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CASE REPORT

To treat or not to treat: A rare case of response to pembrolizumab-based immunotherapy-chemotherapy in non-small cell lung cancer with acute liver failure due to multiple bile duct metastases

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Abstract

About 40% of non-small lung cancer (NSCLC) patients have metastatic disease at the time of diagnosis. However, metastatic NSCLC in the biliary duct system is extremely rare. A high proportion of patients with acute liver failure due to advanced NSCLC do not receive any treatment due to organ dysfunction or poor performance status. Here, we report a case of successful treatment with chemo-immunotherapy in a young woman with obstructive jaundice and acute hepatic failure due to multiple intrahepatic bile duct metastases.

Key points

Significant findings of the study
Chemotherapy in NSCLC patients with liver failure is a therapeutic challenge. Acute hepatic failure are often exclusion criteria for therapy of NSCLC. Some reports showed a benefit of ICIs plus chemotherapy for NSCLC with liver metastases.

What this study adds
Combination of ICIs and chemotherapy is effective and safe in critically ill patients with lung cancer and impaired liver function.

Introduction

Non-small cell lung cancer (NSCLC) is one of the most common cancers worldwide, and approximately 40% of patients have metastases at the time of diagnosis.[1] These most commonly affect the skeletal system, lungs, brain, liver, and adrenal glands.[2] Liver metastases rarely involve the biliary duct system, and therefore acute liver failure (ALF) with hyperbilirubinemia is unusual. Treating patients with ALF and lung cancer is challenging, and a large proportion of patients are unfit for therapy due to organ dysfunction or poor performance status.

Here, we present a case of successful treatment with platinum-based chemotherapy in combination with pembrolizumab in a patient with metastatic lung cancer and acute liver failure due to intrahepatic bile duct metastases.

Case report

A 33-year-old Caucasian, non-smoking woman was admitted to a community hospital with a two-week history of abdominal pain, jaundice and fever. Her medical and family history was unremarkable except for arterial hypertension and hypothyroidism.

The laboratory results indicated cholestasis with alkaline liver phosphatase 315 U/L, total bilirubin 97.5 μmol/L (<20.5), alanine aminotransferase 204 U/L (10–35), and aspartate aminotransferase 77.3 U/L (10–35).

