

Case Report

Case Report of Primary Hepatoid Lung Carcinoma in a 45-year-old Woman

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Abstract

A 45-year-old woman initially presented with back pain and was subsequently given a diagnosis of hepatoid adenocarcinoma (HAC) of the lung, stage IV, T3N0M1b. No actionable mutations were detected. A multidisciplinary therapeutic approach, including atezolizumab plus bevacizumab treatment, platinum-based doublet chemotherapy, radiotherapy, and surgery, was applied. The patient remained asymptomatic and disease progression free for approximately 34 months after treatment. HAC is a rare lung cancer subtype for which information regarding systemic treatment is limited. The optimal treatment regimen for this cancer requires further investigation.

Keywords: Atezolizumab, bevacizumab, case report, hepatoid adenocarcinoma, hepatoid adenocarcinoma of the lung

INTRODUCTION

Lung carcinoma is the second most common tumor in both men and women and was the leading cause of cancer-related deaths in the United States in 2023.^[1] Hepatoid adenocarcinoma (HAC) of the lung (HAL) is a rare type of lung cancer that has increasingly garnered attention. HAC exhibits morphological and microscopic features characteristic of hepatocellular carcinoma (HCC) without evidence of primary liver malignancy and is occasionally accompanied by high alpha-fetoprotein (AFP) levels.^[2] HAL accounts for only 2.5% of all HAC cases and is less frequently observed than is HAC in other sites, such as the stomach and ovaries, which account for 63% and 10% of cases, respectively.^[3,4] Therefore, HAL must be differentiated from HAC in other sites.

HAL typically affects middle-aged adults and is predominant among men,^[5] who account for approximately 80% of cases.^[2,6,7] To date, the overall incidence of HAL remains low, and it is especially rare in women. Notably, survival appears to be longer among women than among men with HAL, likely because of the protective effects of an unknown mechanism.^[5] HAL is typically diagnosed at an advanced stage as a large mass in the upper right lung, where pain is a commonly reported warning symptom.^[5]

HAL is commonly diagnosed through immunohistochemical (IHC) staining panels, which typically reveal positive results

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for AFP, arginase-1, cytokeratin 7 (CK7), Hep-Par1, and pancytokeratin and negative results for cytokeratin 20 (CK20), napsin A, and thyroid transcription factor-1 (TTF-1).^[2,6-8] The typical timing of diagnosis at an advanced disease stage leads to a poor prognosis. The median overall survival is approximately 14–16 months, with a 2-year survival rate of 35.3% and a 5-year survival rate of 8.0%.^[5,9,10] Cisplatin-based chemotherapy is the primary treatment for advanced-stage HAL.^[11]

CASE REPORT

A 45-year-old female pharmacist without a prior medical history of HAL initially presented with back pain for 2 months. The patient had no history of recent trauma, lower limb weakness, progressive numbness, or urinary or stool incontinence. No obvious aggravating or relieving factor was associated with the pain. The patient did not consume alcohol, chew betel nuts, or smoke cigarettes.

Magnetic resonance imaging (MRI) revealed lumbar (L1) and sacral (S1) spine metastasis [Figure 1]. Screening for the primary tumor revealed a 60 mm × 44 mm mass in the right lower lobe [Figure 2]. Biopsy guided by computed tomography (CT) revealed carcinoma with hepatoid differentiation. IHC staining revealed negative results for CK7, CK20, GATA3, insulinoma-associated 1, mucin-5AC, napsin A, p40, paired box gene 8, and TTF-1 and positive results for arginase-1, low-molecular-weight cytokeratin, glypican-3, and hepatocyte specific antigen (HSA). A bone scan indicated metastasis to the L1 vertebra. A brain MRI revealed no evidence of intracranial metastasis.

