ROUND 1

2rd October, 2022

Dear reviewers,

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Surgical treatment of liver inflammatory pseudotumor-like follicular dendritic cell sarcoma: A case report and review of literature" (79342).

Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Reviewer #1:

The authors discuss the diagnostic and treatment modalities regarding FDS using a 23 years old female patient case. My comments: 1. Introduction section: a)What is the second variant of FDS that you have mentioned in the text. b)What is the association between EBV and FDS 2. Case report: a) Please explain why you have not used preoperative biopsy b) Please state at which postoperative the patient is in and if used, please state the type of adjuvant therapy used. 3. Discussion: Please make a literature review and indicate how many cases have been reported until now and please state : a)The demographics of the cases b)localization of the reported tumors c) role of preoperative biopsy d)Are there any alternative therapies to resection such as transplantation or locoregional therapies Thank you very much.

1. Introduction section: a)What is the second variant of FDS that you have mentioned in the text. b)What is the association between EBV and FDS.

Response: At present, there are few literature reports on IPT-1ike FDCS, and only dozens of cases are reported in foreign literature. FDCS is a rare malignant tumor, and IPT like FDCS, as its special type, is even rarer. There is a clear boundary between IPT-like FDCS and the surrounding normal tissues. Microscopically, a large number of lymphocytes and plasma cells can be seen in the background with diffused follicular dendritic cells, which look like inflammatory pseudotumor/inflammatory myofibro-blastoma. This is also one of the main differential diagnoses. Bleeding and necrosis can occur in the center. The tumor cells are spindle, oval or round, arranged in a pattern like, fascicular or single scattered distribution.

The cytoplasm of the tumor cells is light stained or slightly eosinophilic red, the cell boundary is unclear, the nucleus is oval or rod-shaped, the chromatin is vacuolated or stippled, small nucleoli can be seen, and mitotic figures are rare. The immune-phenotype of IPT like FDCS is basically the same as that of normal FDC. The immunohistochemical characteristics of FDC mainly include CD21, CD23, and CD35. In addition, CNA-42 is a specific monoclonal antibody. There are two morphologic variants of this tumor: conventional and inflammatory pseudotumor IPT-like FDCS[1].

The etiology and pathogenesis of IPT-like FDCS are not clear. Its occurrence may coincide with EBV infection, because in cases with confirmed IPT-like FDCS, the positive rate of Epstein-Barr encoding region (EBER) through *in situ* hybridization was as high as 92.1%[2]. EBV encoded small RNA (EBER) exists in all tumor cells, and hybridization imprinting test confirmed that the virus exists in the form of a monoclonal free body, suggesting that EBV infection occurred before FDC tumor proliferation. CD21, the receptor molecule expressed on the surface of FDC, is the receptor of EB virus, so scholars speculate that EB virus plays an important role in tumor formation.

2. Case report: a) Please explain why you have not used preoperative biopsy b) Please state at which postoperative the patient is in and if used, please state the type of adjuvant therapy used.

Response: Preoperative biopsy is an indispensable method before many operations, which is important for diagnosis and treatment. In this case, after discussion with the radiologist, it is highly suspected that it is early hepatocellular carcinoma according to the imaging signs and clinical manifestations. Therefore, the patient underwent the surgery.

In addition, there was no other adjuvant treatment for the patient according to the preoperative comprehensive evaluation. So far, no standard treatment method has been established for IPT-like FDCS. Surgical resection is the first choice for patients with localized liver disease. IPT like FDCS is a low-grade malignant tumor with a tendency to recur. Only a few cases can have regional lymph node or distant metastasis. Some studies believe that the tumor with large volume, diameter>6cm, accompanied by coagulative necrosis, tumor cells with obvious hetero-morphism, and mitotic figures>5/10HPF are indicators of poor prognosis. However, there is no comparative study on whether these poor prognostic factors are also applicable to HIPT like FDCS.

