Clinical Oncology: Case Reports

Case Report

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Prolonged Complete Response of Early Stage Primary Adenocarcinoma of the Lung to Nivolumab Monotherapy

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Abstract

Immune checkpoint inhibitors are currently employed for the treatment of various malignancies, including advanced melanoma and non-small cell lung cancer. As more patients are treated with checkpoint inhibitors, situations will arise in which early-stage disease may be subjected, intentionally or unintentionally, to these agents. This is especially relevant for patients presenting with multiple primary malignant tumors (MPMTs). Here we report the case of a patient presenting synchronously with metastatic melanoma to multiple regional lymph nodes and stage I lung adenocarcinoma with high Programmed-Death Ligand 1 (PD-L1) expression. Given the high-risk nature of his melanoma, he was treated with nivolumab monotherapy, and had a durable response of both malignancies to a PD-1 inhibitor. He remains disease-free, off therapy sixteen months after completing a 19-month course of treatment. This highlights the complexity of treating patients with MPMTs in the era of effective immunotherapy and raises the possibility of treating primary lung cancer with systemic immunotherapy in situations in which surgery is not feasible due to comorbidities or other circumstances.

Keywords

Immune checkpoint inhibitor; Malignant tumor; Primary lesion; Therapy; Melanoma; Lung cancer

Introduction

The advent of immune checkpoint inhibitors (anti-CTLA-4, anti-PD-1, anti-PD-L1) has changed standard of care for many types of cancer including, but not limited to, melanoma and Non-Small Cell Lung Cancer (NSCLC). Diseases with historically dire outcomes have seen increases in their rates of response, Progression-Free, and Overall Survival (PFS and OS) from this class of immune-harnessing therapies. Melanoma was first to benefit from the overwhelming success of immunotherapy regimens and now both single-agent and combination checkpoint inhibitors are approved for both metastatic disease and are also approved as adjuvant treatment for stage III disease [1,2]. Immune Checkpoint Inhibitor (ICI) therapy is now established in first-line regimens for locally advanced unresectable and advanced-stage NSCLC. This was based on superiority of anti-PD-1 antibody-containing regimens compared to traditional combination cytotoxic regimens alone and in combination with radiotherapy [3-7]. Considering the favorable outcomes associated with definitive surgical management in resectable early-stage lung cancer, systemic treatment with PD-1 axis inhibitors is not a standard modality. In patients with poor surgical potential or low respiratory reserve, there are several non-surgical options for definitive management of resectable early-stage lung cancer, including Stereotactic Body Radiotherapy (SBRT), other forms of External Beam Radiotherapy (EBRT), radiofrequency ablation, cryoablation, microwave ablation, and photodynamic therapy [8]. However, situations may arise in which the impetus to manage another advanced synchronous or metachronous malignancy may preponderate the immediacy of treatment for early-stage lung cancer.

Here we report a patient with multiple primary malignant tumors (MPMT), presenting synchronously with high-risk stage IIIC (at least) cutaneous melanoma with multiple involved lymph nodes as well as stage I adenocarcinoma of the lung. He had multiple comorbidities including chronic obstructive pulmonary disease, complicated cardiovascular disease with prior coronary artery bypass graft, and aortic valve replacement, making him a high risk for surgical complications for resection of both tumors. Due to the high risk of death from his unresectable melanoma, we elected to attempt to manage his melanoma first with anti-PD-1 therapy prior to definitive management of the early-stage lung cancer lesion. However, both tumors responded completely to the PD-1 inhibitors and definitive surgery was deferred. The patient remains off treatment for a year, under close surveillance, without recurrence of either tumor. An extensive literature search yielded one account of a patient with multiple primary malignant tumors (MPMT) treated with ICI therapy [9]. This patient with advanced NSCLC and a localized gastric tumor had radiographic response of both primary tumors but the short follow-up (3 months) at the time of the report. Due to the paucity of information about ICI therapy in the setting of MPMTs, combined with lack of information on the treatment of primary lung tumors with anti-PD-1 monotherapy, we are reporting this case of a patient with a durable complete response and one-year treatment-free survival after monotherapy.

