Two Cases of Subsequent Hepatocellular Carcinoma in ICI-Responsive Non-Small Cell Lung Cancer

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PII: S2666-3643(22)00172-2
DOI: https://doi.org/10.1016/j.jtocrr.2022.100448
Reference: JTOCRR 100448

To appear in: JTO Clinical and Research Reports

Received Date: 20 July 2022
Revised Date: 5 December 2022
Accepted Date: 9 December 2022

Please cite this article as: Cheunkarndee T, Guo MZ, Birkness-Gartman JE, Oshima K, Lin CT, Marrone KA, Two Cases of Subsequent Hepatocellular Carcinoma in ICI-Responsive Non-Small Cell Lung Cancer, JTO Clinical and Research Reports (2023), doi: https://doi.org/10.1016/j.jtocrr.2022.100448.

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Disclosures: TC, MZG, JEB, KO, and CTL have no disclosures to report. KAM reports consulting fees from AstraZeneca, Janssen, Mirati, and Amgen and grant funding from BMS and Mirati.

Acknowledgements: The authors thank Mark Yarchoan and Paige Griffith for helpful discussion.

Word Count: 1,806

Figure Count: 4

Abstract: As novel therapeutic regimens continue to lead to increased survival of lung cancer patients, it is imperative to remain mindful of the accompanying increase in the incidence of new primary malignancies. While the most common secondary malignancies in patients with lung cancer have historically included colon, rectal, esophageal, and thyroid cancers, we report here two rare cases of new primary hepatocellular carcinomas (HCC) in patients receiving immune checkpoint inhibitor (ICI) therapy for non-small cell lung cancer (NSCLC). In both cases, the diagnosis of HCC, rather than assuming a hepatic metastasis, was crucial for determining the appropriate approach for treatment. These cases thus underscore the importance of appropriate diagnostics to ensure that the proper therapeutics are chosen and present important considerations for the lung cancer community going forward.

Key words: Non-small cell lung cancer; immune checkpoint inhibitor therapy; hepatocellular carcinoma; multiple primary malignancies

Introduction: With the onset of novel oncologic therapies such as immune checkpoint inhibitors, survival rates have significantly improved among patients with non-small cell lung cancer (NSCLC).1–4 The incidence of lung cancer patients experiencing multiple primary malignancies has also increased in recent decades, with colon cancer, rectal cancer, esophageal cancer, and thyroid cancer identified as the most frequent accompanying malignancies.5 To date, very few cases of concomitant hepatocellular carcinoma (HCC) in patients with non-small cell
lung cancer have been reported in existing literature. Here, we present two cases of patients with NSCLC undergoing treatment with immune checkpoint inhibitors (ICI) who developed liver lesions that were revealed to be new primary HCCs.

**Case Presentation:** Patient A is a 58-year-old male diagnosed with stage IIIC (cT4N2M0) squamous cell carcinoma of the lung in November 2016. He has a history of hepatic steatosis, prior heavy alcohol use, and a 20 pack-year tobacco history. His serology was negative for HBV and HCV. The patient began treatment for NSCLC in March 2017 with concurrent chemoradiation with carboplatin and paclitaxel. However, six months later, a biopsy demonstrated local recurrence in the right upper lobe (Figure 1A). The patient was subsequently referred for a clinical trial of nivolumab, entinostat, and azacitidine vs. nivolumab alone. He was randomized to nivolumab alone and received nivolumab monotherapy from November 2017 to March 2020, when he was removed from the trial due to a growing liver lesion. Retrospective review of imaging found that this liver lesion had been present but stable since May 2018 and was suspicious for metastasis (Figure 2A-D). His lung disease remained stable while on nivolumab monotherapy. He was referred for interventional radiology-guided liver biopsy for entry into a clinical trial. Surgical pathology review was reviewed which revealed insufficient tissue but was suspicious for HCC. Despite the stability of his lung lesions over the last 2.5 years, a diagnosis of HCC was confirmed in November 2020 through re-biopsy with concomitant microwave ablation (Figure 1B-D). Given his stable lung disease, the patient had also continued to receive nivolumab monotherapy off-trial since May 2020. In April 2021, however, he contracted SARS-CoV2. After he recovered following hospitalization and HFNC, the decision was made to discontinue nivolumab in the context of the stability of his lung lesions and risk of toxicity. In December 2021, surveillance imaging demonstrated mild focal enhancement in the right hepatic lobe at the tip of the microwave ablation tract, concerning for residual HCC. His AFP remained stable. The patient received a second microwave ablation in February 2022. Subsequent imaging demonstrated no definite residual tumor and no new liver lesions.

