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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Pathological complete response after primary tumor surgery following chemoimmunotherapy and stereotactic radiosurgery of initially metastatic non-small-cell lung cancer

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SUMMARY

Introduction Surgery of the primary tumor following extended course of chemoimmunotherapy has only recently been recognized as a feasible and safe option for selected groups of patients with initially unresectable non-small cell lung cancer.

Case outline Here we report a case of a 49-year-old female patient, who never smoked, that was diagnosed with metastatic non-small cell lung cancer. Lesions were evident in both lungs and the brain. She underwent stereotactic radiosurgery for brain metastases and combination therapy of chemotherapy, atezolizumab and bevacizumab. Response to therapy was both remarkable and durable. Ten cycles into treatment, magnetic resonance imaging of the brain revealed no metastatic lesions. Positron emission tomography / computed tomography revealed a single lesion in the right upper lobe 22 × 23 mm in diameter. The patient underwent a right upper lobectomy. Pathohistological evaluation of the specimen revealed complete pathologic response. The patient recovered from surgery and continued chemoimmunotherapy. Four months post-surgery she is disease free and of excellent performance status.

Conclusion Primary tumor surgery following extensive chemoimmunotherapy regiment is feasible and could be considered as a treatment option. Further research is warranted to define a patient population that stands to benefit the most from this modality.

Keywords: chemoimmunotherapy; combination therapy; atezolizumab; lung cancer; thoracic surgery

INTRODUCTION

Immune checkpoint inhibitors (ICI) based therapies have become standard of care for the treatment of metastatic non-oncogene addicted non-small cell lung cancer (NSCLC) leading to significant and durable responses in some patients [1]. Recently, surgery of the primary tumor following extended course chemoimmunotherapy therapy has been deemed feasible and safe in selected patients with initial diagnosis of unresectable NSCLC [2, 3]. While there is evidence that local radical therapy is beneficial aid to immune checkpoint inhibitor based systemic therapy in improving clinical outcomes of patients with oligometastatic NSCLC, the role of primary tumor surgery remains undefined [1]. Here we report a case of an oligometastatic NSCLC patient that successfully underwent primary tumor surgery following remarkable response to extended course of chemoimmunotherapy, antiangiogenic agent, and stereotactic radiosurgery (SRS).

CASE REPORT

A previously healthy 49-year-old female patient, who never smoked, presented to the emergency room after a transient loss of consciousness. Magnetic resonance imaging (MRI) of the brain revealed four lesions – two in the left temporal lobe and another two in the left frontal lobe. Further radiographic evaluation of the chest and upper abdomen revealed a spiculated lesion in the right upper lobe 55 × 43 mm in diameter, a subpleural nodule in the left upper lobe 10 mm in diameter. Signs of necrosis were evident in the right hilar mediastinal lymph nodes (Figure 1). Pathohistological evaluation of transbronchial biopsy specimen of the lesion in the left upper lobe confirmed the diagnosis of lung adenocarcinoma. Results of *EGFR* mutations and *ALK* translocations testing came back negative, and the tumor was found to have programmed death ligand1 (PD-L1) tumor proportion score (TPS) of 10%. Given her excellent performance status decision was made to start the treatment with the combination of chemotherapy, atezolizumab, and bevacizumab. The patient also underwent SRS procedure for

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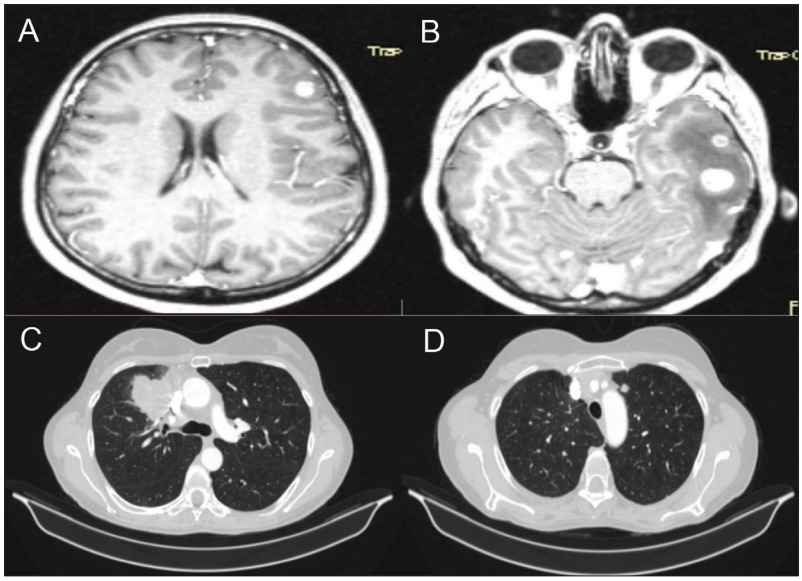