Analysis of tumor markers revealed considerably elevated AFP levels (21,905.4 ng/mL) but carcinoembryonic antigen levels within the normal limits (<0.5 ng/mL). Lactate dehydrogenase (464 U/L) was mildly elevated. In consideration of the hepatoid differentiation morphology and elevated AFP level, we performed liver MRI to exclude primary liver tumor,

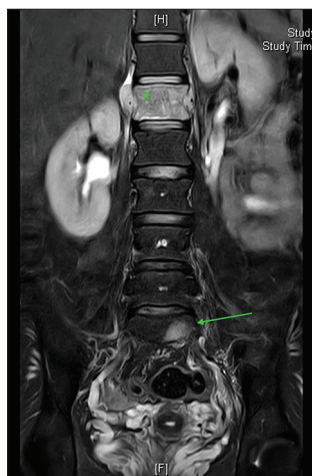


Figure 1: Magnetic resonance imaging revealed lumbar spine (L1, asterisk) and sacral spine (S1, arrow) metastasis

the results of which revealed no space-occupying lesions. The specimen revealed low programmed-death ligand-1 expression, with a tumor propensity score of 5%. The patient was therefore given a diagnosis of metastatic HAL, T3N0M1b, in accordance with the eighth edition of the *American Joint Committee on Cancer Staging Manual*. The patient received ACT GENOMICS ACTLung™ panel. The next-generation sequencing report was negative for epidermal growth factor receptor, ROS proto-oncogene 1, anaplastic lymphoma kinase, V-Raf murine sarcoma viral oncogene homolog B, mesenchymal epithelial transition factor receptor, rearranged during transfection, and neurotrophic tyrosine receptor kinase. Platinum-based doublet chemotherapy was suggested as the first-line systemic therapy. However, the patient refused chemotherapy because of the potential for hair loss. After discussion, the patient was instead administered atezolizumab (1200 mg) and bevacizumab (15 mg/kg) once every 3 weeks in accordance with the IMBrave 150 protocol. Concurrent radiotherapy at 3000 cGy was administered to the thoracic (T12) to lumbar vertebra (L2) and sacral vertebra (S1–S2) for local control of bone metastasis.

After the patient received the sixth cycle of atezolizumab and bevacizumab, her AFP levels decreased from 21,905.4 to 3895.0 ng/mL. However, subsequent imaging revealed progressive disease, with a new mass in the left lung and retrocardiac region [Figure 3] accompanied by an AFP increase to 4952.9 ng/mL. A restaging workup, conducted through positron emission tomography (PET), revealed lesions in the right lower lung and right femur [Figure 4a and b]. A brain MRI revealed no new intracranial metastasis.

The patient was subsequently treated with palliative chemotherapy, including cisplatin (75 mg/m²) once every 3 weeks and etoposide (100 mg/m²) on days 1–3 once every 3 weeks. The size of the tumor in the right lower lobe decreased from 60 mm × 44 mm to 52 mm × 39 mm after four chemotherapy cycles. The tumor also became more hypodense on CT, suggesting necrotic content [Figure 5a and b]. No new metastatic lesions developed. Therefore, radiotherapy of 5400 cGy and a subsequent fifth cycle of chemotherapy were applied to the tumor in the right lower lung, which lowered AFP levels to 1213.0 ng/mL. Radiotherapy at 3200cGy was applied to the right femur head and proximal shaft for metastatic bone lesion control.

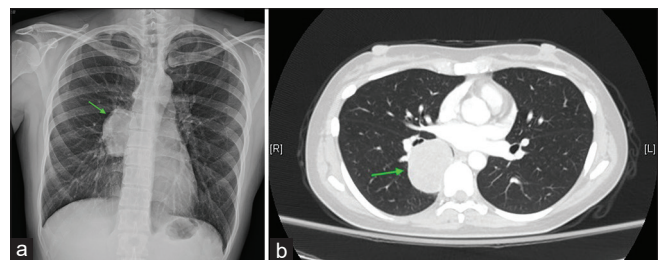


Figure 2: (a) Chest X-ray revealed a right perihilar mass (arrow). (b) Chest computed tomography revealed bilateral, subpleural fibrotic bands at the apical lung regions and a 60 × 44 mm mass in the right lower lobe (arrow)