Case Presentation

A 67-year-old man was diagnosed in March 2017 with a 1.7 mm non-ulcerated melanoma of the vertex of the scalp. The lesion was a superficial spreading melanoma, with 4 mitoses/mm^2, brisk tumor-infiltrating lymphocytes, and no microscopic satellite lesions. Three of three sentinel lymph nodes were positive for metastatic melanoma including a left parotid lymph node and two right-sided cervical lymph nodes. BRAF and NRAS were not mutated. A PET/CT scan done in May 2017 revealed multiple hypermetabolic lymph nodes in the right postauricular, right cervical, and right supraclavicular regions, concerning for metastatic involvement. There was also an isolated intensely hypermetabolic nodule (SUV max 9.2) in the right lower lobe of the lung, which was not associated with hilar or mediastinal lymphadenopathy. A dedicated Chest CT confirmed a spiculated 1.7 cm solid pulmonary nodule with cavitation in the right lower lobe with no associated adenopathy. Bronchoscopy with endobronchial biopsy of this nodule revealed adenocarcinoma, which was positive for

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Thyroid Transcription Factor-1 (TTF-1) by immunohistochemistry and was negative staining for melan-a and gata 3. PD-L1 expression was assessed using the Dako 22c3 PharmDx antibody and >50% of tumor cells were positive. Further tumor profiling revealed a KRAS mutation (G12C). Endobronchial sampling of a right-sided hilar lymph node was negative for carcinoma. His final staging was consistent with a pT2aN3aM0, stage IIIC (at least) metastatic melanoma, and a cT1bN0M0 stage IA2 lung adenocarcinoma.

The patient was seen by thoracic surgery and radiation oncology and was found to have enlarging palpable cervical lymphadenopathy. He was felt to be a moderately good surgical candidate; he had a history of tobacco use, chronic obstructive pulmonary disease, aortic valve replacement, coronary artery bypass graft, hypertension, and hypercholesterolemia. Given the higher likelihood of death from melanoma if treatment were delayed, compounded by the involvement of multiple lymph node basins by the melanoma and bilateral neck involvement, the decision was made to treat his melanoma with systemic therapy and delay definitive therapy of the lung cancer (surgery or radiation). He was started on treatment with the PD-1 inhibitor, nivolumab, in July 2017.

Staging CT scans done after 4 cycles of nivolumab showed a mixed response of his cervical adenopathy. The right cervical level V node had increased in size, while the retroauricular lymph node and supraclavicular adenopathy had decreased in size (Figure 1). Interestingly, the right lung adenocarcinoma had completely resolved (Figure 2). He was seen again by thoracic surgery who discussed consolidative right upper lobectomy but considering that the location was not amenable to wedge resection and given his poor respiratory reserve with an FEV1 of 40%, the team decided to observe him and consider this only upon recurrence or regrowth of the adenocarcinoma nodule. After nine cycles of nivolumab he developed hypopituitarism, but treatment was continued after steroid repletion due to persistence and slight growth of the cervical lymph nodes. After ten cycles of nivolumab his cervical lymph nodes started to shrink, and treatment was stopped after a dose administered in February 2019 resulted in worsening of his fatigue despite adequate steroid repletion. His cervical lymphadenopathy had resolved by April 2019. He has not had a recurrence of either malignancy.

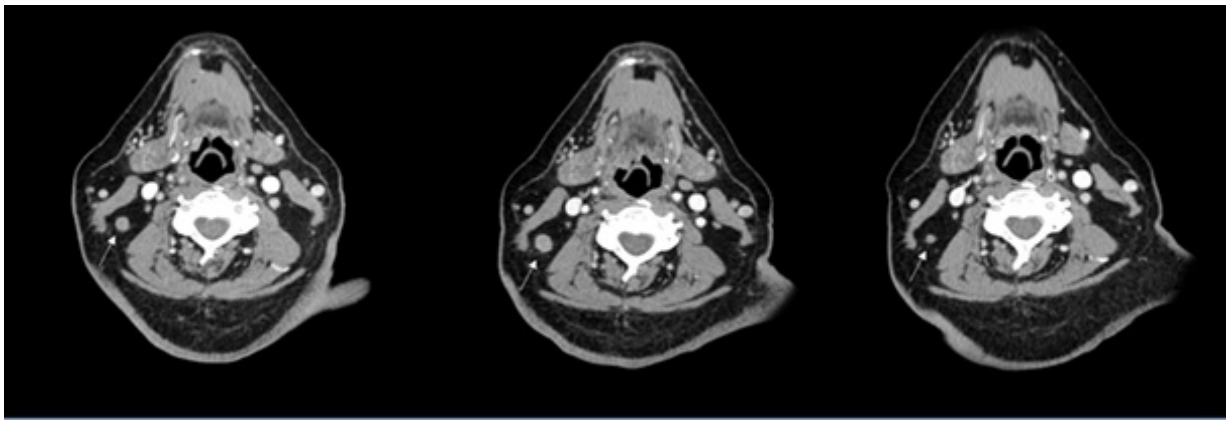

Figure 1: Posterior cervical lymph node (thin arrow) prior to treatment with nivolumab (left), after three months of treatment with nivolumab (middle), and after 12 months of treatment with nivolumab (right).