Figure 1. Magnetic resonance imaging of the brain revealing brain metastases in the left frontal and temporal lobes (A, B); multi-slice computer tomography of the chest showing tumor mass in the right upper lobe (C), and a spiculated nodule in the left upper lobe (D) as well as mediastinal lymphadenopathy

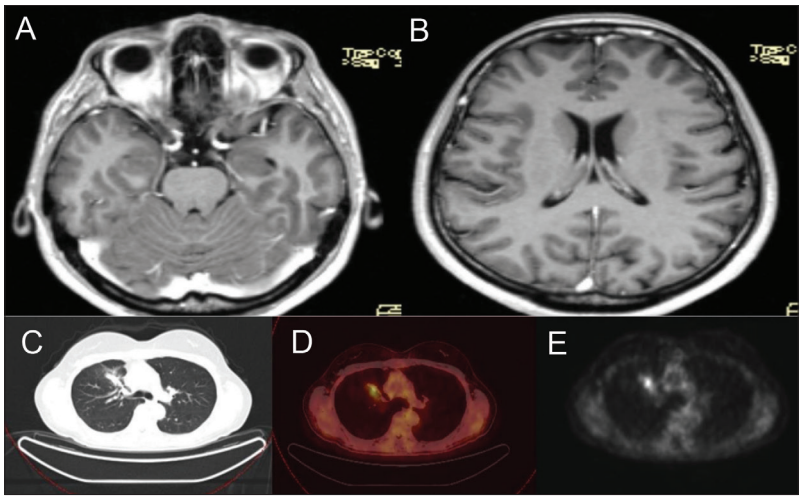

Figure 2. Magnetic resonance imaging of the brain preformed after stereotactic radiosurgery procedure with no detectable lesions (A, B); positron emission tomography / computed tomography following ten cycles of systemic therapy, showing a maintained partial response to therapy and a significant radiopharmaceutical uptake in markedly reduced tumor mass (C, D, E)

the treatment of brain metastases (BM). The radiographic evaluation following the first four cycles revealed partial response per iRECIST criteria with more than 45% reduction in sum of target lesion diameter. MRI of the brain following the SRS procedure showed complete disappearance of the lesions without residual signal changes. Following the eighth cycle of therapy, a further reduction of 17% of sum of target lesions was displayed. Ten cycles into treatment another MRI of the brain revealed no metastatic lesions and PET/CT was performed. (Figure 2) Significant uptake of fludeoxyglucose (SUVmax 4.8) was evidenced only in the lesion in the right upper lobe now 22 × 23 mm in diameter and in the right hilar lymph nodule. The patient underwent a right upper lobectomy with the removal of 12 lymph nodes from the 4R,10R,11R and seventh station ten months after commencing the treatment with chemoimmunotherapy. The postoperative period was uneventful. Pathohistological evaluation of the surgical specimen revealed a pathologic complete response (pCR). She has since continued atezolizumab-bevacizumab therapy and is without tumor reoccurrence four months after surgery.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments and comparable ethical standards. Written consent to publish all shown material was obtained from the patient.

DISCUSSION

Chemoimmunotherapy is now the standard of care for patients with metastatic non-oncogene addicted NSCLC with PD-L1 TPS of 1–49% [1]. With several chemoimmunotherapy regiments recommended, selecting the optimal for a particular patient is a task encountered repeatedly by tumor boards worldwide. Siciliano et al. [4] compared different ICI based treatment strategies for advanced NSCLC in a recently published metanalysis. They found that atezolizumab-bevacizumab-chemotherapy was best ranked in terms of progression free survival (PFS) in non-squamous NSCLC and PD-L1 TPS 1-49% subgroups of patients. Atezolizumab-bevacizumab-chemotherapy ranked best overall for objective response rates [4]. Impressive objective response rates and estimated PFS make this regiment suitable for downstaging of advanced non-squamous NSCLCs as evidenced in our patient's case.

Repots and case series of primary tumor surgeries following downstaging after systemic mono-ICI therapy only recently started surfacing as operating on such patients was deemed risky due to mediastinal and hilar fibrosis that occurs in response to ICI treatment, proving their feasibility in selected group of patients [3, 5, 6, 7]. Recently, reports of patients safely undergoing pulmonary resection following chemoradiotherapy and durvalumab maintenance for initially unresectable NSCLC have been described [6]. This highlights the feasibility of primary tumor surgery even in situations where higher rates of mediastinal and hilar fibrosis are expected.

