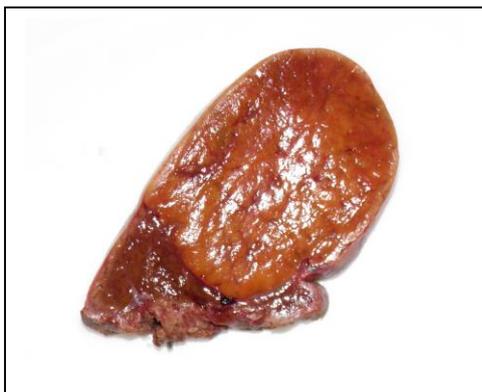


Both focal nodular hyperplasia (FNH) and hepatocellular adenoma (HA) represent benign proliferations of hepatocytes that result in a mass lesion arising in a non-cirrhotic liver. Whilst both entities occur much more commonly in women, there are otherwise striking differences in their clinicopathological features.

Focal nodular hyperplasia (FNH) is by far the more common of the two entities. It represents a polyclonal proliferation of hepatocytes that is likely to reflect a response to a localized increase in blood flow. FNH is not associated with OCP use and can be managed conservatively unless there is a concern regarding the diagnosis. The natural history is for these lesions to remain stable over time. They can be multiple or associated with haemangiomas or adenomas. Histologically there are nodules of hepatocytes separated by fibrous bands with a ductular reaction at the interface as well as a central fibrous scar with dystrophic vessels.



Hepatic adenomas (HCA) are a monoclonal proliferation of well differentiated hepatocytes without portal tracts and bile ducts.

Four major molecular subtypes are now identified each with specific phenotypic features and clinical implications. Histological assessment of these lesions requires interpretation of immunoperoxidase stains for LFABP, SAA, CRP, GS and β catenin (see below) in addition to morphology.

1. HNF1A mutated adenoma (H-HCA)

(30-40%)

- Inactivating mutation of HNF1A gene with dysregulation of glucose and lipid metabolism
- Rare (10%) have germline inherited HNF1A mutation associated with maturity onset diabetes type 3 (MODY3) and adenomatosis
- Histology – marked steatosis; loss of staining of liver fatty acid-binding protein (LFABP)

2. Inflammatory adenoma (I-HCA) (40-50%)
- Previously designated as telangiectatic FNH
 - Activating mutations of either IL6ST (gp130), STAT3 or GNAS genes leading to activation of JAK/STAT inflammatory pathway
 - Histology – inflammatory infiltrate, sinusoidal dilatation and bile ductular proliferation (mimicking FNH); overexpression of serum amyloid A (SAA) and CRP. Adjacent liver can show steatosis or steatohepatitis
 - Clinically – associated obesity and high alcohol intake. May see a systemic inflammatory syndrome and anaemia which resolves following resection.
3. β catenin activated adenoma (b-HCA) (<10%)
- Activating mutation β catenin with activation of Wnt/ β catenin pathway
 - Mutually exclusive of HNF1A mutation but can be combined with gp130 or GNAS mutations (inflammatory adenomas)
 - Histology – nuclear staining for β catenin and strong homogeneous cytoplasmic staining for glutamine synthetase; usually with features of inflammatory adenoma
 - Clinically – usual subtype seen in males
4. Unclassified (10-40%)

Risk factors: Hepatic adenomas are associated with exogenous oestrogen use and androgen use is a risk factor particularly for the β catenin activated subtype. Regression can be seen following steroid withdrawal. Inflammatory adenomas are associated with alcohol consumption and obesity.

Complications: Haemorrhage is a risk in tumours >5cm but it remains unclear if this applies across the various subtypes. The risk of malignancy is estimated at 4-8% (but likely to be much less) and seems to be even lower in HNF1A mutated adenoma. Male sex and β catenin activating mutations are particular risk factors for malignant transformation.

Management: Surgical resection is indicated for tumours >5cm and all hepatic adenomas in male patients. In women with tumours <5cm resection should be considered if there is evidence for β catenin activation on histology. Pregnancy in the presence of known hepatic adenoma (<5cm; no β catenin activation) is not necessarily contraindicated with close follow up.

Diagnostic considerations:

1. FNH vs inflammatory adenoma. This is less of an issue when morphological features can be interpreted along with immunoperoxidase stains. FNH shows strong map-like staining with GS; stains for CRP and SAA are negative.
2. Hepatocellular adenoma vs well differentiated hepatocellular carcinoma (HCC). β catenin activated inflammatory adenomas can show atypia and pseudoacinar change. Adenomas are rare in men, adolescents and post-menopausal women.

Further reading

Nault J-C, Bioulac-Sage P, Zucman-Rossi J. Hepatocellular benign tumors – from molecular classification to personalized clinical care. Gastroenterology 2013; 144: 888-902

Shafizadeh N, Genrich G, Ferrell L, Kakar S. Hepatocellular adenomas in a large community population, 2000 to 2010: reclassification per current WHO classification and results of long-term follow-up. Hum Pathol 2014; 45: 976-983