3. Discussion: Please make a literature review and indicate how many cases have been reported until now and please state : a)The demographics of the cases b)localization of the reported tumors c) role of preoperative biopsy d)Are there any alternative therapies to resection such as transplantation or locoregional therapies

Response: We analyzed all the current literature on IPT-like FDCS, more than 60 cases of IPT-like FDCS have been reported in English literature, mainly located in the liver[3-6] and spleen[7-10], and to a lesser extent in the colon[11-13], lungs[14], and pancreas[15]. More than 20 cases have been reported in the liver, more than 30 cases in the spleen, 1 case in the pancreas, 6 cases in the colon,

and 1 case in the lung. The tumor mainly occurs in middle-aged and elderly people, with a female-to-male ratio of 2.2:1, and a median age of 56.5 years.

If it is highly suspected to be IPT like FDCS, it is important to perform routine puncture biopsy. But many false negative cases have been encountered due to less amount of obtained puncture tissue. Its definitive diagnosis mainly relies on immunohistochemical and *in situ* hybridization analyses of surgically obtained tumor specimens. In the treatment of HIPT-like FDCS, complete resection of tumor is the best treatment, but there is still a dispute about whether conventional radiotherapy and chemotherapy are needed after surgery. Chemotherapy and/or radiotherapy can be used for patients with recurrence or surgery that cannot be cured[16-18].

Special thanks to you for your good comments.

Reviewer #2

This is a case report about inflammatory pseudotumor-like follicular dendritic cell sarcoma (IPT-like FDCS), which is rare with low malignant potential. The patient was asymptomatic at presentation, and the findings from routine laboratory examinations were normal except for slightly elevated alpha-fetoprotein levels (AFP). The patient was diagnosed with HCC before hepatectomy. However, the tumor specimens submitted for pathological analyses revealed HIPT-like FDCS. The author concluded that HIPT-like FDCS is difficult to distinguish from HCC. However, they had not shown a detailed discussion about how to distinguish between HIPT-like FDCS and HCC in the discussion section. Additionally, adding detailed information on survival, recurrence, and metastasis of HIPT-like FDCS in the discussion section may be more appropriate. Finally, what are the possible causes of the patient with slightly elevated AFP before hepatectomy? And whether the AFP level returned to normal after the operation?

1. However, they had not shown a detailed discussion about how to distinguish between HIPT-like FDCS and HCC in the discussion section.

Response: Because the imaging manifestations of IPT-like FDCS of the liver are nonspecific, CT usually shows low-density nodule enhancement, which is characterized by non-uniform enhancement in the arterial phase and resolution in the delayed phase. Some highly differentiated HCCs can also show resolution in the delayed phase; therefore, HIPT-like FDCS should also be differentiated from HCC with internal necrosis via imaging findings. The latter often has peripheral structural invasion, accompanied by cirrhosis and portal hypertension, and may have tumor thrombus formation.

This patient has chronic hepatitis B, and AFP is elevated. The value of alpha beta protein (AFP) level, is 12.31 ng/mL (normal=0.00 – 7.00 ng/mL). Combined with imaging characteristics, we finally diagnosed hepatocellular carcinoma clinically. Therefore, we should pay attention to the possibility of this disease in addition to the huge mixed echo mass in the liver. The final diagnosis still requires needle biopsy or pathological analysis after surgical resection.

The diagnosis should be confirmed by immunohistochemistry; In terms of immunohistochemistry, inflammatory pseudotumor like follicular dendritic cell sarcoma expresses one or more characteristic markers, including CD21, CD23, CD35, and EB virus encoded mRNA, which often need to be used together. When one or more positive expressions occur, it is helpful to improve the diagnosis of inflammatory pseudotumor like follicular dendritic cell sarcoma by combining histological morphology.

2. Additionally, adding detailed information on survival, recurrence, and metastasis of HIPT-like FDCS in the discussion section may be more appropriate.

Response: The incidence of IPT like FDCS is very low, in the review, the

recurrence and metastasis rate and mortality rate of previously reported liver cases were very low, and 4 cases recurred or metastasized, the recurrence rate was 11.8%, and the mortality rate was 2.9%[2]. The remaining cases survived well.

Because inflammatory pseudotumor like FDC sarcoma and traditional FDC sarcoma both show relatively inert clinical behavior, the latter is more aggressive than the former (recurrence or metastasis, even death). Complete surgical resection is important for the prognosis of patients. Therefore, it is very important whether the surgical resection is complete. It is recommended that doctors carefully check the surgical resection specimens to ensure that the cutting edge is clean. Surgical resection is the first choice for the treatment of hepatitis pseudotumor like follicular dendritic cell sarcoma. Most patients can be cured by surgical resection of the lesion, but there is still a dispute about whether conventional radiotherapy and chemotherapy are needed after surgery[16-18].

