Review

Focal nodular hyperplasia: a case report and literature review

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ABSTRACT

Focal nodular hyperplasia (FNH) is a rare benign hepatic tumor that originates from epithelial tissue and is composed mainly of hepatocytes and Kupffer cells. It usually presents as an asymptomatic abdominal mass and is typically an incidental diagnosis because majority of patients lack symptoms. Symptoms are more frequent in women using contraceptive steroids. It must be distinguished from other more common benign and malignant lesions because of different therapeutic approaches. It occurs in all age groups, but more than 50% of the patients are women between 25 and 44 years of age. The etiology of this condition remains obscure. Various causes have been proposed for FNH, including localized ischemic injury related to vascular anomaly, vascular injury such as thrombosis and induction of hepatocellular proliferation by oral contraceptive (OC) steroid ingestion. The standard treatment of FNH is to manage asymptomatic lesions conservatively, and operative resection for symptomatic ones. We present the clinical course as well as clinicopathologic implications of a 20-year-old female patient with FNH who was not a user of oral contraceptives, and a review of this rare hepatic lesion.

KEYWORDS: focal nodular hyperplasia; oral contraceptives; occupational medicine; rehabilitation; surgery; liver

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INTRODUCTION

FNH is the second most common benign hepatic tumors, constituting about 8% of primary hepatic tumors in an autopsy series (1). Synonyms of this entity include variety of terms such are «focal cirrhosis» (2), «mixed adenoma of the liver» (3), «benign hepatoma» (4), «hamartomatous cholangiohepatoma» (5), «hepatic hamartoma» (6), «hepatic inflammatory pseudotumor» (7), and, unfortunately, « hepatic adenoma» (8), a obviously different benign tumor of hepatic parenchyma. «Focal nodular hyperplasia» the most widely used term, was introduced by Edmondson (9) in 1958 and is the one adopted by the World Health Organization (10) in 1975 and by the Fogarty International Center and the International Association for the Study of the Liver (11) in 1976.

It is a well-circumscribed lobulated benign epithelial hepatic lesion composed of multiple, spherical aggregates of hepatocytes held together in a fibrous meshwork with prominent scar tissue (12). FNH lesions lack normal architectural patterns and elements such as central veins or portal tracts; and abnormal vessels are scattered through the lesion (13,14,15,16,17,18).

The pathogenesis of this benign hepatic lesion that predominantly affects women and is often discovered coincidentally during an imaging study done for another reason is not well understood (19,20). Proposed mechanisms include

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(a) compensatory regeneration from localized ischemic injury related to vascular anomaly (21); (b) hepatocellular proliferation induced by vascular injury such as thrombosis, intimal hyperplasia, high sinusoidal pressure, or increased flow (16,18,21,22); and (c) hepatocellular proliferation due to oral contraceptive steroid ingestion (23,24). OC use has been conclusively linked to both development and complications of hepatocellular adenomas, but their influence on FNH is controversial (25,26,27,28,). Furthermore, FNH was described prior to widespread use of OC and has been found in children and men (29,30). On the other hand Whelan et al (21) have presented an excellent discussion of the evidence that FNH may be related to a vascular malformation of the liver resulting in local injury and repair. Lough et al (31) have suggested that repeated vascular thrombosis may result in vascular narrowing and FNH with thrombosis due to recurrent and progressive endothelial injury.

The decision between an expectant approach versus a surgical approach of FNH should be based on individual findings e.g. age, symptoms, complications, size, and location of the lesion. It is sufficient for asymptomatic FNH lesions to be observed only by repeat ultrasound (32). Surgery is indicated in cases of diagnostic difficulties, complications, compressed adjacent organs, lesion progression, or for symptomatic patients (33).

CASE REPORT

A 20-year-old white female was admitted in the Department of Internal Medicine, for evaluation of recurrent mild abdominal pain with no other symptoms. She was otherwise healthy and did not take any medications including the OC. Laboratory findings demonstrated mildly elevated serum gamma glutamyl aminotransferase level (88 U/l, normal values 11-55 U/l). Other liver function tests and coagulation studies were normal, and tumor markers (e.g., α-fetprotein and β-human chorionic gonadotrophin) were negative. Viral serologic tests for hepatitis A, B and C were negative. Ultrasonography (US) demonstrated a hypoechoic mass in right liver lobe. Liver computed tomography (CT) revealed a 10x10-cm focal hepatic lesion. An injection of contrast material demonstrated a hyperdense mass with a hypodense center. Magnetic resonance imaging (MRI) scanning showed liver mass with central avascular scar in right liver lobe. These findings were interpreted as being compatible with a focal nodular hyperplasia although liver cell adenoma could not be excluded.

Thus, on February 6th, 2002, elective surgery was performed. At operation, large, nodular hepatic mass on the surface of the fifth segment of the right liver lobe was found, with prominent vessels on its surface. Diagnose of FNH was confirmed by intraoperative biopsy. Therefore, resection of the fifth liver's segment with the tumor, at the same time was performed. No transfusions were required. The procedure was well tolerated, and the postoperative recovery passed without complications, thus she was discharged on February 13th, 2002.

