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Case Report

Synchronous Double Primary Malignancy of Non-Small Cell Lung Cancer and Glioblastoma: A Case Report and Literature Review

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Synchronous primary · Glioblastoma · Non-small cell lung cancer · Brain metastasis

Abstract
Introduction: Non-small cell lung cancer (NSCLC) is the most common form of lung cancer and has a propensity to metastasize to the brain. It is incredibly difficult to distinguish between a primary brain lesions and a solitary metastasis from distant occult disease using current imaging techniques. Further, complications arise from the shifting paradigm in how medicine views NSCLC brain metastasis due to contemporary nonsurgical curative treatments and the recent increase in the number of multiple primary malignancy (MPM) diagnoses associated with NSCLC. There is a dearth of reports regarding synchronous double primary malignancies involving separate lung and brain pathologies. Importantly, understanding the underlying cancer etiology is necessary for efficacious treatment strategy. ***Case Presentation:*** A 65-year-old white male patient presented with node-positive NSCLC and a solitary intracranial lesion. The lung mass responded favorably to chemoradiotherapy while the brain lesion continued to progress despite stereotactic radiosurgery treatment. Subsequent resection of the brain lesion, conducted 8 months after initial presentation, surprisingly revealed a second primary cancer diagnosis of glioblastoma (GB). Unfortunately, despite revision of systemic therapeutic strategy, the patient continued to progress through treatment and ultimately died 16 months after the initial diagnosis. ***Conclusion:*** Herein is the third report regarding synchronous double primary malignancies involving non-small cell lung cancer (NSCLC) and GB. This report of an assumed metastatic NSCLC patient with a solitary brain lesion, history of smoking, and COPD underscores the need for pathological confirmation of all new

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presentations of metastatic disease via biopsy and highlights the importance of including the possibility of a second primary in the differential diagnosis. Additional reports of NSCLC and synchronous solitary brain lesions are needed to further elucidate pertinent patient characteristics and better inform clinical decision making.

Introduction

Lung cancer is the leading cause of cancer-related deaths in the USA and around the world [1, 2]. It is the 3rd most commonly diagnosed cancer (1st most common breast and 2nd prostate), with a projected 234,580 new US diagnoses in 2024 along with 125,070 deaths [1]. Lung cancer is divided into two main subtypes predicated on histology; small cell (SCLC) and non-small cell (NSCLC), which comprise 13% and 84% of lung cancer cases, respectively [3]. NSCLC itself is further comprised of multiple histologically distinct cancers: adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, large cell carcinoma, and sarcomatoid carcinoma. Treatment for lung cancer is dictated by the cancer subtype, stage, and molecular characteristics. The cornerstone of SCLC treatment is chemotherapy with surgery and radiation providing additional benefit where appropriate. Conversely, early stage NSCLC (stage I–II) management incorporates surgical resection or ablative radiotherapy, with chemotherapy reserved for tumors greater than 4 cm in size. Patients with pathological N1/2 disease receive adjuvant chemotherapy. Along with this, stereotactic body radiotherapy (SBRT) is an alternative for inoperable early stage NSCLC. Studies have shown that the addition of SBRT leads to local control rates of 90% or greater for inoperable tumors [4–6] as well as improvements in overall survival [6, 7] and progression-free survival [8]. Later stage patients, such as those with clinically N2/3 disease (i.e., stage III), often receive either neoadjuvant systemic therapy ± radiation followed by surgery or definitive chemoradiation alone.

Just 16% of lung cancer is diagnosed with only local disease and prior to any detectable metastasis (regional or distant) [9]. Therefore, unfortunately, a large majority of lung cancer patients present with metastatic disease. One common site of metastasis in the setting of lung cancer is the brain. In fact, studies suggest 15–50% of NSCLC patients will develop brain metastasis at some point during the disease [10–13]. In conjunction, the overwhelming majority of brain metastasis from extracranial solid primary tumors, as high as 88% in one study, are from lung cancer [10].

While aggressive surgical resection for limited brain metastasis (1–4 lesions) improves survival [14], many NSCLC patients lack the fitness required to undergo surgery or are unwilling to accept the morbidity associated with surgical resection. The evolution of contemporary therapeutic modalities (e.g., ablative radiotherapy) has provided non-surgical options for definitive treatment of these oligometastatic patients. Focal, ablative radiotherapy provides a progression-free (PFS) and overall survival (OS) benefit when treating oligometastatic NSCLC in a myriad of sites [15–17], including the brain [18].

