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The Benevolent Wen-Hepatocellular Adenoma

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Short Communication

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Abstract

Hepatocellular adenoma emerges as a benign, solitary neoplasm of hepatocellular origin preponderantly arising within non cirrhotic hepatic parenchyma. Lesion occurs secondary to obesity, metabolic syndrome and consumption of anabolic steroids or non-contraceptive oestrogen supplements. Concurrent to genetic mutations, hepatocellular adenoma is categorized as hepatocellular adenoma associated with HNF1A genetic mutation, hepatocellular adenoma associated with β catenin genetic mutation, inflammatory hepatocellular adenoma, sonic hedgehog (SHH) hepatocellular adenoma or hepatocellular adenoma, not otherwise specified. Cytological assessment exhibits bland, uniform hepatocytes permeated with regular nuclei and decimated nucleocytoplasmic ratio. Tumefaction may display a pseudo-acinar arrangement, foci of steatosis and attenuated, mildly thickened one to two cell thick cell plates with a well-defined perimeter and characteristic unpaired arterial configurations. Hepatocellular adenoma appears immune reactive to HepPar1 or reticulin and immune non-reactive to glypican 3, CD34 or HSP70. Neoplasm requires segregation from neoplasms such as focal nodular hyperplasia, well differentiated hepatocellular carcinoma, mass effect due to an adjacent mass lesion, haemangioma, lymphoma, echinococcal cyst, hepatoblastoma, and localized fatty change or metastatic lesions arising from various primaries, confined to hepatic parenchyma. Hepatocellular adenoma may be appropriately managed with surgical extermination.

Keywords: Hepatic Lesion; Solitary; Unpaired Arterial Structures

Abbreviations: TACE: Transcatheter Arterial Chemoembolization; LFABP: Liver Fatty Acid Binding Protein; PS: Performance Status; AFP: Alpha Fetoprotein; MRI: Magnetic Resonance Imaging; BCLC: Barcelona Clinic Liver Cancer; CRP: C - Reactive Protein.

Introduction

Hepatocellular adenoma emerges as a benign neoplasm of hepatocellular origin which preponderantly incriminates non cirrhotic hepatic parenchyma. Predominantly solitary, neoplasm is designated as hepatic adenomatosis wherein lesions exceed> 10. Exceptionally, neoplasm is associated with glycogen storage disease type 1a, maturity onset diabetes of the young type 3 and Fanconi's anaemia. Tumefaction is additionally designated as hepatic adenoma or liver cell adenoma. Contingent to concurrent genetic mutations, hepatocellular adenoma is categorized as

- Hepatocellular adenoma associated with HNF1A genetic mutation
- Hepatocellular adenoma associated with β catenin genetic mutation ~inflammatory hepatocellular

adenoma
- Sonic hedgehog (SHH) hepatocellular adenoma
- Hepatocellular adenoma, not otherwise specified

Commonly incriminating the hepatic parenchyma, hepatocellular adenoma exhibits a female predominance. Neoplasm is associated with significantly elevated incidence within female subjects upon oral contraceptives [1,2]. Factors contributing to emergence of hepatocellular adenoma appear as obesity, metabolic syndrome and consumption of anabolic steroids or non-contraceptive oestrogen supplements. Mean age of disease emergence is between 37 years to 41 years. Paediatric subjects are infrequently incriminated [1,2]. Specific subtypes of hepatocellular adenoma demonstrate varied pathogenesis described as:

- Hepatocellular adenoma associated with somatic mutations of TCF1 or HNF1A gene and exceptional (< 5%) heterozygous germline mutations within CYP1B1 gene augment lipogenesis by boosting synthesis of fatty acids and downregulating liver type fatty acid binding protein (LFABP).
- Hepatocellular adenoma associated with β catenin gene activating mutations confined to exon 7, exon 8 or exon 3 induces stabilization of β catenin protein and elevated, non-transient activation of Wnt / β catenin signalling pathway.
- Inflammatory hepatocellular adenoma exemplifies gain of function genetic mutations within IL6ST gene along with activation of STAT3 signalling pathway and acute phase inflammatory response.
- Sonic hedgehog (SHH) hepatocellular adenoma enunciates activation of sonic hedgehog pathway through fusion of promoter of INHBE with GLI1. Besides, upregulation of argininosuccinate synthase 1 is observed, indicative of enhanced possible occurrence of haemorrhage [1,2].

