Case Report

Advanced non-small cell lung cancer treated with palliative systemic therapy complicated by calvarial metastasis: a case report

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Background: Bony metastases are often seen in advanced cancers and lead to deterioration in patient quality of life with common complications of pain, bone fractures, and hypercalcemia. While most sites of metastasis to bone are observed in the axial skeleton from patients with a primary lung, breast or prostate cancer, metastases to the calvarium from lung cancer are less common, and thus less likely to be identified and managed.

Case Description: A 69-year-old Caucasian female with advanced non-small cell lung cancer (NSCLC) presented with worsening symptoms of widespread body pain, fatigue, and weight loss. Physical examination was remarkable for a palpable protrusion on the patient's head. Imaging revealed a parieto-occipital calvarial lesion, a likely metastasis from her lung cancer. A previously performed CT-guided lung biopsy was evaluated for actionable tumor markers to allow for more specific and efficacious line of treatments; the patient's tumor had lacked any notable gene mutations. The treatment plan included radiotherapy, combined immunotherapy and chemotherapy consisting of pembrolizumab, pemetrexed, and carboplatin. Despite the treatment, the patient's skull lesion had continued to grow, and her overall condition deteriorated to the point where she required hospice.

Conclusions: Given the unique location of calvarial metastases, early detection appears to correlate with improving patient outcomes and quality of life. A multimodal approach with a high index of suspicion is essential for diagnosing and managing rare presentations of metastatic disease.

Keywords: Non-small cell lung adenocarcinoma; palliative systemic therapy; parietal bone metastasis; oncogenic mutations; case report

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Introduction

Lung cancer imparts the highest mortality rates of any type of cancer in the United States. Post-mortem examinations identified bony metastases in 36% of patients with primary lung cancer. Bony metastases are frequently associated with cancer-related pain and poor outcomes due to a number of complications including pathologic bone fractures and hypercalcemia secondary to metastatic bone disease. Bone metastases are most commonly found in the axial skeleton of patients with a primary breast, prostate, or lung cancer; skull metastases are typically less common and observed in only 3% of cases (1,2). Further magnetic resonance imaging (MRI) studies identify breast cancer as the most common origin of calvarial metastases (54.9%), followed by lung

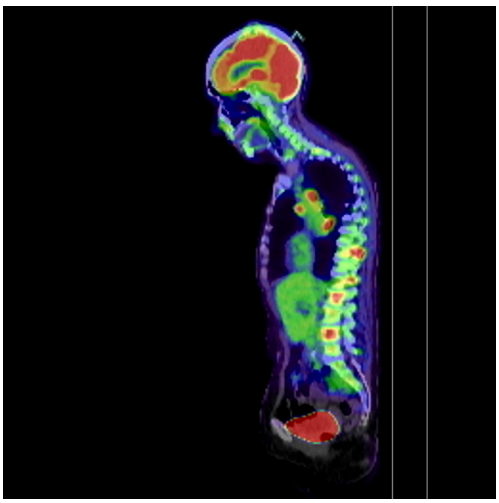

Figure 1 PET scan remarkable for metastasis to right parietal bone, L3-L5, right ilium (not shown in pane), left ischium (not shown in pane). PET, positron emission tomography.

cancer (14.3%), and prostate cancer (6.3%) (3).

In this report, we present the case of a 69-year-old Caucasian female diagnosed with advanced non-small cell lung adenocarcinoma and a rapidly progressing solitary calvarial metastasis. This case is of significant clinical consideration due to the lack of specific treatment guidelines in the literature of primary lung adenocarcinoma with skull metastases. Additionally, the patient's tumor lacked oncogenic driver mutations, such as epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase fusion oncogene (*ALK*), which are normally found in over 50% of lung adenocarcinomas (4), causing challenges in personalized, genotype-directed therapy. We present the following article in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1038/rc).

