

## High Grade Glioma after Prophylactic Cranial Irradiation for Small Cell Lung Cancer

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### ABSTRACT

*We report a patient with an initial diagnosis of small cell lung cancer treated with prophylactic cranial irradiation (PCI), who subsequently developed a second primary brain neoplasm within the PCI volume. Pathology review was consistent with astrocytoma, WHO grade IV (Glioblastoma Multiforme). After describing our case, we review the literature on the development of a second brain primary after treatment with PCI and discuss potential etiologies.*

### INTRODUCTION

In patients with small cell lung cancer (SCLC), the brain represents one of the major sites of relapse with autopsy series documenting a prevalence of up to 50% [1]. The use of prophylactic cranial irradiation (PCI) reduces the incidence of brain metastases at three years by 25% [2] and improves overall survival by 5% at 3 years in both limited [2, 3] and extensive stage SCLC [4]. Published literature supports standard practice of PCI delivery to a total dose of 25 Gray in 10 fractions for limited or extensive stage SCLC

patients who respond to first-line chemotherapy [5].

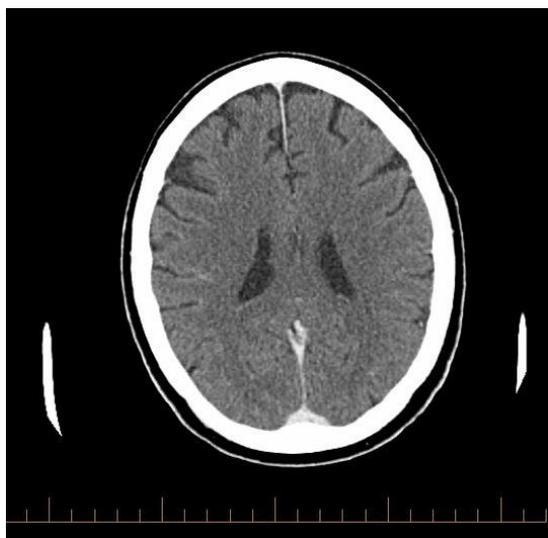
One of the potential, although exceedingly rare, side effects of CNS radiotherapy (RT) is radiation-induced glioma. Most RT-induced gliomas are diagnosed years after treatment for acute lymphocytic leukemia (ALL) or a primary CNS tumor [6-8]. PCI-induced gliomas in ALL survivors, for example, are complex in their etiology as these patients are generally young, usually receive intrathecal chemotherapy, and may have a coexisting genetic predisposition for the development of glial tumors.

RT-induced gliomas after PCI for SCLC have not to our knowledge been previously described. We report a patient who developed a high grade glioma approximately 20 months after receiving PCI following complete response to chemoradiotherapy for limited stage SCLC.

## CASE REPORT

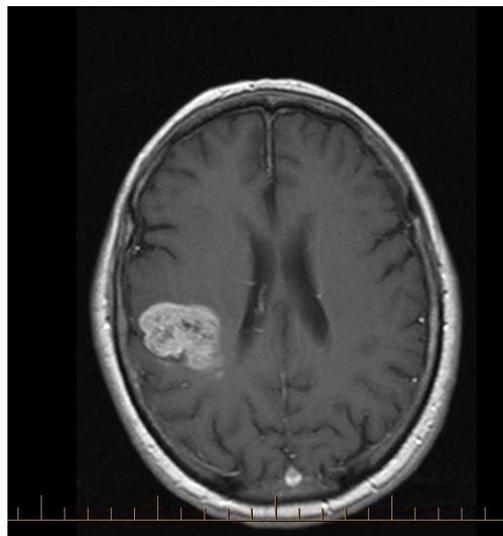
In September 2006, this 66 year-old female sustained a right rotator cuff tear. A right upper lobe lung mass was incidentally discovered in the process of imaging this injury. On review of systems, the patient had longstanding hoarseness but no other symptoms. She had a 40 pack-year smoking history but had quit three months prior. Family history consisted of first degree relatives with renal cell carcinoma, pancreatic cancer, leukemia of unknown type, head and neck malignancy and gastric carcinoma, but no lung or CNS tumours. She had had a normal chest x-ray two years prior.

Computed Tomography (CT) scan of the chest confirmed a 3.3 cm lobulated mass in the superior right lower lobe without regional lymphadenopathy. Staging was completed with a bone scan and CT head, both of which were negative for malignancy (November 2006). CT-guided biopsy revealed poorly differentiated carcinoma, compatible with SCLC. Discohesive clusters of malignant small cells were seen with cytoarchitectural features of poorly differentiated neuroendocrine carcinoma. Immunohistochemical staining was positive for synaptophysin and chromogranin.



**Figure 1A.** Enhanced CT head performed prior to

prophylactic cranial irradiation (February 2007). A subtle infarct within the right MCA territory is suggested.

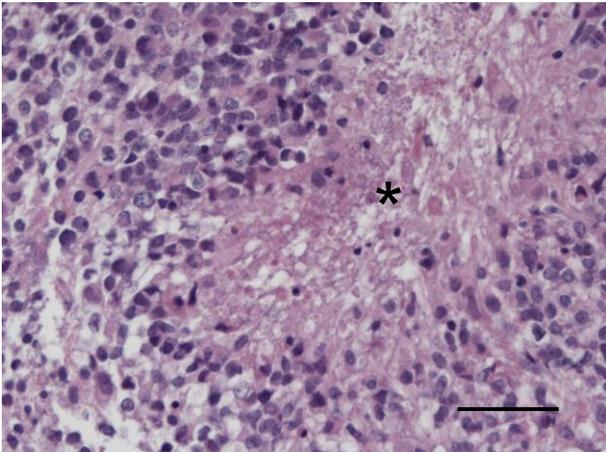


**Figure 1B.** T1-weighted post gadolinium MRI (December 2008).

The patient received curative-intent concurrent chemoradiotherapy for her limited-stage SCLC with four cycles of cisplatin and etoposide and thoracic RT (50 Gray in 25 daily fractions), completed January 2007. She had near complete response to treatment with an 11 mm residual mass (February 2007) and retained an excellent performance status (PS). Restaging enhanced CT head (Figure 1A) described possible small vessel disease in the middle cerebral artery territory but no other abnormality. PCI was delivered to a total dose of 25 Gray in 10 fractions via standard whole brain fields from April 3-17, 2007.