Before the sixth scheduled cycle of chemotherapy, the patient experienced neck numbness and lightning sensations upon neck flexion. Plain film revealed a mild compression fracture (grade 1, 20%–25%) over cervical (C4–C5) vertebrae. Cervical spine MRI indicated mild sclerotic changes in the cervical (C6) vertebral body but no abnormal enhancement of the cervical spine [Figure 6a and b]. The patient experienced Lhermitte's sign, likely cisplatin-related; consequently, the sixth chemotherapy cycle was withheld. A PET/CT scan revealed considerable regression in the right lower lung mass and bone metastases, with newly noted lesions in the right renal fascia, potentially indicating pseudoprogression during the restaging workup [Figure 7]. No new intracranial lesions were noted on brain MRI.

Given the tumor shrinkage and absence of new lesions, the patient underwent a thoracoscopic right lower lung lobectomy and mediastinal lymph node dissection [Figure 8], which revealed no residual malignancy of the right lower lobe or pleural and lymph node. During active surveillance, a PET scan revealed no uptake in the right renal fascia, and lumbar (L1) vertebra and right femur neck bone metastasis were only observed on a bone scan [Figure 9]. Additional radiotherapy at 3000cGy was applied to the right proximal femur bone. At 2 weeks after radiotherapy completion, monthly subcutaneous injection with denosumab (120 mg) was prescribed for the metastatic bone lesions and to prevent further pathological

fracture. The AFP levels remained below 10 ng/mL. After the last chemotherapy dose, the patient experienced no disease progression. In summary, the patient was given a diagnosis in March of 2021 and achieved an overall survival of approximately 46 months after the treatment series.

DISCUSSION

Cisplatin-based chemotherapy regimens are considered the best first-line treatment for metastatic HAC (mHAC); they are associated with an 81% response rate in actual clinical

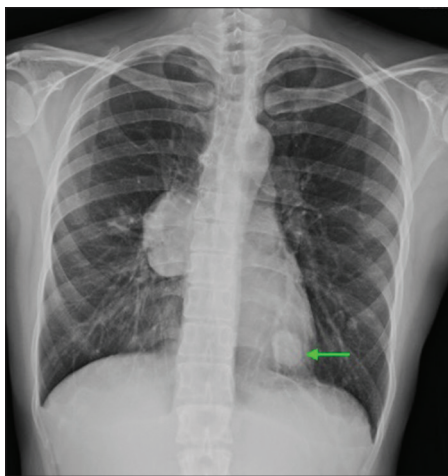


Figure 3: Chest X-ray revealed progressive disease with a new lung mass in the retrocardiac region (arrow)

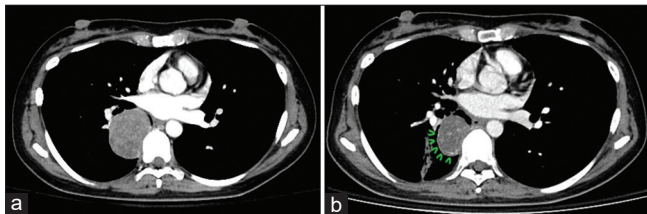


Figure 5: (a and b) Serial computed tomography revealed decreased tumor size (arrowhead). Intratumoral content became more hypodense, suggesting the tumor consisted of less viable tissue and became necrotic after treatment