Chemoimmunotherapy regiments have now found their place in neoadjuvant setting. Results of CheckMate816 trial, evaluating nivolumab-chemotherapy versus chemotherapy alone as neoadjuvant regiment for resectable NSCLC demonstrated significant rates of pCR in the experimental arm (24% *vs*. 2.2%, $p < 0.0001$) highlighting the efficacy of ICIs in this setting [8]. Similar rates of pCR (23.1%)

were observed by Galetta et al. [3] in patients undergoing surgery of primary tumors for previously unresectable NSCLC after tyrosine kinase inhibitor and ICI treatment. After median follow-up of 28.7 months, 82% of patients were alive and the projected five-year survival rate is 66% [3]. In another publication, Higuchi et al. [2] reported pCR rate of 30.8% and two year overall survival rate of 76.2% for advanced NSCLC patients that received mono or chemoimmunotherapy. The median systemic treatment duration prior to surgery of the primary tumor was 10.1 months, similar to our case. None of the patients' treatment regimen however, included an antiangiogenic agent. To the best of our knowledge this is the first case of surgery of the primary tumor following the systemic treatment that includes chemotherapy, atezolizumab and bevacizumab for metastatic NSCLC [2]. Both publications mentioned above included patients with BM at baseline, showing that surgery of primary tumor could be considered following BM treatment. He et al. [9] found that upfront treatment of BM followed by surgery of primary NSCLC was associated with improved survival. Authors concluded that it was the patients that received brain surgery as opposed to radiotherapy for BM treatment derived the most benefit [9]. None of the patients however received ICI in the mentioned study. The abscopal effect has been well recognized, therefore it could be hypothesized that the patients on ICI based therapy stand to benefit more from the addition of BM radiotherapy than those treated with chemotherapy alone [10]. In addition to that, bevacizumab is thought to trigger T-reg cell proliferation and increase T cell infiltration and thus could have contributed to chemoimmunotherapy efficacy in our case [11]. Furthermore, an exploratory analysis of IMpower150 trial found that combination of atezolizumab and bevacizumab could delay the onset of new brain lesions [12]. With all of this in mind decision has been made to continue with the atezolizumab-bevacizumab maintenance therapy as per IMpower150 trial protocol following surgery of the primary tumor [12]. Oligometastatic NSCLC is a vaguely defined condition due to its heterogeneity, but it is thought to be best managed by combining systemic and local radical therapy [1] Surgery of the primary tumor after downstaging is now considered feasible following extended course of chemoimmunotherapy and could provide a good chance for long-term survival for some initially unresectable NSCLC patients. Pathological downstaging and pCR rates after surgery for initially unresectable NSCLC, post-extended chemoimmunotherapy are similar to those in pivotal neoadjuvant trials for resectable NSCLC. pCR has been adopted as an endpoint in neoadjuvant trials for resectable NSCLC and has been associated with favorable clinical outcomes [8]. Its role should be carefully evaluated in patients with initial diagnosis of metastatic NSCLC even after successful downstaging, as it may not reflect complete eradication of the disease thus leaving a gap in knowledge regarding the optimal postoperative treatment and follow-up strategies.

Due to the present widespread use of chemoimmunotherapy and its efficacy, more patients are expected to be eligible for surgery of the primary tumor following downstaging. Further research is warranted to define a patient population that stands to benefit the most from this modality as opposed to multidisciplinary treatment without it.

Conflict of interest: None declared.

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Комплетан патолошки одговор после операције примарног тумора и примене хемоимунотерапије и стереотактичне радиохирургије иницијално метастатског неситноћелијског карцинома плућа

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САЖЕТАК

Увод Хирургија примарног тумора после дуготрајног лечења хемоимунотерапијом недавно је препозната као изводљива и безбедна опција за одабране групе болесника с иницијално нересектабилним неситноћелијским карциномом плућа.

Приказ болесника Представљамо случај 49-годишње болеснице, непушача, код које је дијагностикован метастатски неситноћелијски карцином плућа. Иницијално метастатске лезије биле су присутне у оба плућна крила и мозгу. Мождане метастазе су третиране стереотактичном радиохирургијом, а системско лечење је започето применом хемотерапије, атезолизумабом и бевацизумабом. Одговор на терапију био је изузетно добар и дуготрајан. После десет циклуса терапије, на магнетној резонанци ендокранијума нису детектоване метастатске лезије. Скрининг позитронском емисионом томографијом / компјутеризованом томорафијом открио је само једну лезију у десном горњем режњу, димензија 22 × 23 *mm*. Болесница је подвргнута лобектомији десног горњег режња. Патохистолошка анализа узорка показала је потпуни патолошки одговор. Болесница се опоравила и наставила лечење хемоимунотерапијом. Четири месеца после хируршког захвата, болесница је без детектабилне болести и одличног општег стања.

Закључак Хирургија примарног тумора после продуженог режима хемоимунотерапије изводљива је и може се сматрати опцијом лечења. Потребна су даља истраживања како би се дефинисала популација болесника која би највише имала користи од овог начина лечења.

Кључне речи: хемоимунотерапија; комбинована терапија; атезолизумаб; карцином плућа; торакална хирургија