Hepatic Adenomas
Classification, Controversies, and Consensus

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KEYWORDS

• Hepatic adenoma • Heptaocellular adenoma • Histology • Pathology • Classification
• Inflammatory adenoma • HNF1 alpha inactivated adenoma • Beta-catenin activated adenoma
• Androgen adenoma • Pigmented adenoma • Myxoid adenoma • Malignant transformation

Key points

- Hepatocellular adenomas are classified using immunostains in order to identify tumors at greatest risk for malignant transformation and for hemorrhage.
- These three rare types of hepatocellular adenomas do not fit as well in the current classification system, but are also at high risk for malignancy: androgen related hepatocellular adenomas, pigmented hepatocellular adenomas, myxoid hepatocellular adenomas.
- Risk factors for malignant transformation include patient gender, patient age, adenoma size, cytological atypia, beta-catenin activation, adenoma subtype.

ABSTRACT

Rapid advances in molecular and anatomic pathology have greatly improved our understanding of hepatocellular adenomas. Principle among them is a clinically relevant, histology-based classification that identifies hepatic adenomas at greatest risk for malignant transformation. This new classification system has led to general consensus on the major subtypes of hepatic adenomas. However, controversy remains regarding how to incorporate less common types of hepatic adenomas into the classification system and how to incorporate adenoma subtyping into clinical care. This article provides an in-depth review of how adenomas are classified, with a focus on the current rationale, the consensus, and controversies.

OVERVIEW

There have been rapid advances in our understanding of hepatic adenomas over the past decade or so. Notable advances include a clinically relevant, histology based classification system, recognition that fatty liver disease is a risk factor for inflammatory adenomas, and further clarification of risk factors for malignant transformation. In terms of nomenclature, hepatic adenoma and hepatocellular adenoma are synonyms and can be used interchangeably. Liver adenoma or liver cell adenoma are sometimes used, but are less desirable terms, because a bile duct adenoma would in theory also be covered by these more generic terms.

DEFINITION

Hepatic adenomas are benign, clonal proliferations of phenotypically mature hepatocytes. By light microscopy, they have no or minimal cytologic or architectural atypia. By molecular analysis they are chromosomal stable, with few mutations compared with hepatocellular carcinomas. Hepatic adenomatosis is defined as the presence of 10 or more adenomas. Hepatic adenomas occur in livers without cirrhosis. In most cases, the background liver is histologically normal, but steatosis or steatohepatitis can be found and are recognized as risk factors for inflammatory adenomas.[1]

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HEPATIC ADENOMA-LIKE NODULES IN CIRRHOTIC LIVERS

Several studies[2–5] have described nodules in alcohol related cirrhotic livers that are positive for serum amyloid A (SAA) by immunohistochemistry, and some studies have suggested using the term *hepatic adenoma* for these lesions. Although the data are interesting and important, the suggestion to call these lesions adenomas is premature and not warranted by the currently available data. The argument for calling these nodules adenomas is essentially that they are not hepatocellular carcinomas, they look somewhat like adenomas by light microscopy, and a subset stain with SAA and/or C-reactive protein (CRP) by immunohistochemistry. However, the morphology is often not typical of inflammatory adenomas.[2] In addition, a subset of both ordinary cirrhotic nodules and of hepatocellular carcinomas stain with CRP and SAA, so the mere fact of staining for these proteins does not indicate their proper classification is hepatic adenoma. Put another way, shared dysregulation of a common cellular signaling pathway by 2 lesions does not mean they are the same tumor. For example, fibrolamellar carcinomas can show reduced or absent expression of liver fatty acid binding protein (LFABP),[6] but this does not make them HNF1-alpha–inactivated hepatic adenomas. Nor is it informative if these SAA-positive lesions are clonal, because macroregenerative nodules are frequently clonal in cirrhosis.[7]

There are plausible scenarios to explain rare lesions that morphologically resemble inflammatory adenomas in cirrhotic livers. For example, the hepatic adenomas could have developed first because of the alcoholic liver disease, with the subsequent development of cirrhosis, also secondary to the alcohol use. Even if this were the case, the biological behavior of these lesions is not known. In contrast, the natural history of hepatic adenomas is well-established—they are benign with a small risk of malignant transformation, a risk that is predicted by clinical, histologic, and molecular findings. Lumping these entities together is currently not supported by published literature and it is hard to see how such an approach is in the best interest of patients.

For these reasons, making a diagnosis of a hepatic adenoma in a needle biopsy of a nodule in a cirrhotic liver is very strongly discouraged. In a fully resected specimen, the distinction is perhaps more of academic interest than clinical relevance, but classifying these SAA-positive nodules as definite hepatic adenomas still erodes the well-established clinicopathologic entity known as hepatic adenoma. Perhaps the landscape will change in the future, but at this point it is best to not classify these lesions as hepatic adenomas.

CLINICAL FINDINGS

Overall, 80% to 90% hepatic adenomas occur in one of the following settings[8]: (1) young to middle-aged women with exogenous estrogen use and (2) young to middle-aged women with fatty liver disease, a risk factor that also is most likely acting through endogenous estrogen increases. Excess androgen exposure in either young men or young women is also a well-recognized risk factor for hepatic adenomas. Other risk factors for adenomas include mechanical diseases leading to abnormal hepatic blood inflow (eg, Abernathy syndrome) or abnormal blood outflow (eg, Budd–Chiari syndrome),[9,10] genetic metabolic diseases (eg, glycogen storage disease, principally but not exclusively type 1), and McCune–Albright syndrome.[11]

Serum levels of CRP can be increased in cases of inflammatory adenomas, but practically speaking there are no blood tests clinically helpful in diagnosing or managing hepatic adenomas. Serologic studies show normal levels of alpha-fetoprotein and normal or mild nonspecific increases in liver enzymes.

CLINICAL MANAGEMENT

Guidelines from both the European Association for Study of the Liver[12] and the American College of Gastroenterology[13] do not recommend a routine role for biopsy in the diagnosis of hepatic adenoma, or for histologic subtype determination, but instead recommend biopsies only if imaging findings are not typical for a hepatic adenoma. This clinical management approach is based on published papers that report a very high sensitivity and specificity for diagnosing hepatic adenomas using MRI—performance characteristics that do not always match the experience of many clinicians in their local practice, so biopsies for diagnosing hepatic adenomas are still fairly common. Once a hepatic adenoma is diagnosed by imaging or histology, most cases are managed by the risk factors of gender and lesion size and interval growth, with tumors referred for surgery when they are in men, greater than 5 cm, or show interval growth during follow-up. When available, histologic risk factors (atypical cytology, beta-catenin activation) can also be used to guide management.

DIAGNOSTIC APPROACH

Hepatic adenomas are well-differentiated tumors with little or no cytologic atypia. At high power, the tumor cells should look essentially like the hepatocytes in the background liver (**Fig. 1**A, B). Mild patchy nuclear enlargement is common in