Case presentation

A 69-year-old Caucasian female presented to a community hospital from home with the chief complaint of worsening fatigue, confusion, and left sided weakness. History was significant for hypertension, chronic obstructive pulmonary disease (COPD) (with >40 tobacco pack year history), hepatitis C and newly diagnosed lung adenocarcinoma (T4N3M1c). She was able to answer basic questions but was not fully oriented to place or time and unable to provide a full history. Her spouse reported that the patient had experienced progressive weakness over the last week with eventual loss of movement of her left upper extremity. Associated symptoms included cough and subjective fevers over the past few days as well as weight loss over the past few weeks. Also, she had no known occupational exposure to carcinogens or illicit or recreational substance use. She had no allergies and surgical history was significant for carpal tunnel release. Family history was significant for multiple myeloma in her father and ovarian cancer in her mother.

Four weeks prior, the patient had a lumbar MRI done for back pain that showed lesions in the lumbar spine leading to a PET scan which showed potential sites of bony metastasis, including a mass in the right parietal bone (4.7 cm × 4.3 cm × 3.5 cm) with mild mass effect (*Figure 1*). Upon admission, CT-guided biopsy then revealed right-sided advanced non-small cell lung adenocarcinoma. The tissue was sent for pathological evaluation. Mutation analysis for EGFR mutations and BRAF V600 mutations were negative. Additionally, a fluorescence in situ hybridization (FISH) test using two multiplex problem stain procedures showed no evidence of a rearrangement of ALK (2p23) and ROS1 (6q22). Lastly, PD-L1 testing by immunohistochemistry (IHC) resulted in no PD-L1 expression or tumor proportion score (TPS) <1%. With no evidence of somatic driver mutations (EGFR and ALK) and an undetectable level of PD-L1 expression in the newly found tumor, the patient's antitumor therapy could not be more targeted and the patient was continued on carboplatin, pemetrexed, and pembrolizumab, as well as targeted radiation therapy (*Table 1*).

On examination, the patient was febrile at 101.0 F, tachycardic, and tachypneic with a normal oxygen saturation on ambient air. She appeared chronically ill and cachectic. She had a palpable mass on the right parieto-occipital region of her skull. Pulmonary exam revealed poor inspiratory effort, wheezing, and decreased left-sided breath sounds. On neurological exam, the patient was able to follow commands but was not fully oriented and tangential. She had poor eye tracking to the right and positive dysmetria. Muscle strength was 2/5 in the left upper extremity and 4/5 in the right upper and bilateral lower extremities. Deep tendon reflexes were 1+ in her left upper extremity and 2+ in the rest of her extremities.

Labs were significant for pancytopenia, borderline hypocalcemia and hypophosphatemia. CT scan of head showed a 4.6 cm × 4.8 cm × 6.2 cm rim enhancing destructive lesion on the right parieto-occipital calvarium with a mild mass effect on the brain (*Figure 2*). Additionally,

Table 1 Patient's radiotherapy for widespread metastatic disease

Treatment site	Energy	Dose/fraction (centigray)	Total dose (centigray)	Elapsed days
R. parieto-occipital bone	6×	400	2,000	6
L3-5	15×	400	2,000	6
Right ilium	15×	400	2,000	6
Left ischium	15×	400	2,000	6