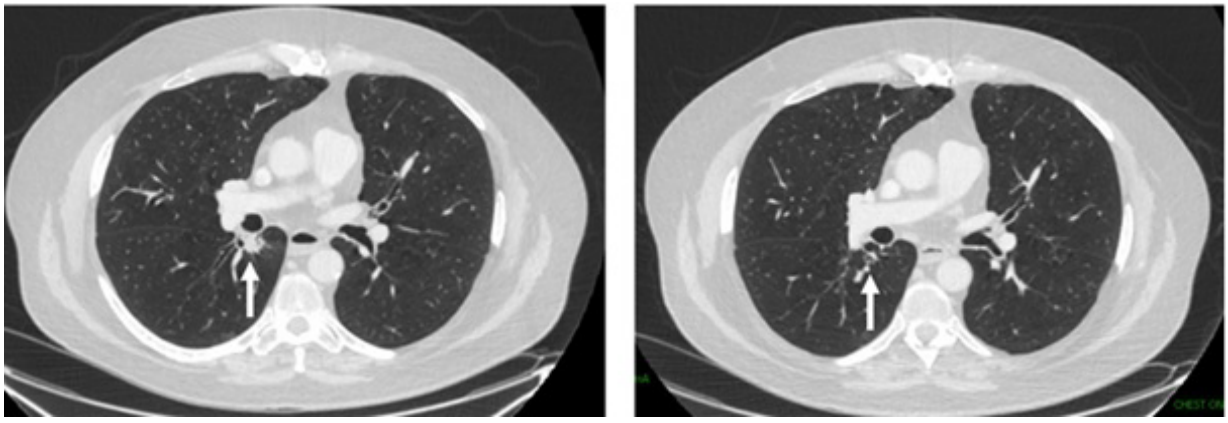

Figure 2: Right lower lung nodule (thick arrow) prior to treatment with nivolumab (left) compared to complete response 3 months after treatment initiation (right).

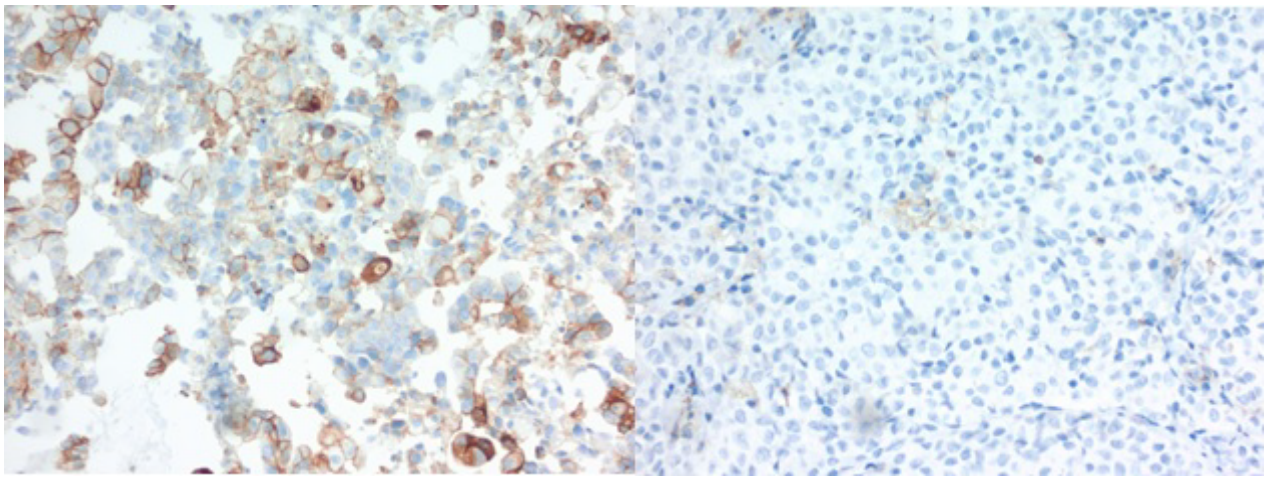

Figure 3: PD-L1 staining by immunohistochemistry. Greater than 50% of lung adenocarcinoma cells stain positive (left), while 1% of melanoma cells stain positive stains (right).