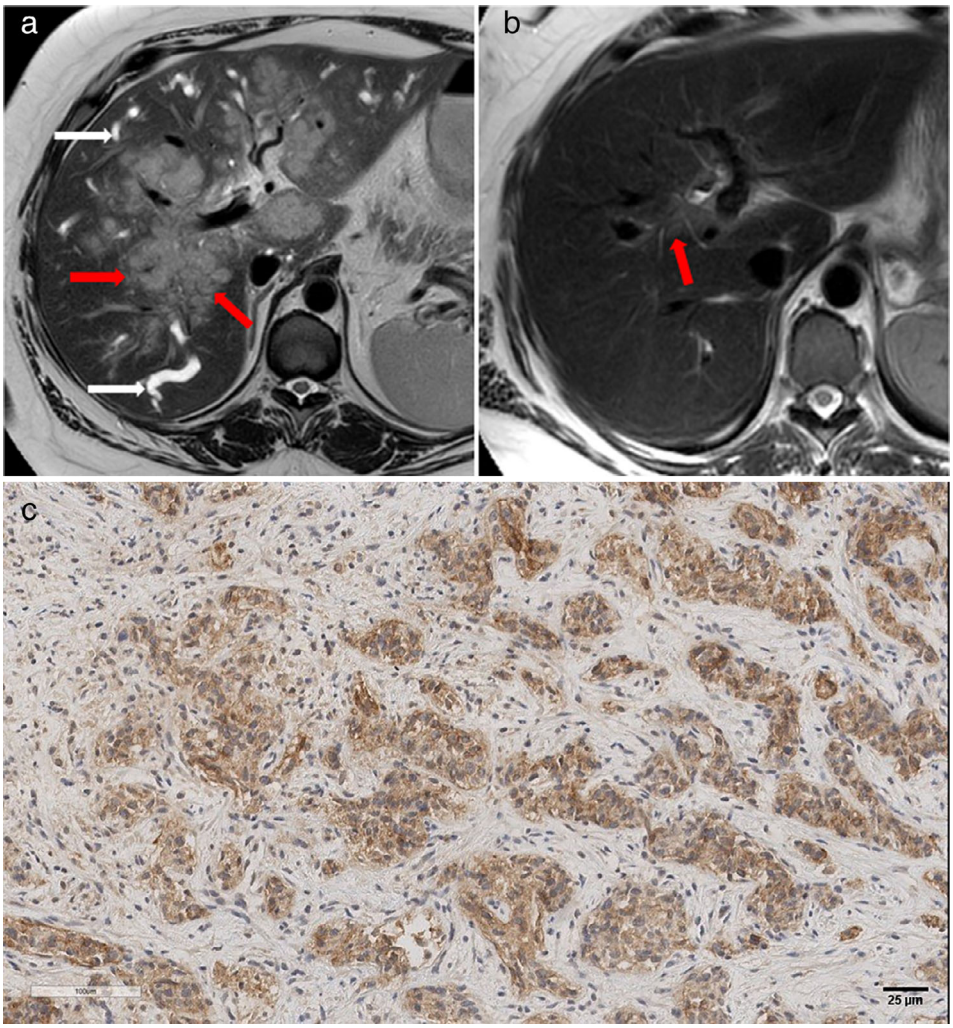

Figure 1 (**a**) Axial native T_2-weighted image, acquired on a 1.5 Tesla MRI. Visualization of hyperintense tumor tissue (red arrows) with infiltration of the biliary ducts and consecutive cholestasis (white arrows). The tumoral mass exhibited intense contrast enhancement and FDG avidity. (**b**) Follow-up nine months later. Axial native T_2-weighted image, acquired on a 3 Tesla MRI. Only residual tumor tissue (red arrow) is left with a complete resolution of cholestasis. (**c**) Liver biopsy: immunohistochemistry showing high PD-L1-expression (TPS 5, 70%) (magnification 20×).

Due to biliary obstruction endoscopic retrograde cholangiopancreatography (ERCP) was performed, and a stent was placed in the common bile duct (CBD). Computed tomography (CT) revealed a large mass in the left lung, multiple liver lesions and enlarged mediastinal, paratracheal and hilar lymph nodes as well as bone metastases. The liver biopsy showed malignant cells with immunohistochemistry positive for CK 7, Napsin A and TTF-1. In conjunction with the pathological and radiological findings a final diagnosis of metastatic pulmonary adenocarcinoma stage IVb was made.

Due to the rapidly increasing bilirubin level with beginning acute liver failure and poor performance status, she was considered unsuitable for chemotherapy and was discharged home for palliative care.

Two days later the patient was admitted to our hospital with laboratory findings indicating progressive hepatic failure: total bilirubin 383 µmol/L, aspartate aminotransferase 67 U/L, alanine aminotransferase 53 U/L, lactate dehydrogenase 387 U/L (135–214), lipase 143 U/L (13–60), and INR 1.74.

Abdominal ultrasound confirmed persistent biliary obstruction, ERCP revealed obstruction of CBD and dilatation of multiple intrahepatic bile ducts. The stent in the CBD was replaced, and a second stent was placed in the right hepatic bile duct. A biopsy confirmed metastatic NSCLC.

Magnetic resonance imaging (MRI) of the liver showed diffuse metastatic infiltration of the intrahepatic bile ducts (Fig 1a).

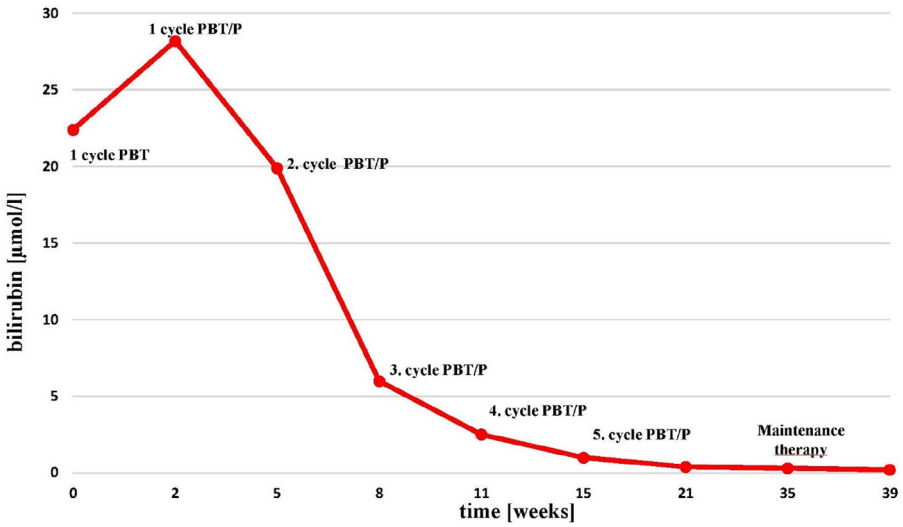

Figure 2 Course of bilirubin during treatment. P, pembrolizumab; PBT, platinum-based treatment.