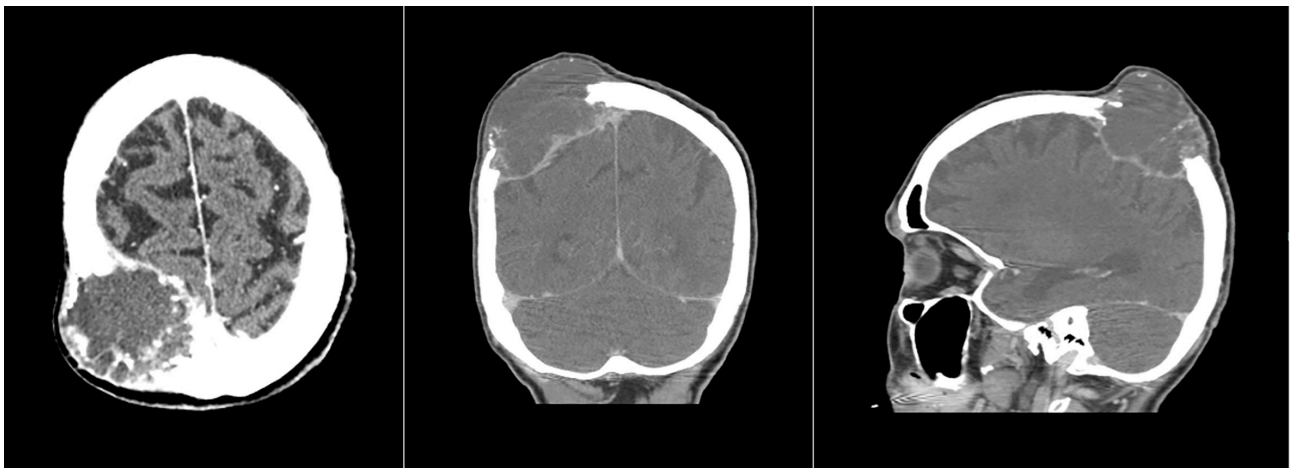

Figure 2 CT scan imaging revealing a solitary metastatic lesion with mass effect. CT, computed tomography.

chest CTA showed a 6.2×5.0 cm right-sided lung mass with new nodules, left-sided pneumonia with pleural effusion and increased size of the metastatic lesions in the right chest wall.

The patient was admitted for sepsis secondary to pneumonia as well as progression in her cancer with worsening neurological findings. She was given antibiotics for pneumonia as well as dexamethasone and levetiracetam prophylactically for seizures. Neurosurgery and oncology were consulted who together determined that the patient was a poor candidate for neurosurgical intervention given her poor functional status and prognosis. Despite the chemotherapy and radiation that she had previously received, there were no improvements in either the primary lung mass or the secondary skull metastasis—in fact there had been progression in both with worsening neurological status and pain. Oncology further recommended that she would be unlikely to tolerate any additional chemotherapy or radiology treatments. As the patient had shown no improvement during the hospital course with likely continuation of poor quality of life, palliative services were consulted. She was transitioned to comfort measures, admitted to hospice, and passed away the next evening.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

This report expands upon previous investigations of metastatic lung adenocarcinoma by describing a patient with a unique parietal calvarial lesion. Additionally, a skull metastasis is a rare feature in a patient with primary lung cancer. The key features of this case include the lack of common oncogenic driver mutations (EGFR and ALK) in the primary lung cancer along with a solitary parietal calvarial metastasis. Small molecule EGFR and ALK inhibitors are currently considered first-line therapy for patients with advanced non-small cell lung cancer (NSCLC)

who express these actionable tumor markers (5). The lack of oncogenic driver mutations in our patient led to the use of a combination of radiotherapy, adjuvant chemotherapy and immunotherapy, including pemetrexed, carboplatin, and pembrolizumab.

In patients with NSCLC without EGFR or ALK rearrangements, testing for programmed death ligand 1 (PD-L1) expression is considered the next step in treatment. Pembrolizumab, a humanized monoclonal antibody, interferes with programmed death protein 1 (PD-1) signaling, which can be beneficial in reversing immune tolerance toward tumor "self-antigens" (6). The diagnostic assay found 0% expression of PD-L1 on the patient's tumor cells, further complicating treatment in our patient. Califano *et al.* (6) suggests that with pembrolizumab therapy, unselected populations have a response rate of 14–23%, while patients with PD-L1 expressing tumors have a 16–48% response rate. Therefore, the preferred option of treatment in patients with an unknown or low PD-L1 expression is chemotherapy with adjuvant pembrolizumab. In the phase III Keynote-189 trial, patients with nonsquamous NSCLC were shown to have a greater 12-month overall survival (OS) when receiving adjuvant pembrolizumab rather than treatment with chemotherapy alone. The greatest improvement in OS was shown in patients with greater than 50% PD-L1 expression. However, patients with <1% PD-L1 expression still showed an overall 10% increase in OS with treatment using pembrolizumab and chemotherapy compared to chemotherapy alone (7,8). Additionally, nonsquamous histology is sensitive to pemetrexed in combination with a platinum-based antineoplastic drug, such as cisplatin or carboplatin. Phase III trials comparing pemetrexed plus cisplatin against gemcitabine plus cisplatin showed the former combination to significantly prolong survival (median, 12.6 versus 10.6 months) (9,10). Lastly, carboplatin was administered instead of cisplatin due to a higher therapeutic index.

