Current Problems in Cancer 44 (2020) 100530

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Tumor Board Report: The value of tissue diagnosis

Adham Hijab[a], Ayelet Eran[b], Tzahala Tzuk-Shina[c], Orit Kaidar-Person[a,c,*]

[a] Radiation Oncology Unit, Oncology Institute, Rambam Medical Center, Haifa, Israel
[b] Radiology Department, Rambam Medical Center, Haifa, Israel
[c] Neuro-Oncology Unit, Oncology Institute, Rambam Medical Center, Haifa, Israel

A B S T R A C T

Intracranial lesions in the presence of a known cancer are highly suspicious for brain metastases. Lung cancer is the most common solid tumor responsible for brain metastases. This case emphasizes the importance of multidisciplinary tumor boards including a dedicated neuroradiologist in the management of patients with cancer.

A R T I C L E I N F O

Keywords: Lung cancer; CNS; Brain tumor; Glioblastoma; Radiation therapy

Clinical presentation

A 74-year-old male patient was referred to chest imaging due to productive cough, hemoptysis, and weight loss. Chest X-ray revealed a suspicious mass located in the right upper lobe. The patient underwent a chest CT scan which was significant for a lesion measuring $8 \times 8.6 \times 10$ cm in the apex of the right lung with direct involvement of the ribs and extrapulmonary exten-

☆ Conflict of interest: None.

* Correspondence to: Orit Kaidar-Person, MD, Radiation Oncology Unit, Neuro-Oncology Unit, Oncology Institute, Rambam Medical Center, Haifa, Israel.
E-mail address: o_person@rambam.health.gov.il (O. Kaidar-Person).

https://doi.org/10.1016/j.currproblcancer.2019.100530
0147-0272/

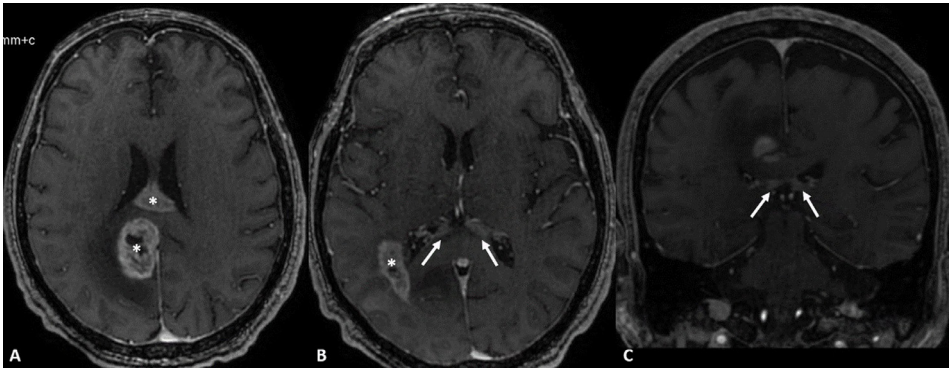

Fig. 1. Axial (A, B) and coronal (C) T1-weighted images following intravenous contrast administration showing multiple enhancing brain lesions (asterisks A, B). The lesions are located in the right parietal and temporal lobes, and in the corpus callosum with extension to cerebral fornices bilaterally (arrows).[15,25]