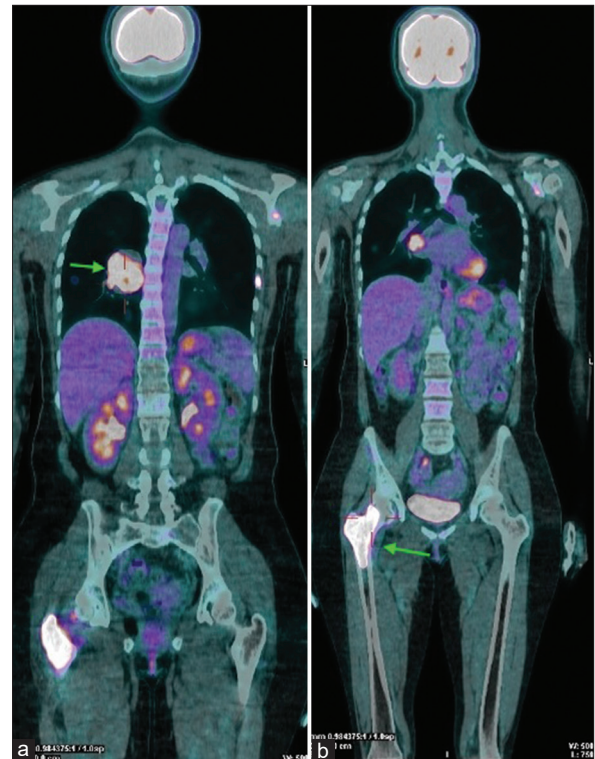


Figure 4: F-18-fluorodeoxyglucose positron emission tomography revealed hypermetabolic lesions in (a) the right lower lung, consistent with primary tumor (arrow), and (b) the right femur (arrow), favoring metastasis

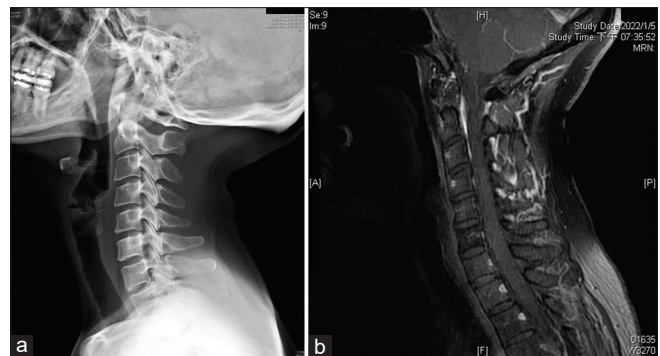


Figure 6: (a) Lateral plain film of cervical spine revealed mild compression fracture at C4/5. (b) Magnetic resonance imaging of cervical spine revealed mild sclerotic changes in the C6 body, including increased fatty bone marrow, suggesting cisplatin-related Lhermitte's sign

