CASE REPORT

Two Cases of Subsequent Hepatocellular Carcinoma in Immune Checkpoint Inhibitor–Responsive NSCLC: A Case Report

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ABSTRACT

As novel therapeutic regimens continue to lead to increased survival of patients with lung cancer, it is imperative to remain mindful of the accompanying increase in the incidence of new primary malignancies. Although 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 in patients receiving immune checkpoint inhibitor therapy for NSCLC. In both cases, the diagnosis of hepatocellular carcinoma, 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.

Keywords: Non–small cell lung cancer; Immune checkpoint inhibitor therapy; Hepatocellular carcinoma; Multiple primary malignancies: Case report

Introduction

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

Case Presentation

Patient A is a 58-year-old man diagnosed with having 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 result was negative for hepatitis B virus and hepatitis C virus (HCV). The patient began treatment for NSCLC in March 2017 with

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concurrent chemoradiation with carboplatin and paclitaxel. Nevertheless, 6 months after, a biopsy result revealed local recurrence in the right upper lobe (Fig. 1*A*). The patient was subsequently referred for a clinical trial. He was randomized to nivolumab alone and received nivolumab monotherapy from November 2017 to March 2020, when he was removed from the trial owing to a growing liver lesion. Retrospective review of imaging found that his liver lesion had been present but stable since May 2018 and was suggestive of metastasis (Fig. 2*A*–*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 revealed insufficient tissue but was suggestive of HCC. A diagnosis of HCC was confirmed in November 2020 through rebiopsy with concomitant microwave ablation (Fig. 1*B*–*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 severe acute respiratory syndrome coronavirus 2. After he recovered following hospitalization and high supplemental oxygen requirements, a 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 revealed mild focal enhancement in the right hepatic lobe at the tip of the microwave ablation tract, concerning for residual HCC. His α-fetoprotein (AFP) level remained stable. The patient received a second microwave ablation in February 2022. Subsequent imaging revealed no definite residual tumor and no new liver lesions.

Patient B is a 75-year-old man diagnosed with having stage IIIC (T1N2MX) adenocarcinoma of the lung in February 2021 after initially presenting with superior vena cava syndrome (Fig. 3*A* and *B*). He has a history relevant 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. Results of his diagnostic positron emission tomography/computed tomography (CT) also revealed multiple hypodense liver lesions that were indeterminate for metastasis (Fig. 4*A* and *B*). A follow-up liver magnetic resonance imaging was performed to better characterize the liver lesions, revealing one multiseptated cystic lesion with an apparent capsule (Fig. 4*C* and *D*). The patient then underwent a liver biopsy of that lesion, which revealed a benign liver parenchyma. Next-generation sequencing 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