Complicating treatment decisions is the recent increase in diagnosis of multiple primary malignancies (MPMs) across a variety of primary disease sites, and more specifically in association with NSCLC (lung [19], all cancer [20, 21]). Of the patients with MPM involving lung cancer, synchronous MPM have a worse prognosis than metachronous (when lung cancer was the initial diagnosis) [19, 22, 23]. While synchronous dual primary malignancies are less common than metachronous [19, 21], their recent increase in frequency, and common association with NSCLC, has significant clinical implications. Further, it can be difficult to

differentiate between primary brain tumors such as glioblastoma from an intracranial metastatic lesion with current imaging modalities.

There is a limited reserve of case reports describing specifically synchronous NSCLC and glioblastoma (GB) [24, 25] and only a single case report of simultaneous GB with SCLC [26]. The rarity of this phenotype, and the similarity of this clinical picture with the more common scenario of primary lung cancer and a solitary brain metastasis, restricts the consideration of synchronous primary tumors in the setting of NSCLC. Thus, any additional clinical knowledge provided by this case documentation is valuable. Herein, we present a case of a 65-year-old white male with simultaneous stage III NSCLC and GB after being initially misdiagnosed with stage IV lung cancer harboring a solitary brain metastasis.

Case

A 65-year-old white male patient underwent a chest X-ray ordered by his primary care physician in June due to a 27.75 pack-year smoking history and strong family history of lung cancer. A mass was discovered in the right upper lobe (RUL) of the lung that prompted a follow-up chest CT. A 1.6 cm spiculated mass was appreciated in the RUL and an additional 3.4 cm mass was revealed in the superior aspect of the right lower lobe (RLL). A biopsy of each lesion 3 weeks later revealed the RLL mass to be consistent with a solitary fibrous tumor, and the RUL demonstrated non-small cell lung cancer with histology favoring adenocarcinoma (i.e., positive staining for CD99, CD34, BCL-2, vimentin, STAT6, TTF-1). He established care with medical oncology and underwent staging PET/CT and MRI brain that same month. PET revealed a 2.2 cm avid lesion (5.9 max SUV) in the RUL, a second 1.1 cm hypermetabolic nodule (3.3 max SUV) in the RUL concerning for metastatic focus, and a single avid subcarinal/lower paratracheal node, which was also hypermetabolic (6.2 max SUV). The brain MRI revealed a single 2.3 cm cystic/solid contrast-enhancing lesion in the right anterior temporal lobe with moderate surrounding vasogenic edema consistent with intracranial metastatic disease (Fig. 1). Endobronchial ultrasound (EBUS) and transbronchial needle aspiration (TBNA) of the PET-avid level 7 node verified malignant involvement. The patient was discussed at thoracic tumor board and in the setting of mediastinal nodal involvement, the decision was made to implement definitive SRS to the brain lesion with chemo-radiotherapy treatment to the thoracic lesions.

One month later, the patient underwent upfront fractionated SRS treatment to the brain lesion with 3,000 cGy in 5 fractions over 6 days. The following week, he began conventionally fractionated RT to the lung lesion and lymph nodes as well as concurrent systemic chemotherapy with carboplatin (target AUC = 5) and paclitaxel (175 mg/m^2). Total RT dose to the thorax was 6,600 cGy in 33 fractions over 44 days. Brain MRI 1 month later found the brain lesion to remain static at 2.3 cm; however, this did demonstrate radiation necrosis, extensive vasogenic edema, stable mass effect, and midline shift. This was interpreted to be treatment-related changes and no additional evidence of metastasis was noted. That same day, the patient experienced a fall after completion of a restaging CT scan and upon evaluation was drooling with associated left arm weakness. In the emergency department, initial CT scan of the head did not reveal any evidence of intracranial hemorrhage and the patient was alert and oriented with no signs of speech or cognitive deficit. With the CT negative for intracranial bleeding, the symptoms were potentially explainable by alternative reasons including the right brain vasogenic edema and a pre-MRI alprazolam dose (1 mg ×2). He was released but advised to closely monitor his neurologic symptoms in the next 3 days and return to the emergency department immediately as indicated. He was prescribed dexamethasone 4 mg PO twice-daily for 2 weeks for presumed radiation necrosis and associated midline shift but was