sion toward the thoracic inlet. A CT-guided fine needle aspiration showed poorly differentiated nonsmall carcinoma (NSCLC) positive for both TTF1 and P40. TTF1 is present in up to 76% of lung adenocarcinoma and rarely in squamous cell carcinoma,[1] whereas P40 is highly specific for squamous cell carcinoma with only 6% of adenocarcinoma staining weakly positive for it.[2] Therefore, a pathological diagnosis of adenosquamous cell carcinoma was established. Molecular studies did not show any targetable driver mutations or translocation (EGFR, ALK, and ROS1) and PDL1 staining was positive in only 5% of tumor cells. Afterward, the patient underwent a Ffluorodeoxyglucose-Positron emission tomography-computed tomography (FDG-PET-CT) scan which showed similar findings to those demonstrated in the chest CT scan with ipsilateral hilar nodal involvement without evidence of distant metastasis. Consequently, the disease was staged as IIIA (T4N1M0). Shortly after his diagnosis, the patient developed right ptosis along with paresthesia and pain in his right arm––a clinical picture very suggestive for Horner syndrome secondary to his malignant disease. Based on the given findings, the patient was planned for definitive chemoradiation. However, he was hospitalized before the initiation of radiotherapy due to sudden left hemiparesis and dizziness, his brain CT scan showed a suspicious lesion in the right parietal lobe. A brain Magnetic resonance imaging (MRI) demonstrated 3 enhancing lesions surrounded by edema; one cortical and subcortical lesion in the right parietal lobe, another lesion lateral to the right atrium in the temporal lobe and a third lesion in the posterior aspect of the corpus callosum that extends to cerebral fornices bilaterally (Fig. 1).

Differential diagnosis

Intracranial lesions in the presence of a known cancer are highly suspicious for brain metastases. Moreover, lung cancer is the most common solid tumor responsible for brain metastases. Approximately 10% of all newly diagnosed patients with advanced NSCLC have brain metastasis. Risk factors associated with the presence of brain metastasis from lung cancer include adenocarcinoma histology, high tumor grade, node-positive disease, large tumor size, and younger age.[3] Some studies indicate that patient with EGFR mutation or ALK rearrangement tends to develop more brain metastases compared to other NSCLC. Conversely, around 40% to 50% of patients with brain lesions suspicious of metastasis harbor primary lung cancer.[4,5]

Brain metastases from solid tumors usually show enhancement on MRI which is most often well-defined and uniform but may be ring-enhancing. On Fluid-attenuated inversion recovery (FLAIR), metastases typically appear as hyperintense with hyperintense peritumoral edema. In the presented case there are multiple lesions, nevertheless they are clustered in one region and involve the corpus callosum with extension to cerebral fornices. This is not a typical imaging

for brain metastases. Therefore, high-grade glioma as additional differential diagnosis comes to mind per imaging.

The age-adjusted incidence rates for all high grade gliomas range from 4.67 to 5.73 per 100,000 persons.[6,7] Therefore, based on statistics and clinical history alone, the diagnosis of brain metastasis seems far more likely in a patient with locally advanced NSCLC than the diagnosis of second primary central nervous tumor. However, the incidence of high-grade glioma rises with age and significantly changes the management of the patient in this case. Eventually, it was decided to obtain a tissue diagnosis from the brain lesion and the biopsy revealed fragments of glioblastoma.

Treatment approach

In view of the possibility of a second primary of high-grade glioma, it was imperative to achieve tissue diagnosis from the intracranial lesion. A stereotactic biopsy was done, as it is a relatively safe and fast procedure. If the brain lesion was found to be a metastasis, the patient could potentially be treated with front-line combination of chemotherapy and PD1 blockers which could significantly improve overall and progression free survival compared to chemotherapy alone.[1] The brain metastasis could be treated with radiation. Current reports indicate that PD1 blockers have activity in untreated NSCLC brain metastases, thus this option should be discussed with the patient as a potential approach.[2]

In the presented case, the primary brain tumour is the key determinant of the patient's prognosis. Unfortunately, the prognosis of high grade gliomas is still poor with 5-year overall survival around 5% and there is still no established role of immune checkpoint inhibitors in treating this disease.

Due to rapid symptomatic progression in both sites, urgent local treatments were needed. Both diseases were considered inoperable due to their locally advanced nature/location. After tumor board discussion, considering the patient's age, disease type and stage, chemoradiation was considered a valid treatment approach for both sites. However, important considerations in this case were choosing effective and safe dose-fractionation regimens of radiation therapy that could be delivered in a short period of time in order to allow treating both sites in a reasonable time manner without compromising therapy or increasing toxicity. Another important questions are which site should be treated earlier to reduce potential harm for the patient and what are the optimal systemic therapies that could be effective in treating both malignancies.

