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LETTER

Complete response of a locally advanced pulmonary hepatoid adenocarcinoma patient to perioperative XELOX-containing chemoimmunotherapy

With morphological features resembling hepatocellular carcinoma, hepatoid adenocarcinoma of the lung (HAL) is a rare and aggressive subtype of lung cancer with a 5-year survival of only 8%.[1] Most HAL patients present increased serum alpha-fetoprotein (AFP) levels that are commonly related to poor prognosis. Most insights into HAL have come from case series or reports, and *TP53* is frequently mutated in HAL. The heterogeneity of HAL complicates the diagnosis. With no established standard, the management of HAL is modeled on that of classical lung adenocarcinoma, although with dismal outcomes.[2] Herein, we reported the effective management of a stage IIIb HAL patient with perioperative chemoimmunotherapy and curative-intent surgery. The patient remained disease-free and minimal residual disease (MRD)-negative for more than one year after surgery.

A 58-year-old male smoker was referred to our hospital in April 2021 with a 2-month history of cough. His serum AFP level was 21979.4 ng/mL (normal range: 0.0–8.1). Chest computed tomography and positron-emission tomography/computed tomography detected a right lower lobe mass (86 mm × 64 mm) and a small mass (6 mm × 7 mm) in the right upper pulmonary lobe invading the right hilar and mediastinal lymph nodes (cT4N2M0, stage IIIb). Histopathologic review of a bronchoscopic biopsy revealed a HAL that stained positively for GPC-3, hepatocyte, AFP, and Ki-67 (70%), and negatively for TTF-1 and Napsin A (Fig. S1). PD-L1 tumor proportion score was 8% (Clone 22C3), and $CD4^+$ and $CD8^+$ lymphocytes were found. Molecular testing identified more than 20 altered genes including *TP53* and *MAP2K1*, and the tumor was considered microsatellite-stable with a tumor mutation burden of 19.6 mutations/Mb. Profiling of circulating tumor DNA (ctDNA) also revealed mutant *TP53* and *MAP2K1* (Fig. S2). The patient was started on capecitabine (1000 mg/m^2, orally, twice daily for days 1–14), oxaliplatin (130 mg/m^2, intravenously, every 3 weeks), PD-1 inhibitor camrelizumab (200 mg, intravenously, every 3 weeks), and bevacizumab (7.5 mg/kg, intravenously, every 3 weeks), which elicited a partial response and ctDNA clearance after two cycles and continued remission after another two (Fig. 1). The right upper lobe lesion had resolved, and the remaining one was evaluated as yT3N2M0. Blood AFP dropped drastically to 20.0 ng/mL. The patient then underwent a right lower lobectomy with the dissection of multiple mediastinal lymph nodes in July 2021. Pathologic examination showed pathologic complete response, the AFP dropped to normal range, and the patient remained MRD-negative. In August 2021, he commenced two cycles of adjuvant capecitabine, oxaliplatin, plus camrelizumab, followed by one year of maintenance therapy with anti-PD-1. The patient showed no evidence of recurrence and had remained MRD-negative for more than 12 months as of the latest follow-up in October 2022.

This is the first case report of a HAL responding to therapeutic strategies for liver cancer, thereby providing a reference for future cases. Several HAL case reports describe the use of NSCLC treatment regimens albeit with limited efficacy. On the other hand, therapeutic options for liver cancer have shown potential anti-tumor activity. The effect of immunotherapy may have been associated with the high mutation burden, a marker of neo-epitope load,[3] and the presence of PD-L1 and $CD8^+$ tumor-infiltrating lymphocytes, which have been reported as correlates of responsiveness to immunotherapy.[4] On the other hand, a study of hepatoid adenocarcinoma of the stomach suggested a generally active but heterogeneous immune

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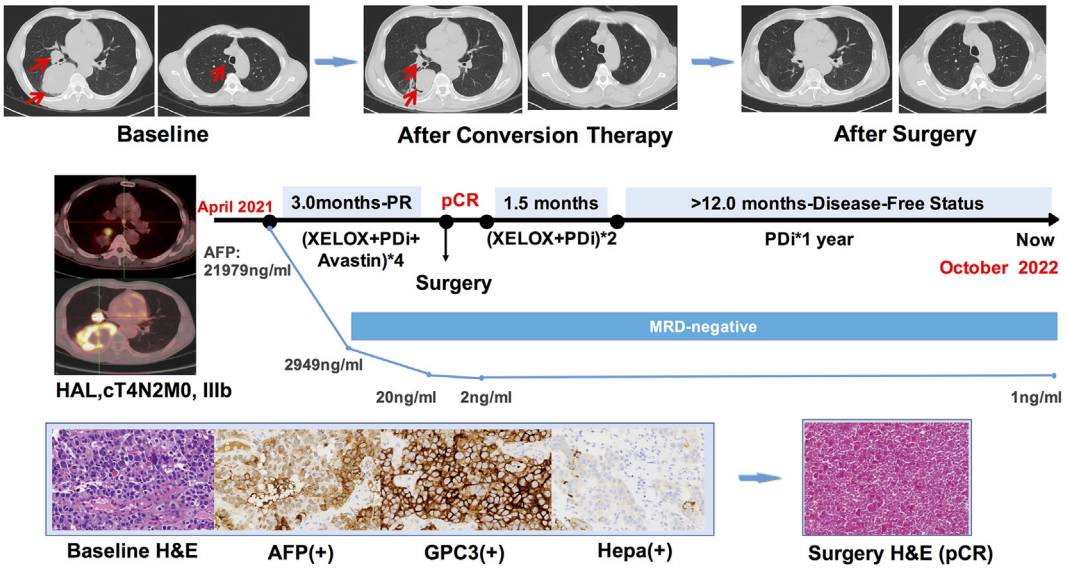

Figure 1 Chronological summary of therapies, imaging studies, pathological pictures, serum AFP, and minimal residual disease (MRD) surveillance. A hepatoid adenocarcinoma of the lung (HAL) patient with stage IIIb (cT4N2M0) responded to combination therapy with XELOX (capecitabine and oxaliplatin), PD-1 inhibitor (camrelizumab), and Avastin (bevacizumab). He then received definitive surgery and two cycles of adjuvant chemotherapy with a PD-1 inhibitor, followed by anti-PD-1 maintenance therapy for one year. He showed no evidence of recurrence and remained MRD-negative for more than 12 months as of October 2022. H&E, hematoxylin and eosin; pCR, pathologic complete response.

microenvironment.[5] It is therefore advisable to explore the functional property of $CD8^+$ T cells and the comprehensive immune features of HAL. Correspondingly, prospective studies are needed to validate and implement the current chemoimmunotherapy model for HAL patients.

Conflict of interests

The authors reported no conflict of interests related to the study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2022.12.006.

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