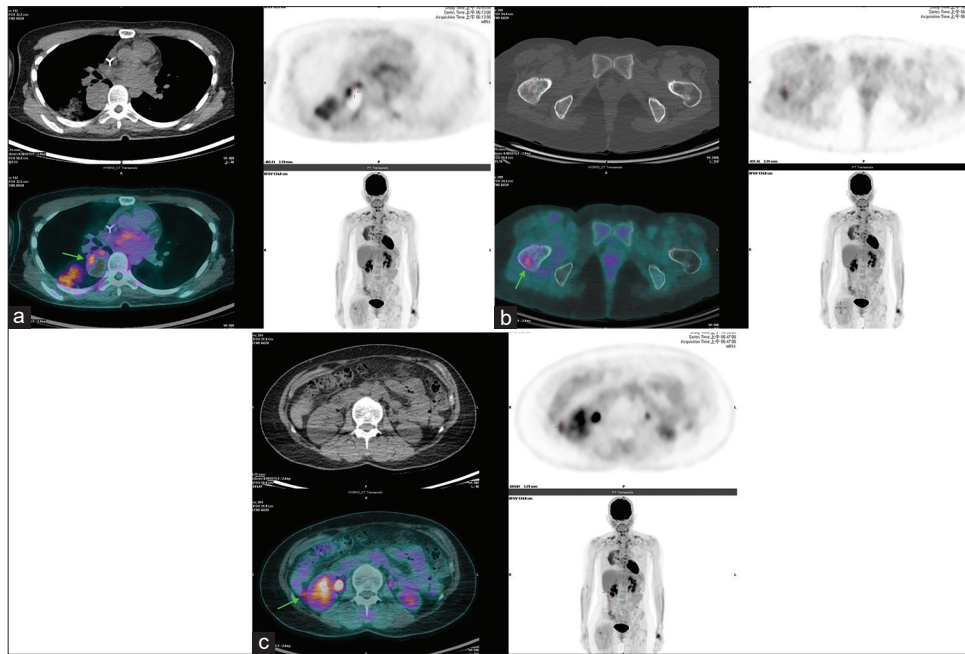


Figure 7: Restaging workup through positron emission tomography revealed pronounced regression in (a) the right lower lung mass (arrow) and (b) bone metastases (arrow); (c) newly noted hypermetabolic lesions in the right renal fascia (arrow), potentially indicating pseudoprogression



Figure 8: Specimens consisted of more than 10 pieces of fragmented lung tissue, measuring up to 19.0 cm × 4.0 cm × 2.3 cm. No evidence of residual malignancy was detected in any specimen

settings.^[11] Two case reports suggest systemic treatment with combined cisplatin and etoposide as an alternative option for patients with mHAC of gastric cardia and synchronous liver metastasis. One of these two patients exhibited a good prognosis after a 9-year follow-up. In a case series of 22 patients with mHAC, treatment included a cisplatin platinum-based regimen and sorafenib target therapy. Five of eight patients treated with the cisplatin-based regimen were responsive (one complete response and four partial responses). Literatures demonstrated cases of mHAC treated with immunotherapy [Table 1].

In another case series involving 59 patients with HAL, the most frequently employed treatment regimens included platinum doublets, chemotherapy combined with immunotherapy, and chemotherapy combined with targeted

therapy.^[11] Platinum therapies were applied in 21 cases (10, 9, and two patients received cisplatin, carboplatin, and oxaliplatin, respectively). A cohort-wide overall survival of 14 months was reported, with the cohort including patients with early-stage disease.

Atezolizumab plus bevacizumab is the standard treatment for unresectable or metastatic HCC. The response rate, median overall survival, and progression-free survival of this regimen are 30%, 19.2 months, and 6.9 months, respectively.^[21] Few reports of HAL treatment with atezolizumab plus bevacizumab exist, and we identified only one such case report in our literature review.^[22] In the report, a 69-year-old male initially presented with a 31-mm lung nodule and a 10-mm liver lesion. The pathology of the pulmonary nodule revealed poorly differentiated carcinoma, leading to an initial diagnosis of metastatic HCC. However, the patient had no history of alcoholism or hepatitis B or C. Consequently, the pathologist performed additional IHC staining, which revealed Hep-Par (+) and CK-7 (+++, diffuse), suggesting another primary cancer in the lung and thus the existence of dual malignancies. Despite this diagnosis, the first two cycles of immunotherapy (combined atezolizumab and bevacizumab) caused tumor shrinkage, prompting the continuation of treatment for an additional 2 months before disease progression.

The factors contributing to the durable response and remarkable progression-free survival of our patient merit closer attention. Previous studies have emphasized the key role of the interaction between cytotoxic chemotherapy and immune checkpoint inhibitors (ICI) in such outcomes.^[23] However, the effect of first-line ICI-based treatment on subsequent second-line chemotherapy and the relationship between

Table 1: Literature review of patients with hepatoid carcinoma treated with immunotherapy