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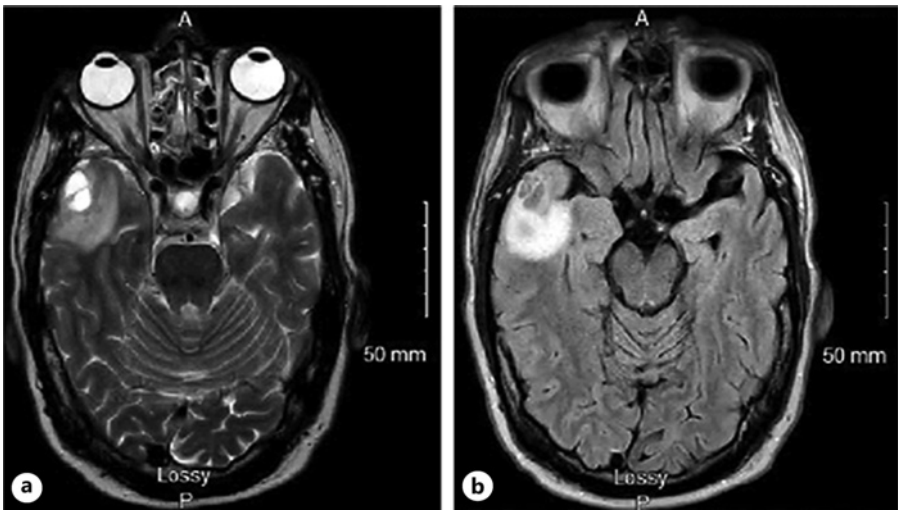

Fig. 1. Axial magnetic resonance imaging (T1 with contrast (**a**), T2 FLAIR (**b**)) demonstrating the identified 2.3 cm cystic/solid lesion in the right anterior temporal lobe with moderate surrounding vasogenic edema appreciated. Findings were suggestive for metastatic disease originating from NSCLC primary diagnosis.

instructed to delay initiation for 3 days, and only if his symptoms are stable/improving, due to the concerns for intracranial bleeding. With this, the patient reported symptom resolution within 48 h of the event.

In January, 6 months following initial presentation, a restaging chest CT found a decrease in the size of the lung lesions as well as the previously hypermetabolic node after initial therapy. With this tumor response, he was scheduled for a follow-up 2 months later. Unfortunately, in less than 1 month, the patient was admitted to the emergency department for an acute, severe headache and left-sided weakness. MRI brain found the temporal lobe lesion to be increased in size to 5.0 cm with new invasion into the insula and basal ganglia along with a concomitant increase in associated mass effect when compared to the imaging completed 8 weeks prior. Right uncal herniation was appreciated with an increase in midline shift to the left from 1.4 to 1.8 cm. A majority of the mass was felt to likely represent necrosis. However, the deep margin of the mass contained an area of increased perfusion and diffusion restriction that was likely to represent viable tumor. Of note, no additional sites of metastatic disease were seen. With the continued concern for radiation necrosis, along with the patient's intractable headache and continued left-sided weakness, he was started on high dose (6 mg) dexamethasone four-times daily for swelling, 500 mg levetiracetam twice-daily for seizure prophylaxis, and a debulking surgery was scheduled. Eight months following the initial cancer diagnosis, the patient underwent a right temporoparietal craniotomy with partial tumor resection. Pathology of the tumor, surprisingly, demonstrated a second primary diagnosis of glioblastoma with focal primitive neuronal component with no methylation of the MGMT promoter region and negative for IDH1 R132H mutation via IHC. There were associated radiation-related changes of the tissue. The day after surgery, postoperative head CT showed a slight decrease in mass effect and the patient did report a reduction in symptoms. His motor deficits and headache continued to improve over the next 5 days leading to his subsequent discharge.

