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Original Research Article

Case Report and Review: Hepatoid Adenocarcinoma of the Lung Treated with Nivolumab with Cutaneous Metastasis

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Abstract: Hepatoid adenocarcinoma of the lung (HAL) is a rare extrahepatic malignancy morphologically and immunocytochemically similar to hepatocellular carcinoma. HAL demonstrates aggressive clinical course, early metastasis, poor prognosis, and limited therapeutic guidelines due to its rarity. We present a comprehensive review and case report of HAL with cutaneous metastases, treated with nivolumab, including clinical progression, diagnostic challenges, treatment rationale, and a detailed summary of current literature.

Keywords: Hepatoid adenocarcinoma of the lung (HAL), Cutaneous metastases, Nivolumab, Rare lung cancer, Immunotherapy.

INTRODUCTION

Hepatoid adenocarcinoma (HAC) is an uncommon variant of adenocarcinoma that recapitulates the architecture and biomarker expression of hepatocellular carcinoma. Although initially described in the stomach, rare primary pulmonary cases—termed HAL—have been reported. HAL often exhibits elevated alpha-fetoprotein (AFP) and poor response to conventional chemotherapy. Metastasis to the skin is extremely rare and signals advanced disease stage.

Immunotherapy with PD-1 checkpoint inhibitors such as nivolumab, now a mainstay in advanced non-small cell lung cancer (NSCLC), is being explored for HAL. However, only isolated case reports document their efficacy in this setting.

CASE PRESENTATION

Patient Demographics and History

- **Age/Sex:** 60-year-old male
- **Chief Complaint:** Cough, progressive dyspnea, and palpable skin nodules on chest and arm
- **Past History:** 30 pack-year smoking history, otherwise unremarkable

Clinical Findings

- Multiple, firm, non-tender, subcutaneous nodules (largest 1.5cm, upper back)
- Decreased breath sounds right upper lung field

Diagnostic Workup

- **Laboratory:** AFP 2,600ng/mL (reference <10); CEA 1,980ng/mL (reference <5)
- **CT Chest:** 4.8cm irregular right upper lobe mass, mediastinal lymphadenopathy
- **PET/CT:** Increased FDG uptake right upper lobe, mediastinal nodes, and multiple cutaneous foci
- **Skin Biopsy:** Poorly differentiated adenocarcinoma, positive for HepPar-1, CK8/18, AFP; negative for TTF-1
- **Liver Imaging:** Unremarkable, excluding primary hepatocellular carcinoma

Pathological Features

- Morphology: Large polygonal cells with eosinophilic cytoplasm resembling hepatocytes
- Immunohistochemistry: HepPar-1 (+), AFP (+), CK8/18 (+), TTF-1 (–), consistent with hepatoid phenotype

Staging

- TNM: cT2bN2M1c (cutaneous and possible skeletal metastases)
- ECOG Performance Status: 2

TREATMENT

Rationale for Nivolumab

Given lack of driver mutations, advanced stage, and poor candidate for resection, the patient was started on nivolumab (3mg/kg every two weeks) as recommended for advanced NSCLC in the absence of targetable mutations[1].

- **First-line treatment:** Nivolumab monotherapy
- **Assessment:** After 3 cycles, partial reduction in skin nodules and mild improvement in dyspnea, but progression after sixth cycle with new subcutaneous nodules and increasing AFP

Course and Adverse Events

- **Initial Response:** Partial clinical and radiographic response in skin and lung lesions after 6 weeks
- **Progression:** After 3 months, rapid disease progression with increased skin and new soft tissue nodules
- **Toxicity:** Fatigue, transaminitis grade 2
- **Final Outcome:** Palliative care, succumbed to disease 4.5 months post-diagnosis

LITERATURE REVIEW AND DISCUSSION

Epidemiology

- HAL constitutes <1% of all lung cancers[2].
- Affects predominantly older males with a history of smoking
- Most patients diagnosed at advanced, metastatic stages