Clinically, lesions may be asymptomatic and discovered incidentally upon imaging of hepatic parenchyma for non-concurrent conditions. Alternatively, hepatocellular adenoma may represent with clinical symptoms as abdominal pain or haemorrhage. Enlarged lesions are associated with enhanced possible occurrence of haemorrhage [2,3]. Upon cytological assessment, hepatocytes appear bland, uniform, permeated with regular nuclei and exhibit decimated nucleocytoplasmic ratio. Mitotic figures are infrequent [2,3]. Appropriate neoplastic discernment and distinction from hepatocellular carcinoma upon singular evaluation of cytological smears may be challenging as occurrence or absence of tumour invasion remains debatable or appears difficult to evaluate [2,3]. Grossly, hepatocellular adenoma configures a predominantly solitary, well circumscribed lesion. Tumefaction is un-encapsulated or demonstrates an inadequately defined pseudo-capsule. Neoplasm enunciates a lighter hue, in contrast to circumscribing hepatic parenchyma. Foci of tumour necrosis, haemorrhage and biliary staining may occur. Generally, hepatic parenchyma appears devoid of nodular lesions, significant fibrosis or centric scarring [3,4]. Upon microscopy, tumefaction is composed of hepatocytes devoid of significant cytological atypia. Neoplasm is configured of attenuated or mildly thickened cell plates which are one to two cell thick. Tumefaction may display a pseudo-acinar arrangement and foci of steatosis. A well-defined perimeter between the lesion and surrounding hepatic parenchyma is discerned. Characteristically, neoplasm demonstrates unpaired arterial configurations. Interlobular bile ducts appear absent. Few instances delineate bile ductules [3,4].

Foci of haemorrhage, ischemia of hepatocytes and necrosis may ensue. Cytological atypia, atypical mitotic figures and infiltration of portal tracts or hepatic parenchyma appears absent [3,4]. Reticulin stain may be beneficially adopted in order to establish near normal thickness of hepatocyte cell plates with focal decimation, especially in zones demonstrating steatosis. Upon reticulin stain, normal hepatic parenchyma is observed. However, few lesions or foci exhibit 'packeting' or prominent pericellular staining with near complete encircling of miniature aggregates of hepatocytes by reticulin fibres [3,4]. Specific subtypes emerge as

- Hepatocellular adenoma associated with HNF1A genetic mutation which characteristically exhibits steatosis or accumulated adipose tissue within hepatocytes configuring the lesion.
- Hepatocellular adenoma with genetic mutations of β catenin demonstrate pseudo-acinar configuration, cytological anomalies as cellular atypia, nuclear pleomorphism, multi-nucleation and prominent nucleoli. Steatosis is exceptionally encountered. Inflammation of hepatic parenchyma is minimal.
- Inflammatory hepatocellular adenoma enunciates irregular, poorly circumscribed perimeter with an inflammatory infiltrate and sinusoidal dilatation. Besides, pseudo-portal tracts constituted of islands of thick walled arteries, indistinct bile ducts and associated ductular reaction may be exemplified.
- Hepatocellular adenoma, not otherwise specified delineates a typical morphology although specific characteristics of individual subtypes are absent. Notwithstanding, lesions with extensive haemorrhage and necrosis are categorized within the subtype [3,4].

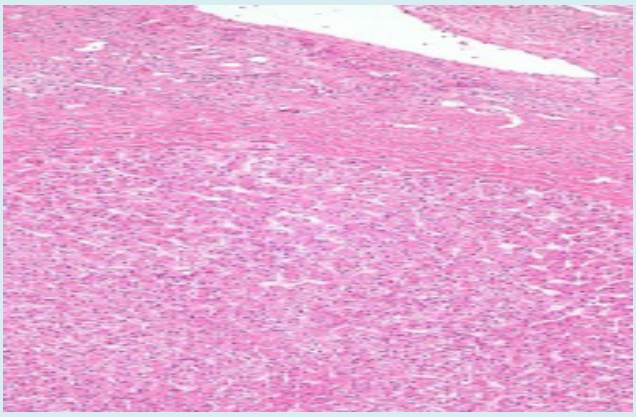

Figure 1: Hepatocellular adenoma delineating aggregates of hepatocyte cell plates imbued with abundant eosinophilic cytoplasm and uniform nuclei surrounded by normal hepatic parenchyma. Foci of cytological atypia or infiltration of portal tracts is absent [5].

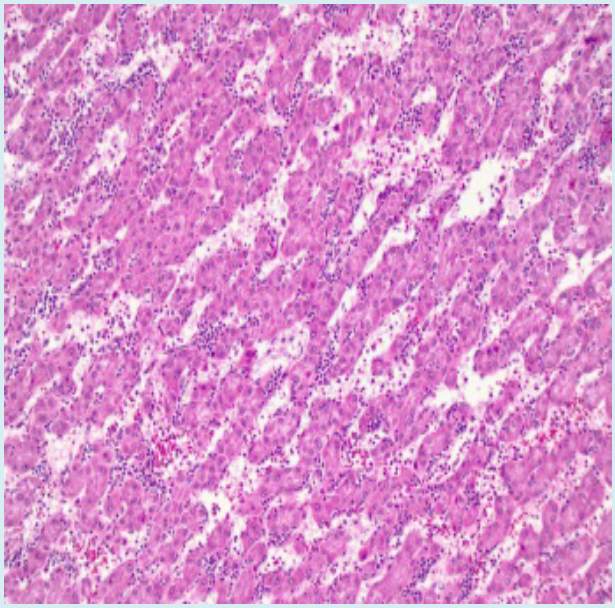

Figure 2: Hepatocellular adenoma delineating mildly thickened hepatocyte cell plates surrounded by uninvolved hepatic parenchyma. Foci of steatosis are discerned. Cytological atypia or infiltration of portal tracts appears absent [6].