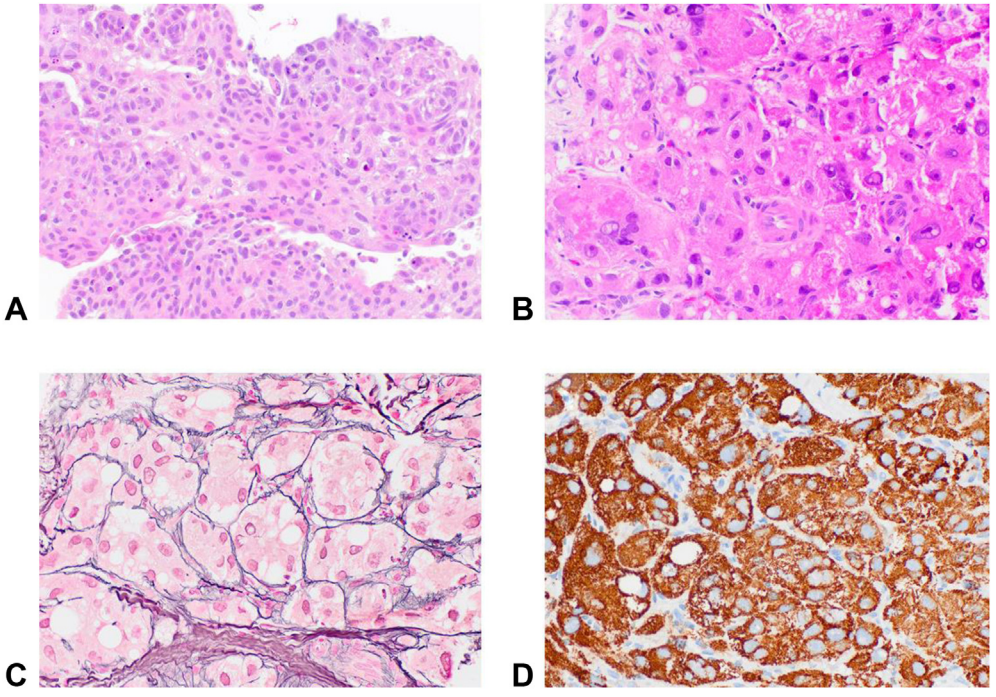

Figure 1. Pathology for patient A. (*A*) H&E stain of lung squamous cell carcinoma (×400). The eosinophilic cytoplasm and whorled growth pattern are suggestive of squamous differentiation, whereas the nuclear enlargement and pleomorphism are indicative of malignancy. (*B*) H&E stain of HCC, revealing malignant cells with eosinophilic cytoplasm and prominent nucleoli (×400). (*C*) A reticulin stain reveals expansion of the hepatic plates in the HCC (×400). (*D*) Immunolabeling for HepPar-1 (hepatocellular marker) supports a diagnosis of HCC (×400). H&E, hematoxylin and eosin; HCC, hepatocellular carcinoma.

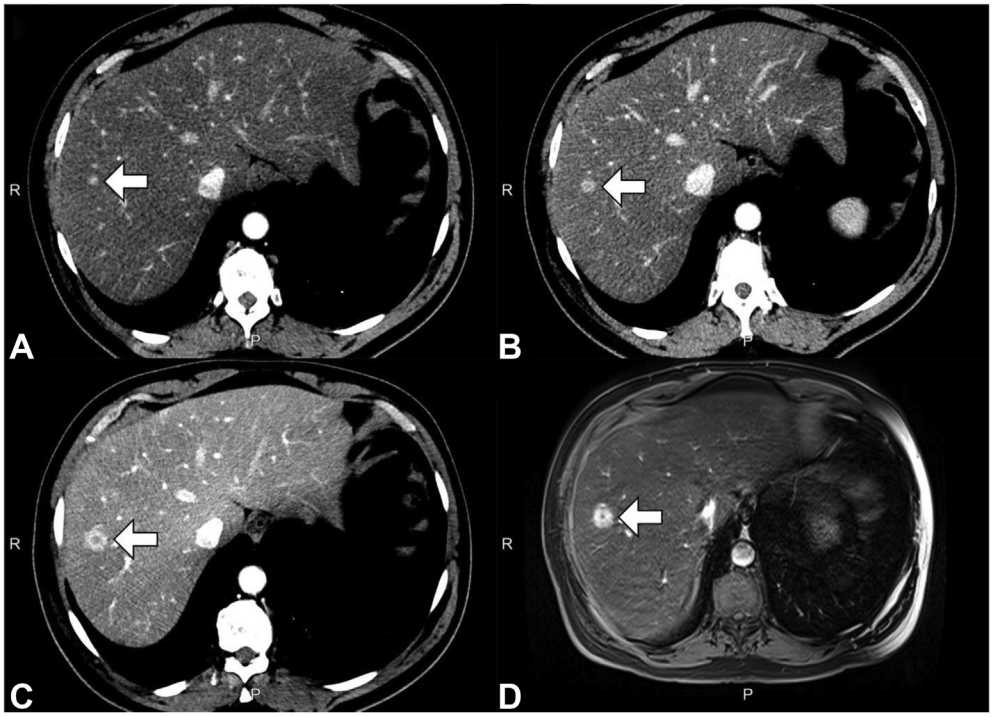

Figure 2. Radiographic imaging for patient A. CT of the liver during arterial phase of contrast administration reveals (*A*) a small lesion in hepatic segment VIII that avidly enhances and progressively enlarges on subsequent scans (*B*) 11 months and (*C*) 22 months after. (*D*) Corresponding hepatic MRI with intravenous contrast reveals the same enhancing liver lesion without additional tumors. CT, computed tomography; MRI, magnetic resonance imaging.