Discussion

We report the case of a man diagnosed synchronously with very high risk, inoperable stage IIIC melanoma and early-stage lung adenocarcinoma. He was treated with nivolumab for 19 months and has remained disease-free and off therapy for sixteen months, after achieving complete radiographic response of both malignancies. The occurrence of multiple primary malignant tumors including NSCLC is not an uncommon scenario. In a retrospective study comparing 344 tumors in patients that had multiple primary malignancies, lung cancer was the most common secondary cancer (26.6%) [10]. Treatment of primary lung cancer can present a conundrum in the setting of a second, more aggressive malignancy.

Five-year disease-free survival (DFS) rates can be quite high for stage IA2 NSCLC after local treatment with curative intent, either with lobectomy (88.3%, 5-year DFS) or wedge resection (74%, 5-year DFS) [11]. The overall survival for stage IA2 NSCLC is approximately 83% regardless of treatment modality [12]. In patients unable to tolerate operative management of stage I NSCLC, SBRT appears similar to surgical resection with respect to safety and survival outcomes [13]. Relative to those of locally advanced or metastatic NSCLC, the impressive cure rates for early-stage disease mandate that clinicians attempt to apply proven strategies to all eligible and willing patients. However, the presence of asynchronous locally advanced or metastatic malignancy may hinder resection or radio ablation of localized NSCLC. For instance, if the coexisting primary usurps priority in management due to attributed symptoms or pace of progression, or if it is thought to be life-limiting relative to the early-stage lung cancer, one may defer treatment for early-stage lung cancer. The prognosis from untreated advanced melanoma is poor, however recently reported follow-up data from Checkmate 067, a trial comparing immunotherapy strategies for metastatic melanoma, shows that 44% of patients treated with nivolumab and 52% of patients treated with nivolumab plus ipilimumab are surviving at 5 years [14]. The impressive survival rates for metastatic melanoma with modern immunotherapy demonstrate that we must use caution when deferring treatment for a coexisting early-stage malignancy as patients may live to experience morbidity or mortality from the other malignancy.

In our patient, there were several reasons for ultimately deferring upfront local treatment for NSCLC. His lymphadenopathy hastily progressed from only radiographically detectable disease at diagnosis to clinically palpable disease within one month while he was undergoing workup for the lung nodule. Moreover, with respect to the potential management strategies, his poor respiratory reserve put him at risk for poorly tolerating a lobectomy, especially considering his untreated metastatic melanoma. After experiencing complete radiographic resolution of the lung nodule with anti-PD-1 therapy, the impetus to surgically resect or consolidate treatment with radiation therapy to this region was less compelling. However, the long-term control of primary non-small lung cancer treated with immune therapy is unknown. Although immature, neoadjuvant data for early-stage NSCLC with anti-PD-1 therapy prior to surgery show that there is potential for the complete pathological response with no viable tumor cells seen on resected specimens [15]. It is, however, important to note that this does not necessarily represent cure and that non-operative assessment of pathologic complete response is not currently possible. Radiographic response does not accurately predict pathologic complete response in lung cancer [16]. Therefore, we continue surveillance imaging with attention to the recurrence of both metastatic melanoma as well as lung adenocarcinoma.

Conclusion

In summary, we present the case of a patient with concurrently diagnosed metastatic melanoma and stage I lung adenocarcinoma with a prolonged complete response of both malignancies to anti-PD-1 therapy. This case highlights the complexities of treatment of patients with two potentially life-threatening malignancies and presents one possible outcome of using immune checkpoint inhibitors as primary therapy in patients with early-stage, PDL1 expressing lung cancers who are not good candidates for definitive surgery or radiation.

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Conflicts of Interest

H. Kluger reports research grants from Merck, Bristol-Myers Squibb, and Apexigen during the conduct of the study, and personal

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Author's Contributions

All authors have been involved in the care of the patient, collecting the imaging and the data, and writing the manuscript. All authors have read and approved the final manuscript.

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