Autopsy Case Reports

Image in Focus
Imagem em Foco

Focal nodular hyperplasia of the liver

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A benign, non-neoplastic, reactive growth of the liver, focal nodular hyperplasia (FNH) of the liver was first clearly described by Edmondson in the 1950's, although there are various prior reports that likely represent the same lesion. A variety of synonyms have been applied including focal cirrhosis, pedunculated adenoma, solitary hyperplastic nodule, mixed adenoma, hamartoma and hamartomatous cholangeiohepatoma. FNH is the most frequent benign, solid hepatic tumor and, after hemangioma, the second most common benign lesion.[1] In an autopsy series comprising 96,625 patients, Craig et al.[2] identified 8% of non-hemangiomatous hepatic lesions as FNH. The various labels applied over the years have

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mostly been reflections of its' histopathology. In 1994 the nomenclature was standardized, placing FNH in the group of regenerative nodules, differentiating it from dysplastic or neoplastic lesions.[3]

The reported prevalence of FNH in the general population ranges between 0.4 to 3%, probably increasing with age.[1] Although, this entity may be found throughout the age spectrum, diagnosis is predominantly made between 20 and 50 years. The female: male ratio is 8 or 9:1, in as many as 80% of cases there is a single, well defined, but generally non-encapsulated lesion that can be as large as 20 cm diameter but generally is between 4 to 8 cm.[4,5]

The most characteristic macroscopic feature is the central, stellate fibrovascular zone, as easily seen in the image, which has the historically entrenched names of "central scar," "fibrous scar" or "scar-like fibrosis".[6]

The central scar usually consists of mature collagen and numerous vascular channels, many of which are medium and large thick-walled arteries which often show fibromuscular hyperplasia, myointimal proliferation and myxomatous change, sometimes with significant luminal narrowing.[6] True portal tracts are not seen but marginal bile ductular proliferation is common and can be very helpful in establishing the diagnosis in biopsy material (see below).

The pathogenesis is not fully understood, but it is highly accepted that an arterial abnormality, often a malformation, causing hypo- or hyperperfusion, which triggers reactive hyperplasia of otherwise normal hepatocytes.[7-10] This hypothesis is strengthened by the association of FNH with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease) and hepatic hemangiomas.[4,10] However a vascular malformation is not identified in all FNHs. Indeed, some lack a dominant feeding artery and are hypovascular or have a peripheral rather than a central blood supply. The liver cells of FNH have been shown to be polyclonal in more than 50% of cases. No somatic mutations in genes have, thus far, been identified in FNH cases.[5] A genetic predisposition to the disease has been suggested by the documentation of FNH in identical twins[11] but there has been no confirmation of this concept.

Gene expression studies have, however, demonstrated molecular features supporting the concept of vascular abnormalities as the principal etiopathogenetic factor; FNH can have increased expression of ANGPT1, classically responsible for vessel formation, and ANGPT2, an antagonist to ANGPT1.[12] The increased expression of these two genes is associated with angiogenesis. Genomic expression studies have shown overexpression of several genes, particularly of the central fibrous scar, relating to activation of the transforming growth factor β (TGF β) pathway. Glutamine synthetase (GS) overexpression is also seen and can be useful in the biopsy identification of the lesion[13] showing a typical map-like pattern of distribution at the periphery of the nodules.

The diagnosis of FNH can be particularly challenging in biopsy material if the central scar is not included in the sample.[6,13] Hepatocytes are almost always cytologically bland but may show mild degenerative change, focal steatosis or increased glycogen. The liver cells are arranged in one- or two-cell thick plates and can form incomplete nodules or pseudonodules sometimes surrounded by slender, fibrous septa, which extend from the central scar but are not always seen in biopsy samples. In biopsy, when the fibrous scar is absent and there are no bile duct-like structures, distinction of FNH from hepatic adenoma is aided by molecular studies confirming that FNH lesions are polyclonal with β-catenin activation without mutation[14] as well as GS immunostaining.[12,13]

Larger and more symptomatic lesions are observed among patients taking oral contraceptives (OCP). Although FNH may be responsive to estrogens, it is clear that the use of OCPs is not required for the development of FNH.[15]

Usually asymptomatic (80% of the cases), FNH not infrequently is incidentally diagnosed due to widespread use of radiologic examinations, as a mass noted at the time of a surgery or at autopsy. This lesion rarely grows or bleeds and has no malignant potential.[16] Symptoms when present are vague and nonspecific. Most series report abdominal discomfort, pain or a liver palpable mass. Fever is present in less than 1 percent of cases. Liver function tests and α-fetoprotein are normal but minor elevations of aspartate and alanine aminotransferase, alkaline phosphatase and gamma glutamyl transpeptidase may be seen.[4,17]

In the past, this tumor was resected due to the difficulty in distinguishing it from hepatic adenoma, but nowadays, with the improvement of imaging techniques and with a combination of imaging

modalities it is now almost always accurately diagnosed with imaging and is not resected.

The evaluation of FNH by ultrasound (US) has a low sensitivity, however the lesion appears as a well demarcated, homogeneous and isoechoic mass relative to the liver parenchyma with a hyperechoic central scar.[4,18] Some lesions may show a hypoechoic surrounding halo.[19] The color and power Doppler US may furnish additional information on the vascularity of the suspected FNH.[19] Triphasic helical computed tomography scan performed without contrast, and with contrast during the hepatic arterial and portal venous phases will often be highly suggestive of the diagnosis. The typical lesion has lobulated contour[19] and may be hypo or isodense on non-contrast imaging with the central scar identified in one-third of patients. Rarely calcifications may be present within the central scar.[20] The lesion becomes hyperdense during the hepatic arterial phase due to the arterial origin of its blood supply. During the portal venous phase the lesion becomes generally isodense, although the central scar may become hyperdense as contrast diffuses into the scar.[17,19] In large lesions feeding arteries may be seen penetrating the central scar as well as draining veins at the surface of the tumor.[1] On MRI, FNH is isointense to mildly hypointense on T1-weighted images (94-100%) and is isointense to mildly hyperintense on T2-weighted images (94-100%).[19] The lesion shows homogeneous-intense arterial phase enhancement and isointensity on the venous and delayed-phase images.[19] The scar characteristics (hyperintense on T2-weighted – 84%)[19] and lack of capsule enhancement help to distinguish FNH from other arterial-phase enhancing tumors, such as hepatocellular carcinoma (HCC), adenoma, and fibrolamellar HCC. Accurate differentiation of FNH from hepatic adenoma is achievable on delayed T1-weighted gradient-echo sequences images after administration of gadobenate dimeglumine. The sensitivity and specificity of FNH from adenoma reach 97% and 100%, respectively.[21-24]

Differential diagnosis of FNH comprises other hepatic tumors that present generally as single solid lesions, and their differentiation is crucial because of diverse therapeutic approaches and prognosis. Unfortunately, the distinction is not always straightforward, particularly with small lesions. Nevertheless, even in the presence of diagnostic evidences, the differential diagnosis should include: hepatic adenoma, HCC, Fibrolamellar HCC, hypervascular metastases, hemangioma and even focal steatosis.[6]

Keywords: Focal Nodular Hyperplasia; Liver Diseases.

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