Anticancer therapy

Traditional radiation therapy for inoperable NSCLC constitutes of 60 Gy delivered in 30 fractions given concomitantly with systemic chemotherapy. Had this regimen been applied in our case, the treatment for the glioblastoma would have been delayed for at least 6 weeks. Our estimation that the patient will not tolerate simultaneous radiation to both sites. Furthermore, given the grim prognosis and incurable nature of his primary brain tumor, the benefit and survival advantage obtained from radical radiation treatment to the lung tumor was questioned. Hypofractionated radiation therapy for locally advanced NSCLC could offer good local control rates and good palliation; therefore it was decided to treat the lung tumor with 30 Gy in 10 fractions given with concomitant weekly carboplatin and paclitaxel. This allowed for a fast symptomatic relief and time to plan treatment for the intracranial disease.

Prior to initiating radiation to the lung lesion, the patient had already received 2 courses of weekly carboplatin (area under the curve [AUC] 2) and paclitaxel (80 mg/m^2 which was subsequently reduced to 45 mg/m^2 with the initiation of radiotherapy). This radiosensitizing regimen was chosen due to its good tolerability profile. Of note, carboplatin had also been shown to have modest efficacy in high grade gliomas.[8]

Radiation therapy is part of the standard therapy for high-grade gliomas. It is usually given in a total dose of 60 Gy in 30 fractions with concomitant temzoloamide. However, shorter courses of chemoradiation can be used for older patients without compromising outcomes.[9,10] Based on the patient's age, performance status, and with the thought that the patient will be given adjuvant chemotherapy for the lung lesion (thus, preferably a shorter radiation course). The patient was treated with a total radiation dose of 39 Gy in 13 fractions[11] with concomitant temzoloamide. This protocol is similar to the protocol used for elderly patients (40.5 Gy in 15 fractions). As the patient had symptoms from his lung malignancy and had difficulty in laying on his back with a thermoplastic mask for treatment of his intracranial lesion, we a short protocol for the brain lesion was used. This also allowed for applying adjuvant chemotherapy as soon as possible.

Adjuvant chemotherapy

One very important question in this case is how this patient should be treated after the completion of local therapies. Adjuvant temozolamide had been shown to improve survival and progression-free-survival in glioblastoma, yet it has limited efficacy in NSCLC. The histologic component of the NSCLC that might represent poorly differentiated squamous cell carcinoma raises concerns regarding the use of Bevacizumab since its use was reported to be associated with life-threatening hemorrhage. Moreover, while the use of Bevacizumab can prolong progression-free-survival in second or further line therapies in gliomas, there is no evidence supporting its use in the primary setting. One option that was favorably considered in this case was a combination of carboplatin and vinorelbine which is an effective regimen in NSCLC. Both these agents also proved to be effective in treating patients with gliomas,[12,13] thus this regimen can potentially address both malignancies effectively.

Novel systemic therapies

In the current case, the lung tumor did not harbor translocation in ALK1 or mutations in EGFR and ROS1. Therefore, the patient is not a candidate for targeted systemic therapy.

Immune checkpoint inhibitors, mainly PD1 and PDL1 inhibitors, are radically changing the treatment landscape of various malignancies. Several prospective randomized trials showed that immunotherapies are effective in treating NSCLC both as monotherapy as well as in combination with chemotherapy in the first line setting for patients whose tumors express high levels of PDL1 and in the second line setting regardless of PDL1 status.[14-18] Moreover, adjuvant treatment with PDL1 inhibitors (Durvalumab) after chemoradiotherapy in stage III NSCLC had been shown to improve progression-free-survival as well as overall survival.[19] On the other hand, current literature still does not provide consistent evidence that these agents are effective in gliomas. A phase III trial which directly compared the efficacy and safety of nivolumab monotherapy vs bevacizumab in patients with glioblastoma with first recurrence after chemoradiation failed to reach its primary end-point of superior overall survival in the nivolumab arm.[20] Furthermore, objective response rates were less common in the nivolumab arm. Yet, in patients who responded to nivolumab, the response was more durable. Several predictive biomarkers that could positively correlate with the efficacy of immunotherapy had been studied, most important of those are microsatellite instability (MSI), high tumor mutational burden (TMB), and PDL-1 expression. A study conducted by Bonviell et al showed that the prevalence of MSI in glioblastoma is only 0.25%.[21] Hodges et al demonstrated that high TMB was found in only 3.5% of GBM patients.[22] Of note, in the previously mentioned study that compared head to head bevacizumab with nivolumab, objective response rates were higher in the bevacizumab arm also among patients that had PDL1 expression $\geq$1%. Thus based on the current molecular landscape of glioblastoma, it seems that anti-PD1 agents have limited efficacy as monotherapy and would not be a good treatment option in case of GBM progression.