The rapid clinical progression of our patient's disease led to an invasive calvarial metastasis which enlarged significantly faster than other metastatic lesions and invaded brain parenchyma. There is general consensus regarding the commonality of primary lung adenocarcinoma metastasizing to the brain; the route of metastasis has not been well identified and many possible mechanisms have been proposed in literature (11). For instance, highly vascularized primary metastasis in mandibular lymph nodes serves to seed new metastatic lesions in adjacent soft tissue through both lymphatic and hematogenous channels (12). Another article concurs, stating the cranium is the site of blood-borne metastases of various malignancies (3). This multifactorial route of spread is plausible due to the rich perfusion to the scalp, dura, cranium, and the extensive drainage system of the dural venous sinuses. In general, calvarial metastases, found in 15–25% of all cancer patients, occurs through three well-identified routes: (I) via direct extension through cranial foramina, (II) retrograde seeding through Batson venous plexus, or (III) hematogenous spread (13). Hematogenous spread appears to be the most common mechanism for brain metastasis as evidenced by the predilection of brain metastasis to appear at the junction of white and gray matter (14). This area contains smaller diameter blood vessels that can stagnate tumor cells. Additionally, brain metastases are more common in areas with less blood flow compared to relative weight. As such, 80 percent of brain metastasis occurs to the cerebral hemispheres with "watershed area", while only 15 and 5 percent occur to the cerebellum and brainstem, respectively (15). Lastly, the type of primary cancer retains a role in establish the area of metastases. Metastases from lung cancers are unique in being equally distributed throughout the brain, while prostatic, uterine, gastrointestinal, and breast tumors are most commonly found to metastasize to the posterior fossa due to cell surface properties of these tumor cells (16).

While there remain many uncertainties about the exact pathophysiologic mechanisms of metastases to the calvarium and brain, the clinical implications of brain metastases also warrants more attention to provide improvements in patient outcomes. The mass effect of our patient's calvarial lesion, resulting in pain and neurological dysfunction, posed further challenges in treatment. Our patient presented with mental status changes, poor eye tracking, decreased muscle strength, and reduced deep tendon reflexes. A study on patients with invasive leptomeningeal metastases showed consistencies with our patient's presentation and suggested that invasion into the dura and intradural space results in increased intracranial pressure, meningeal irritation, and focal neurological signs (17). The clinical manifestations of brain metastasis are profound and can involve focal neurologic dysfunction, seizures, and strokes. While the cumulative incidence of brain metastases in patients with lung cancer is only noted to be 16 to 20 percent, there is reason to suggest that brain metastases are much more common than diagnosed. In a review of autopsy series, brain metastases were found in as many as 64 percent of patients dying from lung cancer (18).

The clinical implication of this would be to be more vigilant in considering brain metastases in cancer patients with that presents with complaints of memory problems, mood or personality changes, new-onset seizures, and other common clinical manifestations of brain metastases. Additional testing with contrast enhanced MRI can help provide a diagnosis. Survival of patient with brain metastases has also improved with systemic therapy and surgical advances. For example, stereotactic radiosurgery (SRS) has been more widely available and is regarded as more efficacious and safer than whole brain radiation therapy (WBRT) (19).

Similar studies have shown early detection, testing for actionable tumors markers, and prompt treatment of calvarial metastases can be crucial towards improved outcomes. Turner *et al.* reports a fronto-parietal mass as the first clinical presentation of a calvarial metastasis with subsequent diagnosis of a primary lung adenocarcinoma. The prominent posterior location of the lesion as well as the extent of pain this patient experienced allowed for early detection and resulted in a favorable outcome following surgical intervention and chemotherapy. Similarly, Mengoli *et al.* (20) identifies a 55-year-old woman who complained of neurologic dysfunction and was found to have a fronto-parietal mass secondary to lung adenocarcinoma. In this case, pathologic examination of the lesion identified a distinct EGFR mutation; treatment with an EGFR inhibitor allowed the patient to reach stable disease status. Of note, our patient presents with a unique location of her aggressive calvarial metastasis in the parieto-occipital region. The lack of mutations in EGFR or ALK and PD-L1 expression also distinguished this case as these factors ultimately affected the treatment she could receive.

