WJH

Response to the reviewer

1- The reviewer is correct, the manuscript was hard to follow through. To improve the easiness without changing the backbone structure of the manuscript, we modified the presentation as follow. For each single type of nodule corresponding to a single clinical case we added in the initial presentation comments of all figures pertaining to this case without modifying the order of the micrographs. It is not entirely satisfactory but it is the only way to maintain our initial choice to proceed step by step (macrographs, micrographs, FNH typical, atypical , etc)
2- We added references whenever justified
3- English was reviewed as requested by a researcher trained for years in English speaking Canada.
4- The reviewer is correct, legend of Fig 1 C was incorrect and was modified accordingly
5- In legend (Fig 9 CD) we mentioned that the presence of rosettes was suggestive of malignant transformation. The reviewer argues against and is partially correct. Indeed, in the present case we should use the appropriate term “glandular formation” instead of rosette formation. Glandular formation is definitely associated with HCC.

Minor issues

1- We provided page number for reference 2
2- we added magnification when needed

Additional modifications

We modified the presentations according to the rules of the journal

We shortened the title, we added a running title, the post code, the author contribution, the core tip

We rewrote (in part) the abstract, we modified slightly the introduction and added a paragraph concerning Material and methods

Recommendations

In this article we have not tried to illustrate the most difficult cases but rather depict routine cases that occasionally give rise to problems in interpretation

The differential diagnosis between FNH and HCA is crucial. In the immense majority of cases, diagnoses can be achieved with high confidence. The diagnosis of “bleeding FNH” or “malignant FNH

transformation" or "mixed tumor", if it ever exists, as published in a few case reports, should be confirmed by experts in the field and by molecular biologists.

The ideal HCA classification combines clinical, biological, radiological and pathological data including routine histology and immunohistochemistry.

As already said, it is important to sample tissue specimens : a) at the border of the nodule in order to be able to compare on the same slide the immunohistochemistry data from the tumoral and non tumoral tissue; b) in different areas of the tumor if the later looks heterogeneous.

Each time difficulties in interpretation are encountered, it is recommended to ask another well-trained liver pathologists to review the case .

It is important to keep in mind that the immunohistochemical classification is not the perfect counterpart of the molecular classification, as such we have to improve our cooperation between pathologists and molecular biologists to give to clinicians meaningful data in terms of diagnosis and prognosis. This is particularly relevant in some circumstances (i.e. men, male hormone administration), in case of underlying liver diseases (i.e. vascular diseases, glycogenosis, familial adenomatous polyposis, etc…), or when all nodules are not resected, or when the margin is minimal or even absent etc….

The malignant transformation of HCA has not been illustrated in this atlas. If rare, it is a reality. We still have to understand the degree of aggressiveness and how it will impact the clinical management.

Finally the behavior of multiple nodules – if not all resected, which is the rule - needs to be evaluated.

We hope that all these changes will be acceptable to the journal