3. Finally, what are the possible causes of the patient with slightly elevated AFP before hepatectomy? And whether the AFP level returned to normal after the operation?

Response: The patient had received entecavir as treatment for her hepatitis B infection 2 years previously, and was a patient with chronic hepatitis B. In clinical practice, some patients with chronic hepatitis B and hepatitis C will have some changes in AFP due to long-term viral stimulation. We consider that the increase of AFP in patients before surgery is related to chronic hepatitis. Because hepatitis B virus causes necrosis of liver cells, proliferation of collagen and fibrous tissue in liver lobules and portal areas, and the formation of regenerative nodules of liver cells, this kind of regenerated immature cells has the ability to produce AFP, resulting in the increase of AFP content, which has a certain impact on the clinical diagnosis of IPT-like FDCS. AFP did not decrease significantly after operation. In other special cases, such

as liver cirrhosis, pregnant women (especially the fetus with severe congenital neural tube defects and stillbirth), serum AFP may increase to varying degrees within a certain period of time.

Special thanks to you for your good comments.

ROUND 2

Reviewer# 3

Unfortunately I have not seen any revisions made in accord with my suggestions. Also the response to reviewers doc does not contain the points addressed by the authors. The manuscript shall be reevaluated after the necessary response has been given.

Response : Dear professors, I have revised the article according to your valuable comments, please review it. Finally, we would like to thank you again for your valuable suggestions, which make our article closer to better. thank you.

Special thanks to you for your good comments.

1 **Pileri SA**, Grogan TM, Harris NL, Banks P, Campo E, Chan JKC, Favera RD, Delsol G, De Wolf-Peeters C, Falini B, Gascoyne RD, Gaulard P, Gatter KC, Isaacson PG, Jaffe ES, Kluin P, Knowles DM, Mason DY, Mori S, Muller-Hermelink HK, Piris MA, Ralfkiaer SH, Su IJ, Warnke RA, Weiss LM, Weiss LM. Tumours of histiocytes and accessory dendritic cells: an immunohistochemical approach to classification from the International Lymphoma Study Group based on 61 cases. *Histopathology* 2002; **41**: 1-29 [PMID: 12121233 DOI: 10.1046/j.1365-2559.2002.01418.x]

2 **Ge R**, Liu C, Yin X, Chen J, Zhou X, Huang C, Yu W, Shen X. Clinicopathologic characteristics of inflammatory pseudotumor-like follicular dendritic cell sarcoma. *Int J Clin Exp Pathol* 2014; **7**: 2421-2429 [PMID: 24966952]

3 **Ana AS**, Rodriguez JC, Jimėnez EG, Baena PB. Inflammatory pseudotumor-like follicular dendritic cell sarcoma of the liver. *Rev Esp Enferm Dig* 2021; **113**: 378-379 [PMID: 33371694 DOI: 10.17235/reed.2020.7602/2020]

4 **Lu SS**, Wang Z, Zhao S, Liu WP. [Hepatic inflammatory pseudotumor-like follicular dendritic cell sarcoma with paravertebral metastasis and recurrence: report of a case]. *Zhonghua Bing Li Xue Za Zhi* 2021; **50**: 958-960 [PMID: 34344089 DOI: 10.3760/cma.j.cn112151-20210325-00234]

5 **Pascariu AD**, Neagu AI, Neagu AV, Băjenaru A, Beţianu CI. Hepatic inflammatory pseudotumor-like follicular dendritic cell tumor: a case report. *J Med Case Rep* 2021; **15**: 410 [PMID: 34321082 DOI: 10.1186/s13256-021-02957-5]

6 **Jin K**, Li MN, Li S, Li J, Chen N. [Hepatic inflammatory pseudotumor-like follicular dendritic cell sarcoma]. *Zhonghua Gan Zang Bing Za Zhi* 2020; **28**: 172-174 [PMID: 32164072; DOI: 10.3760/cma.j.issn.1007-3418.2020.02.015]

