those of any previous neoplasm
3. A sufficient latency or induction period following radiation must elapse before meningioma is diagnosed (5 years suggested)
4. No family history of phakomatosis
5. Tumor must not be recurrent or metastatic
6. Tumor must not be present prior to radiation therapy

The most frequent intracranial tumors resulting from irradiation are meningiomas, gliomas and sarcomas.[5] Post-radiation meningiomas are the most commonly reported radiation-induced neoplasms reported in the literature and there is some suggestion of increasing incidence due to the expanding indications for radiation therapy and increasing longevity of patients after radiation therapy.[5,7] The risk of developing a meningioma in post-radiation patients is described as 6–10× higher than the standard population.[8] Post-radiation meningiomas also differ in characteristics from spontaneous meningiomas having no female predominance and a younger age at presentation.[5] The mean latency for meningiomas after radiation has been reported up to 26.5 years[5,7] with suggestion that younger age at radiation treatment results in a shorter latency period.

1.1. *Case*

A 67-year-old right hand dominant female presented to the care of the Neurosurgery service at our institution with a generalized tonic clonic seizure. She had recently been investigated for right sided visual failure and been found on computed tomography (CT) (see Fig. 1) scan to have a large right sided sphenoid wing lesion, consistent with a meningioma. Magnetic resonance imaging (MRI) was performed and demonstrated an extensive dural tail along the middle cranial fossa. The lesion extended along the planum sphenoidale and across the diaphragma sella but not into the sella. The pituitary stalk was displaced to the contralateral side, along with the basal ganglia. The optic chiasm was also displaced with the right optic nerve difficult to visualize. There was no obvious intraorbital extension of the lesion. Flow voids from the supraclinoid internal carotid artery, the proximal middle cerebral artery and the proximal anterior cerebral artery were noted along the posterior margin of the tumor and appeared to be narrowed by the mass effect (MRI shown in Fig. 2). Formal cerebral vascular imaging was not performed.

The patient's past medical history was significant for hypertension, hypothyroidism with Graves' disease, a

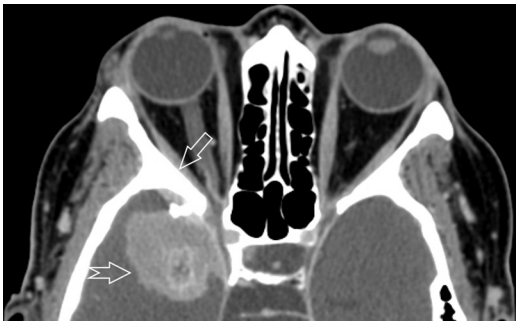

Fig. 1 – Axial computed tomography image without contrast, illustrating right sided sphenoid wing meningioma (notched arrow) measuring 5.4 cm × 4 cm × 5.3 cm (transverse × anterior-posterior × cranial – caudal). The bone along the right sphenoid wing, the anterior and posterior clinoid processes is hyperostotic (arrow). There was 1 cm of midline shift and vasogenic edema present in the right frontal and temporal lobes (not shown). The findings were consistent with meningioma and this was compared to the CT head from 10 years prior which had no evidence of lesion.

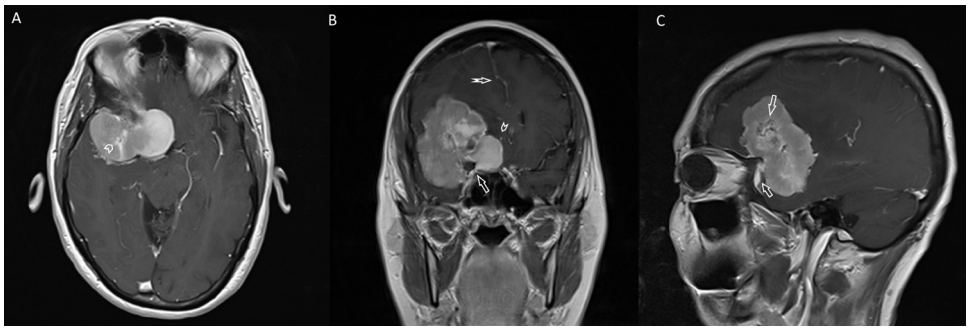

Fig. 2 – From left to right – (A) axial, (B) coronal and (C) sagittal magnetic resonance images (MRI) with gadolinium of right sided sphenoid wing meningioma in index case. A characteristic dural tail is present shown in C by the notched arrow. The lesion extends along the planum sphenoidale. There is no intraorbital extension of the lesion. In (A) the chevron illustrates a vessel flow void traveling through the lesion. In (B) the arrow shows area of internal carotid artery encasement, the chevron illustrates the anterior cerebral artery flow voids displaced medially by the lesion and the notched arrow shows the midline shift of the falx cerebri. In (C) the arrow again illustrates vessel flow voids traveling through the lesion.

history of transient ischemic attacks (TIAs) and known lacunar infarctions. Radiation therapy had been performed for Graves' opthalmopathy 14 years prior to presentation (see Fig. 3 for example of isodense lines in radiotherapy planning for TED). The patient had previously been investigated for the TIAs with a CT head non-contrast 4 years after her radiation therapy and no lesion was identified at that time.