Staging modality of Barcelona clinic liver cancer (BCLC) is constituted of

- Performance status
- Child-Pugh score
- Tumour extent upon radiography
- Tumour magnitude
- Multiplicity of tumours
- Vascular invasion
- Regional lymph node involvement
- Extrahepatic metastases.

Contingent to aforesaid parameters, hepatocellular carcinoma is categorized as

- Stage 0 comprised of preliminary tumour stage or asymptomatic preliminary tumours with performance status (PS) 0, Child-Pugh A and a solitary lesion <2 centimetre magnitude. Neoplasm can be managed with singular surgical resection. Tumefaction associated with portal hypertension or hyperbilirubinemia is optimally subjected to liver transplantation. Tumours associated with diverse clinical comorbidities are appropriately alleviated with radiofrequency ablation.
- Stage A comprised of preliminary tumour stage or asymptomatic antecedent neoplasms with performance status (PS) 0 to 2, Child-Pugh A to C and a solitary lesion >2 centimetre diameter or antecedent multifocal disease with characteristically up to three lesions < 3 centimetre magnitude. Singular neoplasms can be subjected to surgical resection. Multiple lesions are managed with liver transplantation. Tumours associated with diverse clinical comorbidities are appropriately alleviated with radiofrequency ablation.
- Stage B or intermediate stage is comprised of asymptomatic multifocal disease with performance status (PS) 0, Child-Pugh A to C, multifocal disease with ≥ 1 lesion and minimally a singular lesion > 3 centimetre diameter or > 3 lesions irrespective of tumour magnitude. Neoplasm is optimally treated with transcatheter arterial chemoembolization (TACE).
- Stage C or advanced stage is constituted of symptomatic neoplasm associated with tumour invasion and/or distant metastasis with performance status (PS) 1 to 2, Child-Pugh A to C, vascular invasion and/or regional lymph node disease and/or distant metastasis. Neoplasm is managed with varieties of palliative therapy and agents as sorafenib or phase II trial agents.
- Stage D or end-stage disease configures as a terminal stage and enunciates performance status (PS) >2, Child-Pugh C and appears singularly as a clinical stage. Optimally, symptomatic therapeutic options are beneficial. Tumour stage is compatible with Okuda stage III.

Hepatocellular adenoma appears immune reactive to HepPar1 or reticulin. Neoplasms associated with B catenin genetic mutations appear immune reactive to nuclear β catenin and intensely, diffusely immune reactive to glutamine synthetase [7,8]. Inflammatory subtype of hepatocellular adenoma appears immune reactive to serum amyloid A(SAA) and c-reactive protein (CRP). Tumour cells appear immune non-reactive to glypican 3, CD34 or HSP70.

Besides, hepatocellular adenoma associated with HNF1A genetic mutation is immune non-reactive to liver fatty acid binding protein (LFABP) [7,8]. Hepatocellular adenoma requires segregation from neoplasms such as focal nodular hyperplasia, well differentiated hepatocellular carcinoma, mass effect due to an adjacent mass lesion, haemangioma, lymphoma, echinococcal cyst, hepatoblastoma, localized fatty change or metastatic lesions arising from various primaries, confined to hepatic parenchyma [7,8]. Upon biochemical assay, liver function tests are normal although few neoplasms are associated with mild elevation of serum alpha fetoprotein (AFP) levels. Magnetic resonance imaging (MRI) is an optimal imaging modality which may be suitably adopted to discern hepatocellular adenoma. Upon T1 and T2 weighted imaging, hepatocellular adenoma characteristically delineates an intensely hyper-intense signal intensity with cystic areas, focal haemorrhage and diffuse intra-lesional steatosis [7,8].

Certain subtypes of hepatocellular adenoma exhibit pertinent features as

- Hepatocellular adenoma associated with HNF1A genetic mutation exhibits homogeneous signal dropout upon T1 weighted imaging with out of phase sequence
- Inflammatory hepatocellular adenoma exemplifies significantly hyper-intense signal intensity upon T2 weighted imaging. The hyper-intense rim as enunciated upon T2 weighted imaging appears concurrent with sinusoidal dilatation, a feature designated as 'atoll' sign [7,8].

Hepatocellular adenoma arising within male subjects may be appropriately managed with surgical extermination, regardless of tumour magnitude [7,8]. Incriminated female subjects may be treated with surgical eradication of neoplasms exceeding > 5 centimetre magnitude and lesions demonstrating β catenin activating genetic mutations [7,8]. Neoplasms managed with nonsurgical therapeutic strategies may be alleviated with suspension of oral contraceptive pills along with cogent monitoring upon imaging [7,8]. Factors contributing to enhanced possible occurrence of malignant metamorphosis emerge as:

- Neoplasms incriminating male subjects
- Hepatocellular adenoma associated with β catenin genetic mutations
- Enlarged neoplasms [7,8].

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