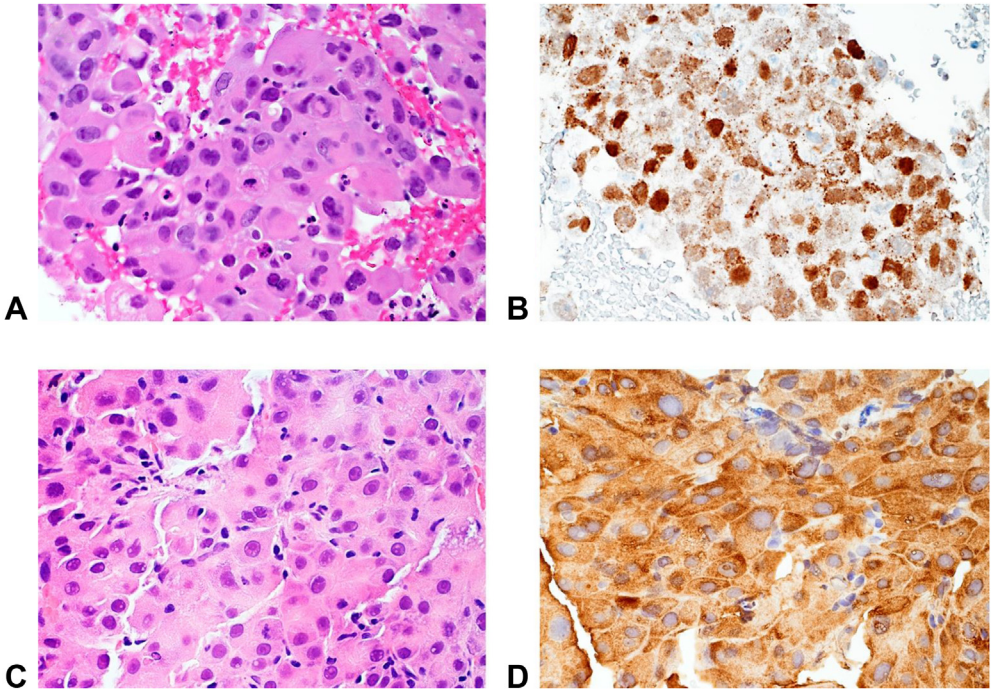

Figure 3. Pathology for patient B. (*A*) Hematoxylin and eosin stain of lung adenocarcinoma (×400). Malignant cells had a high nuclear-cytoplasmic ratio and pleomorphism. (*B*) Immunohistochemical stain for TTF-1 revealed positive nuclear stain and supported lung primary (×400). (*C*) Hematoxylin and eosin stain of hepatocellular carcinoma (×400). Neoplastic cells resembled hepatocytes forming cord structure. (*D*) Immunohistochemical stain for arginase-1 (hepatocellular marker) revealed positive cytoplasmic stain and supported the diagnosis of hepatocellular carcinoma. TTF-1, thyroid transcription factor 1.