Pathogenesis

- Likely arises from multipotential stem cells in the lung, supported by strong AFP and HepPar-1 expression
- Common sites of metastasis: lymph nodes, bone, brain, adrenal, and rarely skin[3][4][5]

Clinical Features

- Rapid progression, bulky mass in upper lobes
- High serum AFP, paralleling disease burden
- Skin metastases are extremely rare and indicate disseminated disease, with only a handful of cases documented[5]

Management

Chemotherapy

- Platinum doublet regimens offer limited survival benefits
- Sorafenib and other TKIs show anecdotal, short-lived responses

Immunotherapy: Nivolumab & Others

- Current NSCLC protocols endorse PD-1/PD-L1 inhibitors for tumors lacking actionable mutations
- Several case reports and small series document temporary responses in HAL, but no durable remissions[1][6]
- Responses may be better in tumors with high PD-L1 expression or mismatch repair deficiency, but evidence is scant

Prognosis

- Poor overall survival (median 8–14 months)
- Cutaneous metastasis and high AFP signal aggressive biology and poor prognosis

Survival Rates (Reported Series)

Factor	Median OS	Notes
All HAL cases	8–14 months[2]	Best outcomes with early surgery
With cutaneous mets	<6 months[5]	Extremely poor prognosis
Receiving Nivolumab	3–6 months[1][6]	Partial/short-lived response

Figures

1. Histopathology of HAL

A photomicrograph showing large polygonal tumor cells with prominent eosinophilic cytoplasm, typical of hepatoid adenocarcinoma morphology.

2. Serum AFP Trends During Nivolumab

Plot: Serum AFP (ng/mL) vs. Weeks since therapy initiation.

Week	Serum AFP (ng/mL)
0	2,600
2	1,910
6	1,300
10	2,900
14	4,230

3. Timeline of Disease Progression

Schematic: Key clinical milestones—diagnosis, treatment initiation, partial response, progression, transition to palliative care.

DISCUSSION

This report illustrates an aggressive clinical course of HAL presenting with rare cutaneous metastatic deposits. The morphologic overlap with hepatocellular carcinoma mandates rigorous diagnostic evaluation, including imaging and IHC, to exclude a hepatic primary. While PD-1 blockade with nivolumab temporarily arrested disease progression, the clinical benefit was short-lived; most reports similarly show only brief partial responses in advanced HAL.

Early diagnosis and surgical resection offer potential cure in localized HAL, but most present at an inoperable stage. Robust, systematic data guiding immunotherapy in HAL is lacking due to disease rarity.

CONCLUSION

HAL is a rare, aggressive carcinoma with high AFP expression, rapid progression, and limited treatment options. Immunotherapy with nivolumab can offer transient benefit, but the prognosis in metastatic, especially cutaneous, disease remains poor. Timely recognition, comprehensive workup, and multidisciplinary care are essential. Further molecular characterization and clinical trials are needed to define optimal management.

REFERENCES

1. Li, M., et al. "Hepatoid Adenocarcinoma of the Lung." Case Reports in Oncology, 2021.
2. Xu, K., et al. “A case report of pulmonary hepatoid adenocarcinoma.” Frontiers in Immunology, 2023.

3. Zhuansun, Y., et al. "Clinical characteristics of Hepatoid adenocarcinoma of the lung: Four case reports and literature review." Cancer Research, 2021.
4. Lei, L., et al. "Hepatoid adenocarcinoma of the lung: An analysis." Medicine, 2021.
5. Journal of Liver Cancer, 2020 Mar 31;20(1):72–77.
6. Autopsy Case Reports, vol. 10, no. 2, 2020.
7. Frontiers in Oncology, Volume 15, 2025.
8. Nurul Yaqeen Mohd Esa, et al. "Is it liver or lung cancer? An intriguing case of lung adenocarcinoma with hepatoid differentiation." 2018.