Patient B is a 75-year-old male diagnosed with stage IIIC (T1N2MX) adenocarcinoma of the lung in February 2021 after initially presenting with SVC syndrome (Figure 3A-B). He has a history significant for HCV treated with ledipasvir/sofosbuvir in 2014, a 90 pack-year tobacco history, and a family history notable for cancer of an unknown type in his mother. His diagnostic PET/CT also revealed multiple hypodense liver lesions that were indeterminate for metastasis (Figure 4A-B). A follow-up liver MRI was performed to better characterize the liver lesions, demonstrating one multiseptated cystic lesion with an apparent capsule (Figure 4C-D). The patient then underwent a liver biopsy of that lesion which demonstrated a benign liver parenchyma. NGS of the primary lung lesion revealed no targetable alterations, and the patient was thus started on concurrent chemoradiation therapy with carboplatin and pemetrexed followed by durvalumab consolidation. After six months of durvalumab, the patient presented with rising LFTs concerning for ICI-induced liver injury (immune-related adverse event hepatitis). Durvalumab was discontinued and an abdominal CT in November 2021 showed a marked interval increase in a right hepatic lobe lesion. Subsequent PET/CT demonstrated a large hypermetabolic lesion in the liver concerning for oligoprogressive disease. A liver biopsy was performed that revealed poorly differentiated HCC with no evidence of irAE hepatitis (Figure 3C-D). AFP measured after the liver biopsy was elevated at 43.2 ng/mL. The patient was subsequently referred for treatment with our HCC colleagues and received TACE therapy in
January 2022 and two doses of nivolumab for control of both the liver lesion and lung primary. Following TACE, the patient’s AFP remained elevated at 19.5 ng/mL. He thus received a second TACE in March 2022, and follow-up imaging revealed an interval decrease in the size of the hepatic mass.

**Discussion:** HCC has rarely been reported as a concomitant primary lesion in patients with non-small cell lung cancer. The cases presented here describe two patients undergoing ICI therapy for NSCLC who developed liver lesions concerning for metastases. Further evaluation with imaging and biopsy revealed that they were instead new primary HCCs. As standard treatment regimens for lung cancer hepatic metastases differ from frontline treatment of HCC, inappropriate cessation of ICI therapy would result in poorer outcomes from both the NSCLC and HCC perspectives. In a growing population of long-term lung cancer survivors on ICI, these patients highlight the need for high acuity in differentiating oligometastatic disease from new primary malignancies, particularly in patients with significant risk factors for other cancers.

Lung cancer patients with oligoprogressive disease are typically treated with either local approaches such as stereotactic body radiation therapy (SBRT), or with salvage systemic therapeutics. Standard salvage therapy for patients whose diseases progress on ICI would be chemotherapy with docetaxel. However, five-year survival follow-up results of CheckMate057 and CheckMate017 demonstrated that nivolumab-treated patients without progression at 2 years, such as our patient A, have a 59.6% likelihood of being progression-free and an 82% chance of survival at 5 years. Similarly, treatment with consolidation durvalumab for stage III NSCLC has an improved five-year OS at 42.9% compared to 33.4% for placebo. Discontinuation of nivolumab for patient A and durvalumab for patient B to treat supposed metastatic disease would have resulted in substandard care for these patients who instead had concomitant primary malignancies.

For their hepatic lesions, our patients were treated with microwave ablation (MWA) and transarterial chemoembolization (TACE), respectively. It is of note that both are HCC-specific therapies: MWA is a newer technique shown to result in greater and faster ablation, and TACE is the standard-of-care for the treatment of nonresectable HCC. Importantly, both patients responded well to treatment, and their lung cancers have remained stable on continued ICI therapy. There are multiple potential reasons for which ICI response may differ between NSCLC and HCC. Unique aspects of the tumor and immune cell interaction, such as antigen presentation and immune cell function, are likely at play and can be considered. Clinical trials of single-agent anti-PD-(L)1 therapies for HCC have shown poor responses, with CheckMate459 yielding an objective response rate (ORR) of 15% for nivolumab monotherapy and KEYNOTE-240 yielding an ORR of 18.4% for pembrolizumab monotherapy for advanced HCC. It is thus perhaps unsurprising that the novel primary HCCs in our patients grew through their nivolumab and durvalumab monotherapy regimens.