In December 2008, the patient presented with a three-month history of progressive, episodic left arm, leg and foot paresthesias. Unenhanced CT head questioned subtle changes suggestive of a right middle cerebral infarct. However, MRI brain (December 14, 2008) revealed a hyperintense lesion within the posterior right frontal lobe with mild mass effect and marked contrast-enhancement (Figure 1B). There was no distortion of the ventricular system, no midline shift and the mass did not display restricted diffusion. Radiologic differential diagnosis included primary or secondary neoplasm. Restaging CT of the chest, abdomen and pelvis showed no locoregional or distant recurrence of the prior lung cancer. Due to her

good PS, lack of extracranial disease and inconclusive imaging, stereotactic biopsy was performed.



**Figure 2.** Right temporal lesion biopsy showing hypercellular neoplasm with geographic necrosis\* consistent with glioblastoma multiforme (H&E staining; bar = 50 $\mu$ ).

The specimen consisted entirely of a hypercellular astrocytic neoplasm with multiple foci of necrosis, abundant mitoses and prominent vascular proliferative change with small regions with oligodendroglial features (Figure 2). Immunolabeling for the proliferative marker MIB-1 was positive in over half the nuclei, the astrocytic marker GFAP was strongly positive whereas pankeratin, synaptophysin and chromogranin were negative. The histopathological features were diagnostic of astrocytoma, WHO grade IV (glioblastoma multiforme [GBM]), with an oligo-dendroglial component.

After discussion at interdisciplinary CNS conference, the consensus management approach was that of concurrent conformal RT (40 Gray in 15 daily fractions) and Temozolamide followed by adjuvant Temozolamide, given her age [9] and previous brain RT. Repeat MRI for RT planning (January 2009) showed marked progression, with moderate vasogenic edema, new subfalcine herniation, and midline shift.

The patient completed RT and concurrent chemotherapy, but unfortunately shortly thereafter experienced clinical deterioration and requested discontinuation of treatment. MRI performed three months after the diagnosis of GBM again showed significant progression. The patient died August 1, 2009, five months after

completing her second course of brain RT.

## DISCUSSION

Even in the post-PCI setting, the subsequent development of a brain lesion usually represents a metastasis, as more than one quarter of patients receiving PCI will experience CNS failure [4]. However, we report a case of a pathologically-proven GBM developing in the PCI volume after curative-intent treatment for limited stage SCLC. Possible etiologies include: an unrelated spontaneous second primary malignancy; a second primary caused by common predisposing factors; or a treatment-induced second malignant neoplasm (SMN).

Patients with SCLC are at increased risk of developing second malignancies, largely as a result of the field effect of smoking, most commonly second lung cancers or leukemias [10]. Risk factors for brain tumors in general, and GBMs specifically, include exposure to vinyl chloride, lead, and radiation [11, 12]. There is minimal evidence that SCLC and GBM share common environmental or lifestyle risk factors to account for their metachronous development in this patient. Although genetic syndromes also increase the risk of malignancy, our patient did not have a pre-existing diagnosis of a clinically recognized genetic cancer syndrome.

A radiation-induced SMN is another potential cause. The original definition of RT-induced malignancy is one which has a different histology from the primary disease, occurs in a previously treated area after a sufficiently long latency period, generally years, without a history of other predisposing factors to tumor development [13]. The latency period is not clearly defined in this or any other definition of SMN. Cranial RT-induced GBM is well-documented [6-8], although the absolute risk after doses in the range our patient received is generally thought to be small [14]. Salvati et al suggests that RT-induced gliomas occur after an average dose of 32Gy and a mean latency period of 9.6 years [6, 7]. However, radiation-induced SMNs have been suggested to occur as soon as one year after treatment [6-8].

All PCI-induced secondary malignancies reported to date have occurred in the setting of PCI for ALL [15, 16, 17]. The pathogenesis of SMN

in the setting of ALL is confounded by intrathecal chemotherapy and genetic predisposition [18]. However, PCI does increase the occurrence of second brain tumours independent of other risk factors in this setting [19].

Finally, the possibility of a spontaneously-occurring GBM unrelated to the first by virtue of treatment, risk factors or genetics must also be considered. There is no way to histologically differentiate a RT-induced GBM from a spontaneously occurring one [20]. The short latency period in our case raises the possibility that this lesion may have been present subclinically prior to initiation of PCI although the putative latency period of GBM is unknown at this time.

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## CONCLUSION

This is a case of a GBM diagnosed 20 months after the administration of PCI post curative-intent chemoradiotherapy for limited stage SCLC. No histological methods exist to conclusively ascertain whether this patient's GBM is a PCI-induced SMN, or a de novo second primary tumour. Regardless of the pathogenesis, the differential diagnosis of a new brain lesion in a patient previously treated with PCI for SCLC should always include a second primary brain lesion in addition to a brain metastasis.

## CONFLICT OF INTEREST

The authors report no conflicts of interest.

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