Given that he had received prior definitive-dose RT to the brain lesion site, further complicated by late radiation necrosis, the decision was made to initiate adjuvant temozolomide therapy and reserve additional RT for disease progression. He began temozolomide at

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150 mg/m^2 5 nights out of every 4 weeks and a follow-up evaluation was scheduled for the end of his first cycle. Unfortunately, prior to this follow-up appointment, the patient was admitted to the emergency room due to a surgical complication of a pseudomeningocele which resolved spontaneously over the course of 10 days. After completing his first month-long cycle of treatment, he began alternating electric field therapy. Four weeks later (after completion of 2-cycles of temozolomide), repeat brain MRI revealed the GB lesion had progressed despite treatment. The tumor showed an increase in volume of the solid component and progressive complex lesional cysts, now with ependymal enhancement and progressive cerebral infiltrative edema with 1.4 cm leftward midline shift which was increased from the previous scan (1.1 cm). A restaging CT chest did not demonstrate a change in the size of the lung lesion and was absent of any suspicious adenopathy as compared to imaging 4 months prior.

With the progression of the brain lesion in the context of stable lung disease, he began treatment with bevacizumab 10 mg/kg every 2 weeks. He continued this treatment for 2 months when an MRI brain revealed a new focus of increased enhancement at the margins of the mass concerning for progressive disease with possible entrapment of the right lateral ventricle, however, the extensive edema surrounding the mass was greatly reduced, likely due to the bevacizumab treatment (Fig. 2). Follow-up CT head 1 month later found the primary mass size to have increased to 5.7 cm in greatest dimension with likely entrapment of the temporal horn of the right lateral ventricle. Four weeks later, the patient was admitted to the emergency department with a sub-acute onset of stroke-like symptoms including left-sided paralysis and vision disturbance. CT and MRI of the brain showed significant interval progression from the previous scan 1 month prior with the tumor now measuring 8.1 cm in greatest dimension with associated extensive ependymal plaque progression, increasing vasogenic edema, and associated mass effect. His symptoms responded well to high dose steroids (4 mg dexamethasone 4-times-daily) and he was discharged home. Two weeks later, he was readmitted with severe dyspnea and hypoxia. CT scan of the chest showed increased bilateral lower lobe atelectasis, tree-in-bud nodularity from a likely infectious etiology, consolidation in the right upper lobe, esophageal thickening possibly related to his prior RT, and a right pleural effusion. He was treated for pneumonia for 9 days when he was subsequently discharged to hospice care.

Discussion

The inherent benefits associated with new ablative therapies directly obfuscate physicians' treatment strategies and can lead to neglect of the accepted practice of defining metastatic disease via biopsy confirmation. Medicine now offers the potential to cure patients, even in the setting of intracranial metastasis, with minimal toxicity associated with the ablative treatments. The diagnosis of metastatic disease is no longer a death sentence for these patients and this fact has led to a paradigm shift in the perceived necessity of a biopsy. Heretofore, patients may have far more to gain from a metastatic site biopsy. If the lesion were found to be curable, i.e., benign disease or a second primary malignancy, and not an incurable lung cancer metastasis, treatment strategy may drastically be altered, and patient lives could be extended. Now, the possibility of cure remains in the setting of brain metastasis, thereby diminishing the impact of the information gleaned from an invasive intracranial biopsy. With this, providers may question the net benefit of such a procedure considering the diminished likelihood that a biopsy would improve therapy selection or patient outcome weighed against the inherent risks associated with the procedure.

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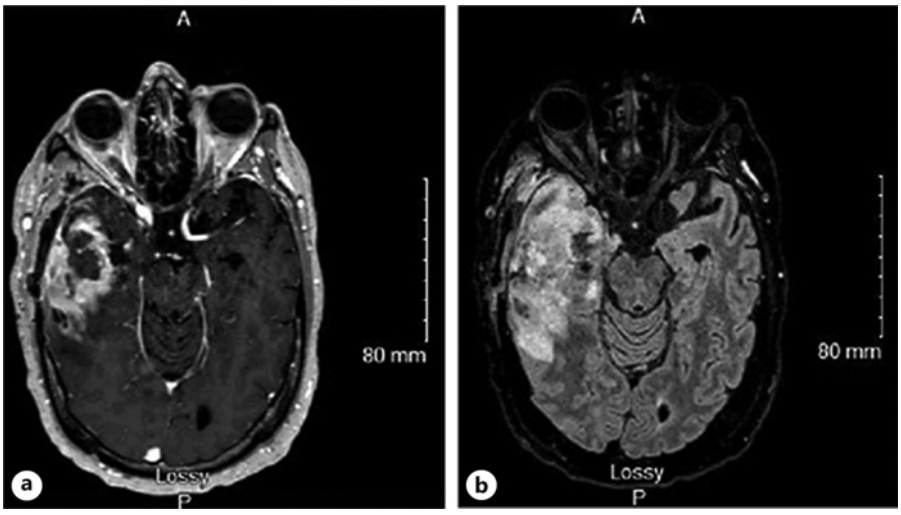

Fig. 2. Axial magnetic resonance imaging (T1 with contrast (**a**), T2 FLAIR (**b**)) revealing new focus of increase tumor margin enhancement and an increase in lesion size, concerning for progressive disease.