7 **Hang JF**, Wang LC, Lai CR. Cytological features of inflammatory pseudotumor-like follicular dendritic cell sarcoma of spleen: A case report. *Diagn Cytopathol* 2017; **45:** 230-234 [PMID: 27775241 DOI: 10.1002/dc.23626]

8 **Kwon H**. Inflammatory pseudotumor-like follicular dendritic cell tumor of the spleen. *Turk J Gastroenterol* 2018; **29**: 128-130 [PMID: 29391320 DOI: 10.5152/tjg.2018.17220]

9 **Li X**, Shi Z, You R, Li Y, Cao D, Lin R, Huang X. Inflammatory pseudotumor-like follicular dendritic cell sarcoma of the spleen: computed tomography imaging characteristics in 5 patients. *J Comput Assist Tomogr* 2018; **42**: 399-404 [PMID: 29287022; DOI: 10.1097/RCT.0000000000000700]

10 **Gong QX**, Fan QH, Zhou ZS, Zhang ZH, Yu MN, Wang Z, Wang C, Zhang WM. [Inflammatory pseudotumor-like follicular dendritic cell tumor of spleen]. *Zhonghua Bing Li Xue Za Zhi* 2008; **37**: 40-44 [PMID:18509984]

11 **Kazemimood R**, Hamedani FS, Sharif A, Gatoinde S, Wiley E, Guilianotti PC, Groth JV. A rare case of Epstein-Barr virus negative inflammatory pseudotumor-like follicular dendritic cell sarcoma presenting as a Soitary colonic mass in a 53-year-old woman; case report and review of literature.

Appl Immunohistochem Mol Morphol 2017; **25**: e30-e33 [PMID. 27299190 DOI: 10.1097/*PAI*.0000000000000405]

12 **Pan ST**, Cheng CY, Lee NS, Liang PI, Chuang SS. Follicular dendritic cell sarcoma of the inflammatory pseudotumor-like variant presenting as a colonic polyp. *Korean J Pathol* 2014; **48**: 140-145 [PMID: 24868227 DOI: 10.4132/KoreanJPathol.2014.48.2.140]

13 **Shi QY**, Zheng Z, Wu HY, Chen JY, Fan XS. [Colonic inflammatory pseudotumor-like follicular dendritic cell sarcoma: report of a case]. *Zhonghua Bing Li Xue Za Zhi* 2022; **51**: 138-140 [PMID: 35152634 DOI: 10.3760/cma.j.cn112151-20210727-00531]

14 **de la Guía-Galipienso F**, Sanchis-Gomar F, Quesada-Dorador A. Diagnostic electrophysiological study in a highly trained young woman with presyncopal symptoms during exercise: a case report. *Ann Transl Med* 2021; **9**: 177 [PMID: 33553370 DOI:10.21037/atm-20-4965]

15 **Mograbi M**, Stump MS, Luyimbazi DT, Shakhatreh MH, Grider DJ. Pancreatic inflammatory pseudotumor-like follicular dendritic cell tumor. *Case Rep Pathol* 2019; **2019**: 2648123 [PMID: 31885993 DOI: 10.1155/2019/2648123]

16 **Zhang BX**, Chen ZH, Liu Y, Zeng YJ, Li YC. Inflammatory pseudotumor-like follicular dendritic cell sarcoma: A brief report of two cases. *World J Gastrointest Oncol* 2019; **11**: 1231-1239 [PMID: 31908727 DOI: 10.4251/wjgo.v11.i12.1231]

17 **Choe JY**, Go H, Jeon YK, Yun JY, Kim YA, Kim HJ, Huh J, Lee H, Shin DH, Kim JE. Inflammatory pseudotumor-like follicular dendritic cell sarcoma of the spleen: a report of six cases with increased IgG4-positive plasma cells. *Pathol Int* 2013; **63**: 245-251 [PMID: 23714251 DOI: 10.1111/pin.12057]

18 **Zhao M**, Du X, OuYang B, Li M, Yang H. Inflammatory pseudotumor-like follicular dendritic cell sarcoma mimicking a colonic polyp. *J Gastrointest Surg* 2021; **25**: 2429-2430 [PMID: 33674906 DOI: 10.1007/s11605-021-04961-y]

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper

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

Once again, thank you very much for your comments and suggestions.

Yours sincerely,

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