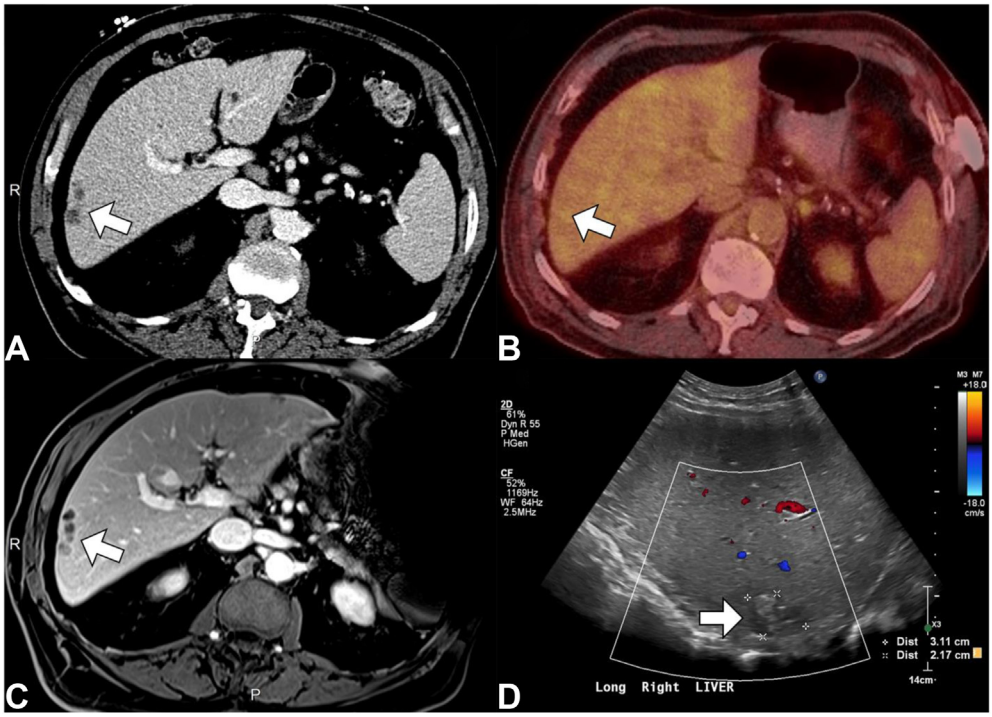

Figure 4. Radiographic imaging for patient B. (*A*) Venous-phase, contrast-enhanced CT reveals a lobulated hypodense lesion within hepatic segment VI, with (*B*) faint corresponding radiotracer activity on PET/CT. (*C*) The lesion consisted of thin enhancing septations and capsule on hepatic MRI and (*D*) a mixture of cystic and solid components without significant internal vascularity on ultrasound. CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

durvalumab consolidation. After 6 months of durvalumab, the patient presented with rising liver function test levels concerning for ICI-induced liver injury (immune-checkpoint inhibitor-induced hepatitis). Durvalumab was discontinued and an abdominal CT in November 2021 revealed a marked interval increase in a right hepatic lobe lesion. Results of subsequent positron emission tomography/CT revealed a large hypermetabolic lesion in the liver concerning for oligoprogressive disease. A liver biopsy was performed which revealed poorly differentiated HCC with no evidence of immune-related adverse event hepatitis (Fig. 3*C* and *D*). His AFP level 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 transarterial chemoembolization (TACE) therapy in January 2022 and continued on nivolumab for control of both the liver and lung primary lesions. After TACE, the patient's AFP level 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 NSCLC. 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.

Patients with lung cancer with oligoprogressive disease are typically treated with either local approaches, such as stereotactic body radiation therapy,[6] or salvage systemic therapeutics. Standard salvage therapy for patients whose diseases progress on ICI would be chemotherapy with docetaxel. Nevertheless, five-year survival follow-up results of CheckMate057 and CheckMate017 revealed 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.[7] Similarly, treatment with consolidation durvalumab for stage III NSCLC has an improved five-year overall survival at 42.9% compared with 33.4% for placebo.[8] 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 and TACE, respectively. It is of note that both are HCC-specific therapies: microwave ablation is a newer technique found to result in greater and faster ablation and TACE is the standard of care for the treatment of nonresectable HCC.[9,10] 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.[11–14] Clinical trials of single-agent anti–programmed death-(ligand)1 therapies for HCC have revealed poor responses, with CheckMate459 yielding an objective response rate of 15% for nivolumab monotherapy and KEYNOTE-240 yielding an objective response rate of 18.4% for pembrolizumab monotherapy for advanced HCC.[15,16] It is thus perhaps unsurprising that the novel primary HCCs in our patients grew through their nivolumab and durvalumab monotherapy regimens.

Both 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 before 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. In addition, the psychosocial effects 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.

Conclusions

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.

CRediT Authorship Contribution Statement

Tia Cheunkarndee: Writing—original draft preparation.

Matthew Z. Guo, Jacqueline E. Birkness-Gartman, Kiyoko Oshima, Cheng Ting Lin: Writing—review and editing.

Kristen A. Marrone: Conceptualization; Writing—review and editing.

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