Clinically, the visual failure in the right eye progressed to no light perception in the right eye. The patient was placed on phenytoin for seizure treatment, and decadron for the neurologic mass effect, but remained confused and drowsy post-ictally. The decision was made to intervene with surgical resection during this hospital admission.

Surgery was performed via a right pterional craniotomy and orbital osteotomy approach. The sphenoid wing was drilled down to the superior orbital fissure; the clinoid was preserved. The tumor was grossly visible through the arachnoid of the proximal sylvian fissure and approached through dissection of the sylvian fissure.

An ultrasonic aspirator was used to debulk the lesion which had varying areas of soft necrotic and tough fibrous tissue. It was adherent to the internal carotid artery, the middle cerebral artery and the anterior cerebral artery. Sharp micro-dissection was required to remove the lesion from these vital structures.

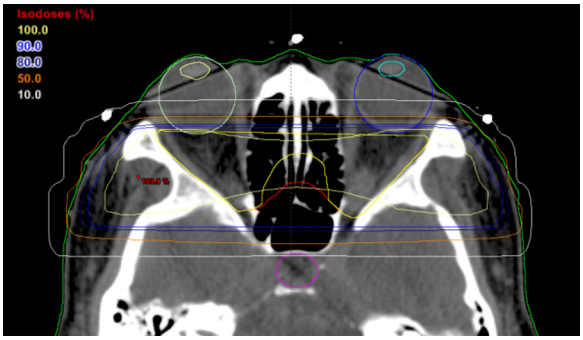

Fig. 3 – Example radiation planning on axial computed tomography (CT) image for patient with TED demonstrating areas of irradiation from the 10% to the 100% isodose lines.

The lesion was encasing the right optic nerve, displacing it extremely medially. The left optic nerve and chiasm were close by, visualized, and uninvolved. The lesion did not appear to extend into the optic canal.

Gross total resection was achieved without removal of the involved dural base, which was coagulated; achieving a Simpson Grade II resection. Post-operative CT scan and MRI (see Fig. 4) confirmed a gross total resection.

Pathology demonstrated a Meningioma WHO grade I. The tumor had delicate fibrovascular septa and moderate cellularity with few areas of mitoses. There were areas of focal increased fibrosis and foci of chronic tumor infarction with liquefaction necrosis, consistent with the intraoperative appearance. The cells had ovoid nuclei with occasional pseudo-inclusions, psammoma bodies were present and cells were arranged in whorls.

Given the identification of this index case, we sought to determine if there were any additional cases of secondary malignancy resulting from radiotherapy for TED treated at British Columbia Cancer Agency (BCCA), which could allow us to determine the rate of secondary malignancy resulting from radiotherapy treatment for TED.

Thus we present the first case of a secondary intracranial malignancy developing in a patient after radiation therapy for TED, along with a review of the BCCA experience of all patients treated with radiation therapy for TED from 1984 to 2010.

2. Methods

A retrospective cohort database review was undertaken following identification of the index patient. Ethics approval for the database review was obtained through the University of British Columbia and the BCCA. This was a review of the BCCA patient database from 1984 to 2010, encompassing all patients registered in British Columbia. There were two separate databases: one for radiation therapy and one for malignancy. The databases were cross-referenced to identify those who had received radiation for TED and who also appeared in the malignancy database. As there is approximately a 1 year lag in a patient's information, diagnosis and