Author	Year	Age/sex	Tumor origin site	Treatment modality	Treatment response
Basse V. <i>et al.</i> ^[12]	2018	43/male	Lung	Durvalumab (lynch)	PR
Anthony El Khoury <i>et al.</i> ^[13]	2019	59/male	Lung	Pembrolizumab + chemo	PR
Galina G.Lagos ^[14]	2021	54/male	Lung	Carboplatin, paclitaxel, and pembrolizumab	PR
Julia E.Seddon ^[15]	2021	33/male	Lung	Pemetrexed, carboplatin, and pembrolizumab	PD
Onder Tonyali ^[16]	2019	62/female	Lung	Nivolumab ×5 cycles	PD
Su-Zhen Xu ^[17]	2022	55/male	Lung	Albumin-bound paclitaxel, carboplatin, and pembrolizumab	PD
Wei Li ^[17]	2020	7 cases	Stomach	Nivolumab, capecitabine, and oxaliplatin	CR:1, PR:5, PD:1
Yunxiang Zhou ^[18]	2023	48/female	Stomach	Terelizumab, SOX (neoadjuvant)	CR
Xin Huang MM ^[19]	2024	73/male	Esophagus	Pembrolizumab, capecitabine and oxaliplatin	SD
Yansha Sun ^[20]	2022	60+/male	Stomach	Sintilimab	CR

PR: Partial responses, PD: Progressive disease, CR: Complete response

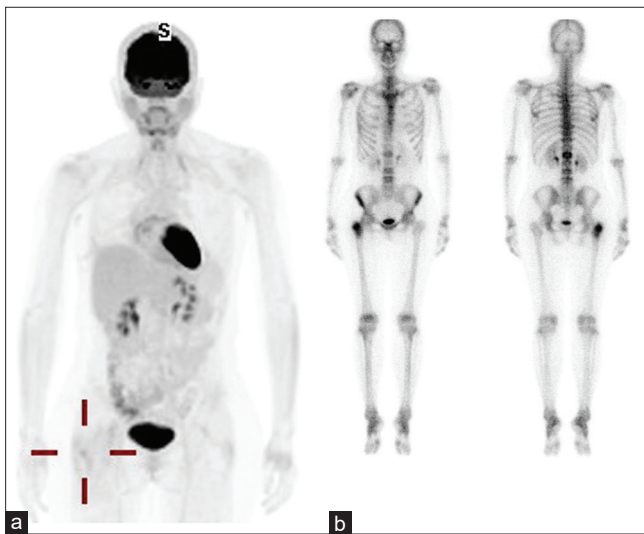


Figure 9: (a) Subsequent positron emission tomography revealed no uptake in the right lung field but faint F-18-fluorodeoxyglucose uptake at the right femoral neck. (b) Bone scan results suggested metastases to L1 and the right femur

treatment sequencing and clinical outcomes remain unclear. Although several retrospective studies have revealed no survival difference between patients administered salvage chemotherapy immediately after ICI and ICI-naïve patients,^[24] other studies have suggested that certain chemotherapy regimens are more effective after immunotherapy.^[25] Nevertheless, data on the effectiveness of chemotherapy following immunotherapy remain inconclusive and insufficient.

Another issue to be discussed is that the diagnosis processes the slight discordance in IHC between typical HAL patterns in the literature review and our case. Typical IHC results include positive staining of AFP, CK7, hepatocyte, Glypican-3, and arg-1 staining, which may be partially or wholly positive.^[7] Nevertheless, our case demonstrated negative CK7 and no IHC for AFP and Hep-Par1. First, the expression of CK7 is not necessary for diagnosis of HAL, although it is usually positive. Study reported that CK18 is positive in HAL, while CK20 is

negative, and CK7 staining may be positive or negative.^[14,26] Besides, in spite of no IHC stain result of AFP and Hep-Par1, positive staining of glypican-3 and HSA showed hepatocellular differentiation. Therefore, our pathologist considered that despite the atypical IHC staining results, the diagnostic process was reasonable.

Finally, our patient achieved excellent outcomes with multidisciplinary therapy, including atezolizumab plus bevacizumab, chemotherapy, radiotherapy, and surgery. Atezolizumab plus bevacizumab represents a potential treatment option. However, this single case report provides limited evidence to support this approach, and the patient's survival outcome cannot be generalized to the majority of other cases. Studies on HAL treatment are lacking because of its rarity. Currently, cisplatin-based chemotherapy regimens are the primary first-line treatment for mHAC, whereas the optimal treatment remains a matter of investigation.

Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

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