Answering Reviewers

Dear Editors and Reviewers:

Thank you for your letter and the editor's and reviewers' comments on our article entitled "CK5/6-positive, P63-positive lymphoepithelioma-like hepatocellular carcinoma: A case report and literature review". These opinions are of great value to the revision and improvement of our thesis. I have carefully responded to the comments and revised them in my re-submitted article.

We would like also to thank you for allowing us to resubmit a revised copy of the manuscript. We hope that the revised manuscript is accepted for publication in the World Journal of Clinical Cases.

Yours sincerely,

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Reviewer #1:

The authors have not properly revised the manuscript according our suggestions. Major changes - still - needed.

Response：Thank you for your comments on the manuscript. I have carefully checked and revised the manuscript according to your suggestions.

Reviewer #2:

Specific Comments to Authors: Why was it positive for vimentin and desmin?

Response：Thank you very much for reading my article and giving valuable comments.I provide answers to your questions in the discussion section, lines 3 to 15 on page 8 of the manuscript (Desmin (DES) belongs to the family of intermediate filament proteins that connect cell organelles by forming a cytoskeletal network.....)

Desmin (DES) belongs to the family of intermediate filament proteins that connect cell organelles by forming a cytoskeletal network. Desmin is muscle specific and is expressed in skeletal, cardiac, and smooth muscle cells,including pericytes aligning

neovessels in angiogenesis. In carcinogenesis, increased numbers of desmin-positive pericytes are observed in late-stage tumors, consistent with increased angiogenesis and microvessel maturation.

Vimentin is one of the most familiar members of intermediate filaments (IFs) which is the characteristic of mesenchymal cells. IFs, actin microfilaments and microtubules are three major structural components of the cytoskeleton which are in charge of contraction and migration of cells. In addition, the stucture where vimentin, actin associate with integrins and where vinculin and plectin recruited were termed as the vimentin associated matrix adhesions (VAMs),with the increasing knowledge about it, we have known that the extensive function of vimentin are far more than these. Numerous studies relating to proteomics have shown that vimentin was metastasis-associated factor in multiple malignancies, such as prostate cancer ,breast cancer, gastric cancer, and galbladder cancer. That suggests that vimentin should play an important role in tumor progression and serve as a potential biomarker for the metastasis. Correlation between expression of vimentin, a canonical marker of EMT, and malignancy has been broadly studied; however, how vimentin regulates tumor metastasis and survival remains under investigation.

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Reviewer #3:

Specific Comments to Authors: Some changes needed: - A linguistic revision should be performed by a professional service since there are some grammar mistakes and oversights to be corrected. - A timeline summarizing the main events of this case report should be included, in order to help readability. - Immune checkpoint inhibitors (ICIs) including pembrolizumab, nivolumab, durvalumab, atezolizumab, etc. have been recently evaluated in HCC patients, and clinical trials assessing single-agent ICI have reported disappointing results. Conversely, immune-based combinations have been more striking. In fact, the phase III IMbrave150 trial assessing the

combination of the antiangiogenic agent bevacizumab plus the PD-L1 inhibitor atezolizumab versus single-agent sorafenib has established a new standard of care for HCC patients with advanced disease. According to IMbrave150, atezolizumab - bevacizumab have reported statistically significant and clinically meaningful benefits in several clinical outcomes, including objective response rate (ORR), progression-free survival (PFS), and overall survival (OS), with these advantages also confirmed by the updated results of this trial, showing a median OS of more than 19 months in HCC patients receiving the immune-based combination. Despite ICI seem to have finally found their role in HCC as part of combinatorial strategies, several questions remain unanswered. Among these, the lack of validated biomarkers of response represents an important issue since only a proportion of HCC patients benefit from immunotherapy. Based on these premises, a greater understanding of the role of potential biomarkers including programmed death ligand 1 (PD-L1) expression, tumor mutational burden (TMB), microsatellite instability (MSI) status, gut microbiota and several others is fundamental. In addition, clinical trials on HCC immunotherapy widely differed in terms of drugs, patients, designs, terms of study phases, and

inconsistent clinical outcomes. Based on these premises, the paper assesses a current, timely topic. The background of the changing scenario of medical treatment in HCC should be better discussed, and some recent papers regarding this topic should be included.

Response：Thank you very much for reading my article and giving valuable comments.I have carefully checked and revised the manuscript according to your suggestions.

A timeline summarizing the main events of this case report :

January 21, 2022　A 38-year-old woman was admitted to Zhongshan People's Hospital of Guangdong Province

January 26, 2022　The patient underwent laparoscopic left hepatectomy plus regional lymphadenectomy based on her medical history, signs, and imaging findings. The hepatectomy encompassed the entire left side of the liver; the lymphadenectomy encompassed the lymph nodes anterior and posterior to the common hepatic artery as well as those posterior to the pancreatic head.

After the operation, the patient received symptomatic treatment including immune and targeted therapies (lenvatinib mesilate capsules: daily dose of 8mg orally once a day; tislelizumab injection: 200 mg given intravenously every 3 weeks)

December 30, 2022,the last outpatient follow-up, CT examination showed no obvious masses in the operative area and no obvious abnormal lymph nodes in the abdominal cavity or retroperitoneum. Tumour marker levels were also reduced.

The background of the changing scenario of medical treatment in HCC should be better discussed, and some recent papers regarding this topic should be included:

I provide the answer to your question in lines 8 through 22 of the discussion section on page 10 of the manuscript (At the same time, PD-1 inhibitors are increasingly being studied as immunotherapeutic agents.....).

The treatment of LELC mainly depends on surgery. Surgical resection is currently the first choice for the treatment of LEL-ICC, while chemotherapy, radiotherapy, and other comprehensive therapies are needed for tumours at an

advanced stage or with metastasis. Platinum-based chemotherapy can be used as the first-line of treatment for LELC at an advanced stage. The response rate of LELC for 5-FU/folic acid/cisplatin treatment was 60%; capecitabine alone could be used as the salvage chemotherapy to maintain the stability of the disease. Meanwhile, PD-1 inhibitors have been increasingly explored as immunotherapeutic agents. The possible mechanism underlying the benefit of TACE combined with a PD-1 inhibitor was revealed: TACE could decrease the ratio of CD4+/CD8+ cells and increase the level of PD-1 mRNA expression in patients with HCC. Therefore, TACE combined with a PD-1 inhibitor might have potential clinical value for patients who are refractory to TACE. The combination of atezolizumab (PD-L1-inhibitor) and bevacizumab (VEGF-inhibitor) showed encouraging antitumor activity and safety in a phase 1b trial involving patients with unresectable hepatocellular carcinoma. Based on the results of the IMbrave-150 trial, the combination of bevacizumab and atezolizumab became a new standard of care in the first-line treatment of HCC in BCLC stage C . In this randomized phase III clinical trial, the combination of atezolizumab and bevacizumab demonstrated superiority compared to sorafenib

(median OS 19.2 months vs. 13.4 months ($p < 0.001$)), which led to its recommendation as first-line therapy in several international guidelines. A good prognosis can be obtained after radical resection, which should be combined with carefully planned adjuvant therapy.

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CONCLUSION

Herein, a rare case of primary hepatocellular lymphoepithelioma-like carcinoma is reported. The patient was followed up for 12 months after surgery and was treated with regular immunotherapy and targeted therapy. No tumour recurrence was found. This case will further expand our overall understanding of the diagnosis and treatment of this rare tumour.

We appreciate for Editors and Reviewers' warm work earnestly and hope that the correction will meet with approval. Once

again, thank you in advance for your time and effort dedicated to the matter.