It would seem sensible to consider treatment with immune check point inhibitors in the case of extracranial progression which would be attributable to the lung tumour coupled with a stable intracranial disease.

Tumor treating fields (TTF) is an emerging modality in the treatment of primary and relapsing glioblastoma. In a randomized prospective trial, the incorporation of TTF with adjuvant temozolamide improved median progression-free-survival and overall survival compared to adjuvant temozoloamide alone.[23] This modality is currently evaluated for NSCLC brain metastases without favorable mutations (NCT02831959). Therefore, this treatment option could also be considered in our case.

Summary

After reviewing the current literature and taking into account patient's age, performance status and disease stage. We pursued hypofractioned chemoradiation strategies for both sites. Treatments were well tolerated without any significant adverse effects. After the completion of the treatments, the patient experienced some improvement in his arm and chest pain (secondary to the lung tumor) and in his dizziness. A CT scan done 1 month after the end of therapies showed an objective response in his lung tumor and a stable disease in the brain.

This case emphasizes the importance of multidisciplinary tumor boards in the management of patients with cancer. First, we demonstrated how diagnostic evaluation could be optimized with the integration of a dedicated neuroradiology expert and we highlight that the diagnosis of metastases in a patient with an established diagnosis of cancer should not be straightforward. Indeed, in the study of Patchell et al, which intended to evaluate the role of surgical resection of brain metastases from primary extracranial primary tumors, 6 out of 54 enrolled patients (11%) proved on resection or biopsy not to have brain metastases, with 3 of those proved to be gliomas and the others benign disorders.[24] Second, some patients require the cooperation of 2 or more dedicated teams dealing with different tumor types. In our case, there was a close cooperation between the thoracic oncology and neuro-oncology units in order to choose the treatment strategies and to coordinate the timing of treatments. Finally, choosing the optimal sequential systemic treatment after local treatments is not always clear. Different tumors demonstrate heterogeneous sensitivity to cytotoxic agents, thus it is not always trivial to choose systemic agents. Moreover, as we stated before, the effective utilization of immunotherapy is still restricted to certain types of tumors while in other cancers the results are less encouraging. Tumor board discussions in such intricate cases allow beneficial inputs from site-specialized experts so that effective as well as safe treatments could be chosen.

References

1. Stenhouse G, Fyfe N, King G, Chapman A, Kerr KM. Thyroid transcription factor 1 in pulmonary adenocarcinoma. *J Clin Pathol*. 2004;57:383–387. doi:10.1136/jcp.2003.007138.
2. Lilo MT, Allison D, Wang Y, et al. Expression of P40 and P63 in lung cancers using fine needle aspiration cases. Understanding clinical pitfalls and limitations. *J Am Soc Cytopathol*. 2016;5:123–132. doi:10.1016/j.jasc.2015.07.002.
3. Devarakonda S, Waqar SN, Samson PP, et al. Non–small-cell lung cancer with brain metastasis at presentation. *Clin Lung Cancer*. 2018;19:e373–e379. doi:10.1016/j.cllc.2018.01.007.
4. Schouten LJ, Rutten J, Huveneers HAM, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer*. 2002;94:2698–2705. doi:10.1002/cncr.10541.
5. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients in the metropolitan Detroit cancer surveillance system. *J Clin Oncol*. 1973;22:2865–2872. doi:10.1200/JCO.2004.12.149.
6. Larjavaara S, Mäntylä R, Salminen T, et al. Incidence of gliomas by anatomic location. *Neuro Oncol*. 2007;9:319–325. doi:10.1215/15228517-2007-016.
7. Gousias K, Markou M, Voulgaris S, et al. Descriptive epidemiology of cerebral gliomas in Northwest Greece and study of potential predisposing factors, 2005–2007. *Neuroepidemiology*. 2009;33:89–95. doi:10.1159/000222090.
8. Warnick RE, Prados MD, Mack EE, et al. A phase II study of intravenous carboplatin for the treatment of recurrent gliomas. *J Neurooncol*. 1994;19:69–74. http://www.ncbi.nlm.nih.gov/pubmed/7815106 .