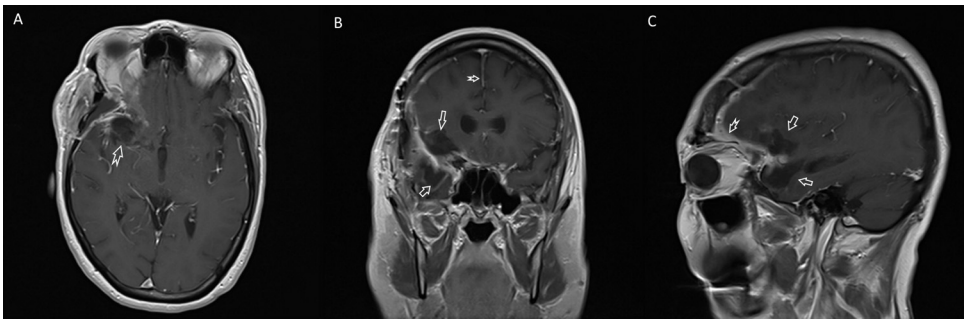

Fig. 4 – Postoperative gadolinium enhanced MRI images with (A) axial, (B) coronal, and (C) sagittal views. The surgical resection cavity with gross total resection is visible on (A) (notched arrow) and delineated by arrows in (B) and (C). The midline shift of the falx cerebri has resolved as illustrated by the notched arrow in (B), and there is dural enhancement visible in (C) (notched arrow) that represents normal postoperative effect.

treatment being logged in the malignancy database, we set a minimum follow-up time of 3 years after radiation, to fully include all possible cases.

The radiation protocol for all the TED patients was stable over the time period from 1984 to 2010. All patients received 20 Gy radiation, given over a two-week period with daily fractions of 2 Gy, 5 times per week.

3. Results

Our patient had postoperative improvement in her vision to finger counting in the right eye prior to her discharge on post-operative day 5. There were no identified peri-operative or post-operative complications. Her vision continued to improve but she did not regain full visual acuity.

Based on a retrospective review of imaging both around the time of her radiation treatment and 4 years later it was determined that the meningioma had not been present at the time of treatment and was a secondary malignancy based on the preceding criteria.[7]

In our institutional review there were a total of 638 patients who received radiation therapy for TED from 1984 to 2010. This consisted of 575 patients (155 male and 420 female) with at least 3 years of follow-up since their radiation (see Fig. 5). The majority of patients received radioiodide therapy in addition to their radiation therapy. The mean follow-up was 14 years, the median follow-up was 10 years, with the longest follow-up at 29 years. The incidence rate of meningioma in our cohort was 13.23 cases per 100,000 person-years.

Of these patients, 86 (21 male and 65 female) were identified who also had a subsequent malignancy. 81 of these were outside the area of radiation on chart review (29 lung, 23 colon, 22 breast, 1 endometrial, 1 cholangiocarcinoma, 2 squamous cell carcinoma of skin outside of involved area, 1 basal cell carcinoma and 2 melanoma). Five patients were selected for further review and included: 1 adenocarcinoma not otherwise specified (breast primary on chart review and then excluded), 1 case of acute myeloid leukemia, 1 B cell lymphoma, 1 essential thrombocytopenia, and 1 meningioma (index case).

This leads to a calculated risk in our population of developing a radiation-induced meningioma after TED with at least 3 years of follow-up of: 1/575 = 0.17%; if we include the

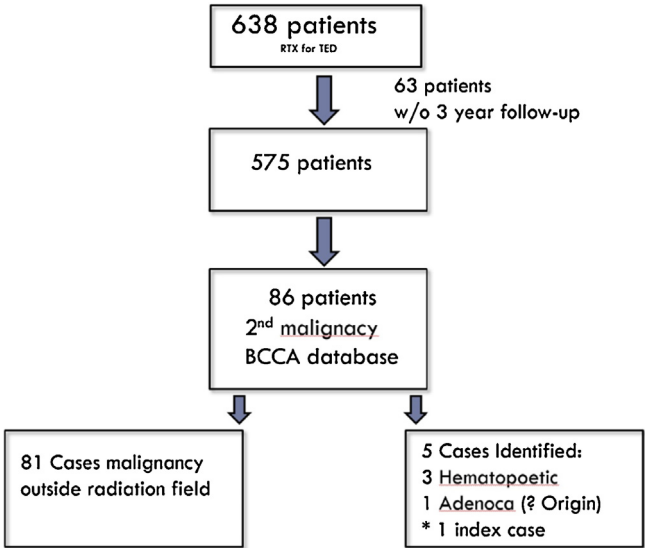

Fig. 5 – Patient selection and inclusion flow diagram for retrospective review of the BCCA database.

hematopoetic malignancies as secondary malignancies the risk for any secondary malignancy becomes: 4/575 = 0.7%. The incidence rate of meningioma in our population was 13.23 cases per 100,000 person-years of follow-up.