It has been a long-time dilemma for physicians to determine if a brain tumor reflects primary neoplasm or has origins in distant occult disease, and various strategies have been proposed to help distinguish between the two with limited success [27–29]. Even though the preponderance of brain tumors are metastases [12], and the great majority of these arise from lung cancer [10, 30], it can still be incredibly difficult to discern the tumor origin prior to biopsy due to image homology. This is especially true in the setting of a solitary metastatic lesion versus gliomas; the most common primary malignant brain tumor [31], which often present as a single lesion. Though reports of extracranial GB metastasis to the lung exist in the literature [32], it is quite rare. Along with this, there are a limited number of retrospective studies on synchronous MPM involving GB/gliomas [31, 33] and only 1 case of synchronous SCLC and GB has been reported [26].

Two prior case reports describe the diagnosis of synchronous NSCLC and glioblastoma, both of which ultimately had multiple brain lesions present on MRI imaging. In the first case, the patient was staged as IIIA NSCLC but later underwent MRI brain in evaluation of neurologic symptoms and was found to have three brain lesions prior to initiation of treatment to the thorax. One of the lesions was biopsied with pathology demonstrating glioblastoma. It is unclear if the other lesions represented de novo metastatic NSCLC (in which case the patient would be stage IVB) or multifocal GB. In this case, the brain lesions were all treated as GB utilizing hypofractionated radiotherapy with concomitant temozolomide [24]. In the second case, a patient with newly diagnosed NSCLC was found to have four intracranial lesions on initial staging MRI brain followed by development of additional metachronous brain metastases later in the course of treatment. Following local progression of a lesion that had received three prior courses of SRS, this lesion was biopsied and found to be glioblastoma which was treated postoperatively utilizing modified Stupp regimen [25]. As in these 2 case reports, if a patient has a known extracranial tumor and is subsequently found to have a brain lesion(s), they are often presumed to have metastatic disease and treated as such. This present case describes, for the first time, a patient with synchronous, localized primary malignancies involving NSCLC and GB. The rarity of this patient presentation, the current paradigm shift in the treatment of oligometastatic disease, and the paucity of known cases with this phenotype led to a belated diagnosis, suboptimal treatment, and delayed systemic therapy for his GB.

Importantly, NSCLC has a propensity to be associated with second primaries when compared to cancers of other origins [34]. In conjunction, the occurrence of multiple primaries in the setting of NSCLC is highly associated with smoking and COPD [19, 35, 36]. One of these studies even found that of the NSCLC patients with synchronous primary malignancies, 85% were smokers [19]. Notably, our stage IIIA NSCLC patient had a single brain lesion as well as a positive history of both smoking and COPD. This constellation of patient factors highlights a situation where brain metastasis from the primary NSCLC may seem clinically obvious. In conjunction, medicine's noninvasive ability (i.e., ablative RT) to treat metastatic NSCLC is dramatically improving. With this, a risky biopsy may seemingly have little value-add, yet could alter the course of treatment and possibly extend survival. While the overwhelming majority of brain lesions presenting with NSCLC are metastases, this case further elucidates the possibility of synchronous MPM that must be considered in the differential diagnosis and highlights the importance of metastatic confirmation via biopsy when safe to obtain.

Statement of Ethics

Ethical approval to report this case was obtained from University of Nebraska Medical Center Institutional Review Board (0398-17-EP). Our institution does not require ethical approval for reporting individual cases or case series. Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images. A CARE checklist has been completed and is available as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000543770).

Conflict of Interest Statement

No conflicts of interest.

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Author Contributions

J.C.: investigation, writing original draft, review, and editing. K.C.J.: investigation, reviewing, and editing. B.K.N.: investigation and writing original draft. N.S., M.B., and C.Z.: conceptualization, reviewing, and editing.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of the patient but are available from the corresponding author upon reasonable request.

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