Both of our patients have significant risk factors for HCC. Patient A had a history of hepatic steatosis and heavy alcohol use at the time of his initial NSCLC diagnosis, and patient B had a history of HCV and family history of cancer. It is also notable to consider that several of these risk factors, such as a history of smoking, alcohol use, or HCV, overlap with those of NSCLC. These patient cases therefore highlight the importance of considering the holistic patient, even in
the context of treating a known primary malignancy. As survival rates continue to increase for patients with lung cancer, an increase in the incidence of patients experiencing concomitant primary malignancies will continue to accompany it. It thus becomes more critical than ever to appropriately consider when to pursue tissue-based diagnostic evaluation prior to changing systemic therapies.

In our patients, diagnostic biopsy and imaging were critical in differentiating concomitant primary HCC from oligometastatic NSCLC. We found that discussion of potential progression on imaging with a multidisciplinary team was integral in considering the need for invasive testing. This will also often be of particular importance in the context of clinical trial continuation or consideration, as was the case for our patient A, or for further molecular interrogation at time of progression. Prognostically, it is quite different for patients who are otherwise having continued benefit with their ICI who have new primary malignancies that can be cured if treated early with an aggressive local approach than would otherwise be considered in the setting of a diagnosis of metastatic NSCLC. Additionally, the psychosocial impacts of disease progression, treatment failure, and delays in appropriate therapy cannot be understated. As our patient population with ICI-treated NSCLC continues to survive and thrive longer, we must ensure that our patients are properly screened, and evaluated for other concomitant malignancies as appropriate. Without tissue interrogation for our patients, discontinuation of effective ICI treatment in favor of salvage chemotherapy regimens would have resulted in poor disease control. Specific to HCC development, further studies are needed to understand potential mechanistic links, as opposed to a potentially unrelated natural history progression of susceptibility, to inform appropriate screening and therapeutic approaches.

**Conclusion:** We report on two cases of patients with NSCLC who developed concomitant HCC while being treated with ICIs. Diagnostic biopsies, obtained to determine clinical trial eligibility and resistance mechanism, distinguished new primary malignancies as opposed to a hepatic metastasis, and treatment with HCC-specific therapies resulted in positive responses of the liver lesions in both patients. As our lung cancer patient population continues to celebrate prolonged therapeutic successes with ICI treatment, we must remember to consider other potential differential diagnoses for new findings on imaging.

**References:**


Figure 1: Pathology for Patient A. (A) Hematoxylin and eosin (H&E) stain of lung squamous cell carcinoma (x400). The eosinophilic cytoplasm and whorled growth pattern are suggestive of squamous differentiation, while the nuclear enlargement and pleomorphism are indicative of malignancy. (B) H&E stain of hepatocellular carcinoma (HCC), showing malignant cells with eosinophilic cytoplasm and prominent nucleoli (x400). (C) A reticulin stain shows expansion of the hepatic plates in the HCC (x400). (D) Immunolabeling for HepPar-1 (hepatocellular marker) supports a diagnosis of HCC (x400).
Figure 2: Radiographic imaging for Patient A. CT of the liver during arterial phase of contrast administration demonstrates (A) a small lesion in hepatic segment VIII that avidly enhances and progressively enlarges on subsequent scans (B) 11 months and (C) 22 months later. (D) Corresponding hepatic MRI with intravenous contrast shows the same enhancing liver lesion without additional tumors.
Figure 3: Pathology for Patient B. (A) Hematoxylin and Eosin stain of lung adenocarcinoma (x400). Malignant cells showed a high nuclear-cytoplasmic ratio and pleomorphism. (B) Immunohistochemical stain for thyroid transcription factor 1 (TTF-1) showed positive nuclear stain and supported lung primary (x400). (C) Hematoxylin and eosin stain of hepatocellular carcinoma (x400). Neoplastic cells resembled hepatocytes forming cords structure. (D) Immunohistochemical stain for Arginase-1 (hepatocellular marker) showed positive cytoplasmic stain and supported the diagnosis of hepatocellular carcinoma.
Figure 4: Radiographic imaging for Patient B. (A) Venous phase contrast-enhanced CT shows a lobulated hypodense lesion within hepatic segment VI, with (B) faint corresponding radiotracer activity on PET/CT. (C) The lesion consisted of thin enhancing septations and capsule on hepatic MRI, and (D) a mixture of cystic and solid components without significant internal vascularity on ultrasound.
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