One of the pathologic features of primary lung adenocarcinoma is metastatic lesions to the bone; these secondary tumors cause significant pathology in local tissue and around the body. This report presents a case of calvarial metastatic lesion secondary to lung adenocarcinoma. Along with its unusual location in the posterior head, which could have been a factor in the delayed diagnosis, the tumor presented a unique challenge to treat as it lacked oncogenic driver mutations. The patient was ultimately treated with a combination of radiation therapy, cytotoxic chemotherapies and small molecule immunotherapy. Despite this combination approach, the tumor continued to grow and caused significant pathology. These unique aspects of this case include the solitary lesion itself, which grew much faster than other metastatic lesions in the patient's lungs and axial skeleton. The lesion also lacked oncogenic driver mutations and had negligible expression of PD-L1. This case prompts a more detailed look into the use of immunotherapy in lesions without significant PD-L1 expression as well as further investigation into possible routes of metastasis to this unique location. Most importantly, it is critical to raise awareness and suspicion index of these lesions amongst clinicians and employ a multimodality approach for early recognition and treatment for their patients with this time sensitive and highly mortal disease.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1038/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1038/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1038/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Qin A, Zhao S, Miah A, et al. Bone Metastases, Skeletal-Related Events, and Survival in Patients With Metastatic Non-Small Cell Lung Cancer Treated With Immune Checkpoint Inhibitors. J Natl Compr Canc Netw 2021;19:915-21.
2. Sugiura H, Yamada K, Sugiura T, et al. Predictors of survival in patients with bone metastasis of lung cancer. Clin Orthop Relat Res 2008;466:729-36.
3. Mitsuya K, Nakasu Y, Horiguchi S, et al. Metastatic skull tumors: MRI features and a new conventional classification. J Neurooncol 2011;104:239-45.
4. Greulich H. The genomics of lung adenocarcinoma: opportunities for targeted therapies. Genes Cancer 2010;1:1200-10.
5. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
6. Califano R, Lal R, Lewanski C, et al. Patient selection for anti-PD-1/PD-L1 therapy in advanced non-small-cell lung cancer: implications for clinical practice. Future Oncol 2018;14:2415-31.
7. Rodríguez-Abreu D, Powell SF, Hochmair MJ, et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. Ann Oncol 2021;32:881-95.
8. Gadgeel S, Rodríguez-Abreu D, Speranza G, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol 2020;38:1505-17.
9. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-51.
10. Syrigos KN, Vansteenkiste J, Parikh P, et al. Prognostic and predictive factors in a randomized phase III trial comparing cisplatin-pemetrexed versus cisplatin-gemcitabine in advanced non-small-cell lung cancer. Ann Oncol 2010;21:556-61.
11. Turner RC, Lucke-Wold BP, Hwang R, et al. Lung cancer metastasis presenting as a solitary skull mass. J Surg Case Rep 2016;2016:rjw116.
12. Wu T, Jiao Z, Li Y, et al. Brain Metastases From Differentiated Thyroid Carcinoma: A Retrospective Study of 22 Patients. Front Endocrinol (Lausanne) 2021;12:730025.
13. Yatsu FM. Neurology in Clinical Practice: The Neurological Disorders, 4th ed. Neurology 2004;62:1657.
14. Aisner DL, Riely GJ. Non–small cell lung cancer: Recommendations for Biomarker Testing and treatment. J Natl Compr Canc Netw 2021;19:610-3.
15. Hu X, Peng F, Chen M, et al. A study of the prognosis of patients with limited-stage SCLC who did not receive prophylactic cranial irradiation after chemoradiotherapy. J Thorac Oncol 2021;16:S178.
16. Quattrocchi CC, Errante Y, Gaudino C, et al. Spatial brain distribution of intra-axial metastatic lesions in breast and lung cancer patients. J Neurooncol 2012;110:79-87.
17. Curcean A, Curcean S, Rescigno P, et al. Imaging features of the evolving patterns of metastatic prostate cancer. Clin Radiol 2022;77:88-95.
18. Mori Y. EP-1688: Evaluation of Automatic Brain Metastasis planning for multiple brain metastasis. Radiotherapy and Oncology 2016;119:S788-9.
19. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol 2014;15:387-95.
20. Mengoli MC, Rossi G, Tiseo M, et al. 'Turban-like' skull metastasis from pulmonary adenocarcinoma. Thorax 2017;72:767-8.

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