9. Malmström A, Grønberg BH, Marosi C, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: The Nordic randomised, phase 3 trial. *Lancet Oncol*. 2012;13:916–926. doi:10.1016/S1470-2045(12)70265-6.
10. Wick W, Laigle-Donadey F, Menten J, et al. Short-course radiation plus temozolomide in elderly patients with glioblastoma. *N Engl J Med*. 2017;376:1027–1037. doi:10.1056/nejmoa1611977.
11. Janssens GO, Jansen MH, Lauwers SJ, et al. Hypofractionation vs conventional radiation therapy for newly diagnosed diffuse intrinsic pontine glioma: A matched-cohort analysis. *Int J Radiat Oncol*. 2013;85:315–320. doi:10.1016/j.ijrobp.2012.04.006.
12. Cappellano AM, Bouffet E, Silva F, et al. Vinorelbine in progressive unresectable low-grade glioma in children. *J Clin Oncol*. 2011;29(15_suppl):9524 -9524. doi:10.1200/jco.2011.29.15_suppl.9524.
13. Cappellano AM, Petrilli AS, da Silva NS, et al. Single agent vinorelbine in pediatric patients with progressive optic pathway glioma. *J Neurooncol*. 2015;121:405–412. doi:10.1007/s11060-014-1652-6.
14. 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;375:1823–1833. doi:10.1056/NEJMoa1606774.
15. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med*. 2018;378:2078–2092. doi:10.1056/NEJMoa1801005.
16. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non–small-cell lung cancer. *N Engl J Med*. 2018;379:2040–2051. doi:10.1056/NEJMoa1810865.
17. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. *N Engl J Med*. 2015;373:1627–1639. doi:10.1056/NEJMoa1507643.
18. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. *N Engl J Med*. 2015;373:123–135. doi:10.1056/NEJMoa1504627.
19. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer supplementary appendix this. *N Engl J Med*. 2017 NEJMoa1709937. doi:10.1056/NEJMoa1709937.
20. Reardon DA, Omuro A, Brandes AA, et al. OS10.3 randomized phase 3 study evaluating the efficacy and safety of nivolumab vs bevacizumab in patients with recurrent glioblastoma: CheckMate 143. *Neuro Oncol*. 2017;19(Suppl 3) iii21-iii21. doi:10.1093/neuonc/nox036.071.
21. Bonneville R, Krook MA, Kautto EA, et al. Landscape of microsatellite instability across 39 cancer types. *JCO Precis Oncol*. 2017;2017 10.1200/PO.17.00073. doi:10.1200/PO.17.00073.
22. Hodges TR, Ott M, Xiu J, et al. Mutational burden, immune checkpoint expression, and mismatch repair in glioma: Implications for immune checkpoint immunotherapy. *Neuro Oncol*. 2017;19:1047–1057. doi:10.1093/neuonc/nox026.
23. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: A randomized clinical trial. *JAMA*. 2017;318:2306–2316. doi:10.1001/jama.2017.18718.
24. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med*. 1990;322:494–500. doi:10.1056/NEJM199002223220802.
25. Goldberg SB, Gettinger SN, Mahajan A, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. 2016;17:976–983.