Although the clinical deterioration and progressive hyperbilirubinemia indicated unsuitability for conventional chemotherapy, dose-adjusted cisplatin (17.5 mg/m^2 day 1) and gemcitabine (250 mg/m^2 days 1, 8) were started on the day of admission. Driver mutation status and programmed death ligand 1 (PD-L1) expression were unknown at that time.

The search for common oncogenic drivers (*EGFR*, *BRAF*, *ROS1*, *ALK*) was negative, and clinical targeted-exome sequencing (TruSight Oncology 500) did not reveal any targetable lesion. PD-L1 immunohistochemistry revealed a tumor proportion score (TPS) of 5 (70%) (Fig **1**c).

Based on these findings and expectations of higher tumor response with chemoimmunotherapy versus immunotherapy alone[3] we continued with the dose-adjusted chemotherapy-immunotherapy (cisplatin [37.5 mg/m^2 day 1]/pemetrexed [250 mg/m^2 day 1]/pembrolizumab [200 mg day 1]). After further three cycles of chemo-immunotherapy the bilirubin level normalized (Fig 2), and MRI revealed partial remission (Fig 1b). The treatment was subsequently switched to maintenance therapy with pemetrexed/pembrolizumab. While maintenance therapy is currently in the seventh cycle, the patient additionally undergoes stereotactic radiation therapy due to oligoprogression with an isolated metastasis in the left adrenal gland.[4,5] With normal laboratory findings, the patient remains in a stable general condition.

Discussion

About 13% of patients with metastatic NSCLC present with liver metastases. The incidence of metastases in the biliary duct system with subsequent development of obstructive jaundice is less than 1%. In the majority of these cases, biliary tract obstructing and jaundice result from metastasis affecting the periportal lymph nodes or the hepatic parenchyma.[6] Only a few cases of primary lung adenocarcinoma with metastatic involvement of the biliary tract have been previously reported in the literature.[6-9]

Development of liver metastasis is generally associated with an adverse prognosis due to the 6 poor response to conventional chemotherapy.[10,11] However, recent reports have suggested survival benefits of a combined treatment consisting of checkpoint inhibition and platinum-based chemotherapy.[12] In an updated analysis of the Keynote-189 trial, Gadgeel *et al.* reported substantial improvement in overall survival (OS) and progression-free survival (PFS) for pemetrexed-platinum plus pembrolizumab versus pemetrexed-platinum plus placebo when administered as first-line therapy for nonsquamous NSCLC with liver or brain metastases, especially in the subgroup of patients with PD-L1 TPS ≥50%.[12] In another approach, targeting VEGF by the addition of checkpoint-inhibition to chemotherapy also showed significant survival benefits in the subgroup of NSCLC patients with liver metastases.[13]

Administering chemotherapy to patients with severely impaired organ function is challenging. Experience with targeted therapy in this group of patients is limited, and physicians are often reluctant to use such treatment options for fear of incalculable side effects.

Nevertheless, there are some reports indicating that treatment with checkpoint inhibitors might be effective and safe in patients suffering from severe organ dysfunction and limited performance status, especially in cases of high PD-L1 expression.[14,15]

In conclusion, advanced NSCLC with severe hyperbilirubinemia remains a therapeutic challenge. Our case illustrates that an attempt with dose-adjusted platinum-based chemotherapy is justified in this situation. However, this aggressive treatment may not be applicable in older patients or those with comorbidities due to high toxicity. Although patients with severe hepatic impairment had not been investigated in pivotal studies, the addition of pembrolizumab was well tolerated without signs of toxicity and might therefore be considered as an additional therapy option in critically ill patients with impaired liver function.

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None.

Disclosure

No authors report any conflict of interest.

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