The time from radiation therapy to development of secondary malignancy was 14 years in the meningioma patient, 7 years for the patient with B cell lymphoma, 6 years for the AML patient, and 4 years for the patient with essential thrombocytopenia. This gives an average time of 5.6 years from the radiotherapy to the development of secondary hematologic malignancy and 14 years from radiotherapy to the development of the secondary meningioma.

4. Discussion

Our patient is the first reported case of a secondary malignancy developing after radiation for TED. The lesion fits the Al-Mefty et al.[7] modification of Cahan's criteria for development of a secondary malignancy. Meningiomas are tumors of

the brain and spinal cord that develop from the arachnoid cap cells on the external layer of the arachnoid membrane and these cells are sensitive to radiation and open to oncogenic stimulation.[8–10] Our post-radiation database incidence rate of meningioma at 13.23 cases per 100,000 person-years is much higher than that reported in the general population at 4.52 per 100,000 person-years or up to 6.01 per 100,000 person-years in females; reducing the probability that the lesion occurred due to chance, especially considering its occurrence within the field of previous radiation.[10]

The lesion was diagnosed as benign meningioma (WHO grade I) and led to secondary visual failure in our patient. The surgical resection was challenging due to the location of the lesion and its involvement of critical intracranial vascular and nervous structures.

The population in our study represents a provincial centralized database where all cases referred and treated in the province of British Columbia have their information stored. Those patients who received radiation therapy from 1984 to 2010 and who also were recorded as having a malignancy in the BCCA database were recorded. Given this centralized population we are able to determine, in our population, that the risk of radiation-induced meningioma after radiotherapy for TED is 0.17 and the risk for any secondary malignancy is 0.7%. This is lower than the predicted risk as proposed by Snijders-Keilholz et al.[4] at 1.2%. Blank et al.[11] provided a differing opinion on the risk of secondary malignancy in their comment on Snijders-Keilholz et al. at 0.3%, our calculated risk is similar to this prediction.

Whether to include the hematopoetic malignancies as secondary malignancies is dependent on the relative involvement of the bone marrow within the irradiated field. In Snijders-Keilholz et al.[4] the effective dose to red bone marrow was second only to the brain after 20 Gy radiation treatment for TED. There is also evidence that the equilibrium between cellular proliferation, apoptosis, quiescence or differentiation can be affected by radiation induced effects.[12] Thus it is possible that these hematopoetic malignancies could be related to the radiation treatment. The other confounder in this scenario is patient treatment with radioiodine therapy for hyperthyroidism. The majority of patients did receive radioiodide therapy including all those who developed hematopoetic malignancies. This a significant confounder that limits the conclusion as to whether these malignancies can be definitively linked to the radiation therapy. Metso et al.[13] determined that radioiodine therapy was associated with an overall increased cancer incidence compared to a population based control group, with a 5 year latency. Specifically looking at the hematopoetic malignancy rates reported in the study, there was a trend toward increased incidence, but this was not significant [incidence (95% confidence interval) in exposed was 6.9 (4.5–10.4) compared to unexposed 5.4 (3.4–8.6)].

There are other recognized limitations in our calculation of the rate of secondary malignancy based on our provincial database. If a patient moved and was treated outside of the province they would not be captured in the data. If a meningioma was managed non-operatively and not referred to BCCA, this would also not be included in the database. Also, although our follow-up period is long, it still does not include the entire lifespan of all the patients and thus our risk value does not encompass a cumulative 'lifetime' risk, which could be higher than what we found.

5. Conclusions

Presented is the first case of a radiation-induced secondary intracranial malignancy after radiotherapy for TED; the theoretical risk of developing secondary malignancy from radiotherapy for TED is real. This additional risk should be considered as part of the risk/benefit ratio when treating patients for TED.[14] The time from treatment to presentation in our meningioma patient was 14 years, and thus long-term follow-up greater than 10 years is required discover any secondary malignancies in treated patients. This can be considered within the context of a reported mean latency period of 26.5 years for radiation induced meningiomas.[5,7] Patients who develop delayed visual failure in this population should have imaging to investigate for intracranial malignancy, although it is recognized that radiation can induce delayed visual deterioration.[7] There is also a high reported incidence of recurrence for post-radiation meningiomas (up to 100%),[5,7] despite 62% of lesions graded as WHO I,[5] necessitating follow-up imaging for a number of years after surgical treatment of the radiation-induced meningioma. In addition to the risk of intracranial secondary malignancy, there also exists the possibility of secondary hematologic malignancy.

Radiotherapy treatment of TED should include consideration for the potential development of secondary malignancy.

Consent

Written informed consent was obtained from the patient for publication of this report and any accompanying images.

Conflict of interest

None declared.

Financial disclosure

None declared.

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