BAISHIDENG PUBLISHING GROUP INC
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242 Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 25527

Manuscript Type: CASE REPORT

Reviewer 1

An interesting case presentation with a long period disease-free up to 5 years. It should be benefit to the knowledge of the hepatologists and keep in mind for the importance of clinical follow up after extensive hepatectomy.

Authors response: none

Reviewer 2

Major comments: 1. The authors need to provide more details on the patient's medical history especially risk factors for developing hepatocellular carcinoma. 2. High AFP level usually is associated with large tumor size, poorly differentiated histology, and macro- and/or microvascular invasion. High AFP is also a risk for tumor recurrence after primary resection. In this case, the authors did not mention if the patient had evidence of microvascular invasion during pathology examination. 3. Sorafenib is not a monoclonal antibody as suggested in introduction. Minor comments: Abstract add '(HCC)' after ... hepatocellular carcinoma Introduction line 2 - suggest changing 'with highest density ...' to 'with the highest prevalence rates ...' line 5 - add 'the' before 'discovery' line 8 - add unit of AFP line 10 - add unit of AFP line 17 - use the full name of OR Discussion line 4 - suggest replacing 'intrahepatic metastases' with 'multifocal tumors

Authors response to major comments:

1. The paper states that she has no history of viral hepatitis, alcoholic liver disease. She also had no history of chronic hepatitis, cirrhosis, tobacco use, diabetes, nonalcoholic fatty liver disease, hemochromatosis, or alpha-1 antitrypsin deficiency

2. The patient did not have evidence of microvascular invasion during pathology examination.

3. Sorafenib is a multikinase inhibitor. This will be corrected.

Authors response to minor comments:

Grammatical errors will be corrected.

Reviewer 3

The authors described a case of recurrence to a solitary suprapancreatic lymph node five years after initial resection. This case report is important because it offers a strategy of resection as a solution to recurrence to a solitary extrahepatic lesion. The contents would give significant information.

Authors response: none

Reviewer 4

This case report is very interesting. Sorafenib is not a monoclonal antibody. It is also used in the treatment of acute myeloid leukemia patients carrying internal tandem duplication of fms-like tyrosine kinase 3 (FLT3-ITD) mutation. After prolonged treatment with sorafenib, cancer cells can become resistant to it. But the combination of an inhibitor of the Na+ / H+ exchanger can restore the response to sorafenib. (Mih?il? RG. A minireview on NHE1 inhibitors. A rediscovered hope in oncohematology. Biomed Pap Med Fac Univ Palacky

Olomouc Czech Repub 2015 Dec; 159(4): 519-526.) There are several grammatical errors that must be corrected. The bibliography is not properly written.

Authors response:

Sorafenib is a multikinase inhibitor – this will be corrected. Grammatical errors will also be corrected. The bibliography will be corrected.

Reviewer 5

This case documents a late metastasis to a solitary node from a liver cancer. Interesting report.

Authors response: none

Reviewer 6

The submitted manuscript presents a case of solitary lymph node metastasis of hepatocellular carcinoma 5 years after hepatectomy including a short review of metastatic HCC to lymph nodes focusing on the importance of surgical treatment. The originality of the case relies primarily on the late recurrence of HCC while surgical resection is considered to be the choice of treatment. Certain corrections and clarifications are necessary. Comments The figures and legends are confusing. The carcinoma depicted in the upper panel corresponds to the primary tumor due to adjacent liver tissue while lymphoid tissue is missing in all 4 figures. The hepatocellular nature of the poorly differentiated metastatic component shown in the lower panel is not unquestionable and immunohistochemical confirmation is required. Hepatic stem cell markers such as keratin 19 should also be examined in order to gain some more information regarding the behavior of the metastatic clone. It is not clear whether metastatic recurrence developed 5 (abstract) or 4 years after hepatectomy (text). There is no comment regarding follow-up.

Authors response:

In the current patient, the combination of tumoral cytomorphology, architecture, and IHC stain pattern, though varying between the two, is diagnostic in both the primary and recurrent HCCa (non-fibrolamellar type). The initial left hepatic lobectomy contained an 11.5cm primary tumor with several smaller 'satellite' nodules, and was completely excised with 1.6cm minimum distance to resection margin. Lymph-vascular invasion was identified (see Figure 1, below). The main recurrent supra-pancreatic mass, initially diagnosed on core biopsy and subsequently resected, was felt by the surgeon to represent nodal metastasis, either as an individual or group of 'matted' nodes, that impression supported by metastatic tumor in the obvious lymph node (see Figure 2, below).

As shown by the combination photomicrograph in Figure 1, the hepatic morphology is focally reminiscent of normal lobular architecture, though the trabeculae, in benign liver usually only a maximum of 2-3 cells thick, are markedly thickened in the tumor, a common finding in HCCa, helpful in diagnosis. IHC stains are negative for Glypican 3 and CK19 in both areas; HepPar1 is negative in the main tumor mass, but borderline positive in the lymph-vascular (L-V) tumor. In Figure 2, the resected recurrent main mass is shown, with abutting but separate recognizable lymph node showing numerous dispersed small collections of obvious tumor cells. Both the main mass and nodal tumor show strong Glypican 3/CK19 dual positivity, and are also positive for HepPar1, the overall findings diagnostic of recurrence with/as lymph node metastasis(es), but now with an ominous IHC stain positivity pattern (as discussed above).

The overall pathology raises unanswered questions and other issues, some of which may be at least partially addressed by more accurate tumor cell analysis, with molecular genetic analysis as the current 'cutting edge' tool for same: The IHC difference between the primary and recurrent/metastatic tumor indicates

clone selection, additionally supported by the contrasting HepPar1 stain negativity in main mass and weak positivity in L-V tumor in the initial resection. Whether clone selection represents a primary phenomenon (before therapy), evidence of therapeutic selection, or components of both, cannot be adequately answered using the information in hand. By convention, only a small minority of tumor was reviewed by the pathologist-of-record on the separate cases, producing an inevitable 'sampling sensitivity' issue (only a small but visually representative minority of large specimens' tumor is sampled/embedded for pathologic analysis, and only a minute fraction of that reviewed on the consequent slides). With its basis in genetic rather than visual appearance, future molecular analysis of fresh tumors, with more comprehensive sampling (than the current formalin-fixed, paraffin-embedded samples with the same 'sensitivity' issue as above), may provide more accurate information regarding 'true' tumor type/subtype, including contradistinctions between primary and metastatic tumor, and predictors of behavior, 'targets' for therapy, and population screening opportunities.