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Original contribution

# Distinction between inflammatory hepatocellular adenoma and mass effect on liver sampling☆

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**Summary** Inflammatory hepatocellular adenoma (IHA) is characterized by sinusoidal dilation, inflammation, and bile ductular reaction. However, these changes can also be seen in nonneoplastic liver tissue adjacent to a mass lesion. This differential may arise in biopsy tissue attempting to sample a liver mass. Serum amyloid A (SAA) immunostaining is useful for the diagnosis of IHA but is not entirely specific. In addition, the histologic pattern of mass effect (ME) has received little formal scrutiny. We compared the clinical, morphologic, and immunohistochemical findings in 18 IHA and 36 livers with ME. Several histologic findings were evaluated in all cases. SAA and CD34 staining were also performed. Patients with IHA were younger ($P < .0001$) and more often female ($P = .0044$) than patients with specimens showing ME, but lesions were multifocal on imaging in two-thirds of patients in each category. Unpaired arteries were only seen in IHA ($P < .0001$), whereas ductular reaction was more common in ME ($P = .012$). Strong SAA immunostaining was observed in 100% of IHAs and 56% of ME cases ($P = .0004$), and CD34 staining was seen in 95% of IHAs and 6% of ME cases ($P < .0001$). Unpaired arteries and staining for SAA and CD34 best distinguish IHA from ME. However, unpaired arteries may be absent because of sampling, and SAA is not available in all laboratories. Ductular reaction can occur in IHA but is more common in ME.
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## 1. Introduction

Hepatocellular adenomas (HCAs) are benign liver lesions that typically occur in young women, especially those with a history of oral contraceptive use [1,2]. Other risk factors include anabolic steroid use, diabetes, galactosemia, tyrosinemia, and glycogen storage diseases I-IV [3]. HCAs can broadly be divided into 3 groups: those associated with an *HNF1A* gene mutation, those associated with a *β*-catenin gene mutation, and those associated with a *GP130* gene mutation [2]. This third category corresponds to the subtype known as *inflammatory hepatocellular adenomas* (IHAs), which represent 50%-60% of all HCAs and histologically are characterized by sinusoidal dilation, inflammatory infiltrates, and focal ductular reaction, in addition to the unpaired arteries characteristic of all HCAs [2-5]. Risk factors specific to the IHA subtype of HCAs include obesity and alcohol intake [2,5]. In addition, most patients have signs and symptoms of a general

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inflammatory syndrome, including elevated C-reactive protein (CRP) [2].

Although the microscopic changes of IHAs are often striking, they are not entirely specific. Space-occupying lesions in the liver (whether primary in the liver or metastatic from elsewhere) can produce adjacent histologic findings that are well known to surgical pathologists but have been little studied. The features characteristic of "mass effect" (ME) include bile ductular reaction, neutrophils in edematous portal tracts, and sinusoidal dilation [6].

Given the common findings of sinusoidal dilation, ductular reaction, and inflammation, IHA and ME can sometimes be challenging to distinguish, especially on core needle liver biopsies. Unpaired arteries should only be encountered in IHAs, but they may not always be present in a small tissue sample. Portal tracts should only be present in ME, but IHAs can contain portal tract–like remnants. Immunohistochemical (IHC) positivity for serum amyloid A (SAA) has been described in IHAs but can also occur in nonneoplastic liver adjacent to a mass lesion [1,7-9]. IHC expression of CD34 has also been reported in HCAs, whereas expression in uninvolved normal liver parenchyma is typically limited to endothelial cells near portal tracts [10].

Following a case at our institution where a biopsy of an IHA was misinterpreted as ME, we undertook this study to investigate whether certain microscopic and IHC findings may help resolve the differential diagnosis of these 2 processes.

## 2. Materials and methods

### 2.1. Case selection

Following approval by the University of Rochester Medical Center Institutional Review Board, 18 IHAs and 36 liver samples demonstrating ME that were biopsied or excised between 2006 and 2016 were retrieved from the surgical pathology departmental archives. Original hematoxylin and eosin–stained slides and formalin-fixed, paraffin-embedded tissue blocks were available for all cases. The slides were reexamined to confirm the original diagnoses. Patient age, patient sex, and liver lesion focality were gathered from each case, and radiologic images were reviewed. Twelve histologic findings were evaluated in all cases: sinusoidal dilation, sinusoidal blood, ductular reaction, macrovesicular steatosis, canalicular cholestasis, lymphocytes (sparse versus abundant), neutrophils, plasma cells, macrophages, acidophil bodies, unpaired arteries, and either portal tract–like remnants (in IHA) or portal tracts (in ME).

### 2.2. Immunohistochemical analysis

IHC for SAA (clone MC1, dilution 1:100; Dako North America, Inc, Carpinteria, CA) was performed on a deparaffinized 5-$\mu$m tissue section from every case using the Dako Flex HRP Detection Kit. Slides underwent proteinase K digestion for 5 minutes, room-temperature incubation with the SAA antibody for 30 minutes, room-temperature incubation with diaminobenzidine as chromogen for 30 minutes, and hematoxylin as counterstain for 5 minutes. The percentage of hepatocytes with cytoplasmic staining was recorded, and staining intensity was graded as absent (0), weak (1+), moderate (2+), or strong (3+) [8]. Staining of at least 1+ in at least 30% of cells was interpreted as positive. Appropriate positive and negative controls were assessed and utilized.

IHC for CD34 (clone QBEnd10, Dako) was used on sections from 50 cases (tissue limitations precluded staining in 4 cases). It was stained on the Omnis Staining platform using the Flex HRP detection system followed by heat-induced epitope retrieval at a high pH from Dako/Agilent Technologies. Presence or absence of sinusoidal staining and the percentage were recorded. Appropriate positive and negative controls were assessed and used.

### 2.3. Statistical analysis

Tabulated histologic findings, patient sex, and lesion multifocality were compared using Fisher exact test on 2 × 2 contingency tables, and patient age and portal tract count were compared using an unpaired $t$ test, all in GraphPad Software online (http://graphpad.com/quickcalcs; GraphPad Software, San Diego, CA, last accessed on November 17, 2016). $P < .05$ was considered statistically significant.

## 3. Results

### 3.1. Case characteristics

Clinicopathologic features are summarized in Table 1. The 18 IHA specimens included 10 biopsies and 8 resections; the 36 specimens with ME included 26 biopsies and 10 resections. The average age of the IHA patients was 39 years compared with 59 years for the patients with a specimen showing ME ($P < .0001$). Seventeen of 18 (94%) patients with IHA were female compared with 20 of 36 (56%) with a specimen showing ME ($P = .0044$). Twelve of the 18 IHA patients had multiple benign liver lesions (usually but not always additional HCAs), and lesion multifocality (typically on imaging) was present in 24 of the 36 patients with specimens showing ME ($P = 1.000$).

### 3.2. Imaging characteristics

The presence and character of ME on imaging depended on the character of the causative lesion. Small hepatic lesions (<3 cm in diameter) caused no definitive imaging characteristics of ME, and lesion number had no correlation with visible ME. Large lesions (>3 cm in diameter) with a capsule caused no ME on computer tomography, but the transition from ME to normal liver parenchyma was visible on magnetic resonance

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