Macroscopically, examination of the resected specimen showed liver tumor that measured 12.5 x 10.5 x 6 cm. The cut surface was yellow tan to brown in color and appeared to be encapsulated. Surrounding parenchyma and vascular structured were compressed. Tumor was subdivided by grayish white fibrous septa that radiated from a central scare zone into lobules of varying sizes.

Microscopically, tumor parenchyma was separated from surrounding liver tissue by thin, discontinuous fibrous capsule, and subdivided by bands of fibrosis. Fibrous septa contained small arteries and veins along with proliferated small bile ducts, most prominent at the interface of septa with parenchyma. Infiltrations of chronic inflammatory cells were periodically seen in the fibrous bands. The parenchyma itself was composed of sheets of benign-appearing hepatocytes arranged in cords of two or three cells in thickness separated by inconspicuous sinusoids, lacking normal cord architecture. The nuclei were uniform with basophilic nucleoli; no mitoses were noted.

DISCUSSION

FNH is the second most common benign hepatic tumor constituting 2% of all diagnosed hepatic tumors (34), but on autopsy series it represents about 8% of primary hepatic tumors (1). These differences in incidence exist since FNH is typically an incidental diagnosis because 50-90% of patients lack symptoms (35,36,37,38). Thus, diagnosis is often made during a routine examination or fortuitously, during an operation or an autopsy.

FNH occurs in all age groups, from newborns to elderly people (0-90 years of age). More than 50% of the patients are between age 25 and 44 and the male: female ratio is 1:5 (30). Approximately 15% of all patients are pediatric cases (0-16 years of age). In pediatric patients FNH is usually associated with other anomalies. These include

multiple telangiectasia on the arms and legs (5), hypospadias, bilateral syndactyly of the toes and bilateral hydrocele (39), left sided hemihypertrophy, syndactyly of second and third left toes, absent distal phalanges of second and third fingers on the left hand, multiple telangiectasia over the face and lips, and an umbilical hernia (39), and Type I glycogen storage disease (40).

In contrast, one third of adult patients have "multiple FNH syndrome" that is defined by FNH occurring with other lesions, such as hepatic hemangioma, arterial structural defects, vascular malformation of the central nervous system, meningioma, and astrocytoma (41).

The pathogenesis of focal nodular hyperplasia is still uncertain. The relation between steroids and FNH suggested the predominant occurrence of the lesion in women of childbearing age and middle age. Some reports have suggested that high-dose of exogenous estrogens and endogenous-during the pregnancy may be associated with enhanced growth and marked vascular changes of FNH lesions (42,43). There are also reports of tumor regression after stopping administration of contraceptive steroids or estrogens (44,45). But there are many studies that suggested that association with oral contraceptives is probably coincidental (46). Results from 9-year study in a large series of FNH patients suggest that FNH development is independent of OC use and no significant differences in number or size of FNH lesions were found between OC nonusers, users of low-dose OCs, users of high-dose OCs, and users of progesterone (20). The mechanism by which sex steroids and in particular estrogen could promote growth of hepatic tumors is unknown. But if contraceptive steroids do not cause focal nodular hyperplasia, then associated tumor growth could represent a parenchymal trophic effect on an underlying lesion (47). Alternatively, enlargement could result from engorgement caused by steroid-induced increase in vascularity and blood flow (13,46,48).

Itisconsiderabletonoticethatthereisadifference however, in the morphology and presentation of FNH in OC users. In these patients, the tumors may be hemorrhagic and occasionally present as acute abdomen secondary to hemoperitoneum or hemorrhage. Lesions in nonusers tend to be smaller and are usually asymptomatic (42,43,49).

Other proposed pathogenic mechanisms for FNH presuppose underlying vascular malformation or thrombosis. Tracers and D'Amato implicated "vascular injury" resulting from increased pressure in the portal veins or in arteriovenous malformations (16). Wanless et al argued that thrombosis and local release of platelet-derived growth factors are the predisposing conditions (18). Lough et al have postulated that vascular thrombosis may result in vascular narrowing and FNH (22). The arguments for a vascular basis have been bolstered by the high incidence of hemangiomas in autopsy liver with FNH. In Ishak and Rabin's serried 2.3% of liver with FNH also had hemangiomas, and in Benz and Baggenstoss's series 20.6% (2,36). This higher-than-expected coexistence of hemangioma and FNH suggests that the lesions are pathogenetically related.

Differential diagnoses of FNH in noncirrhotic livers include liver cell adenoma, large regenerative hyperplasia, partial nodular transformation, compensatory hyperplasia, focal fatty change, and well-differentiated hepatocellular carcinoma (50). But establishing the diagnosis of FNH is difficult especially differentiating the FNH and HA which has a different natural evolution; namely, an increased risk of hemorrhage and rupture, and a well-documented malignant potential. Ultrasonography, computed tomography, and magnetic resonance scanning provide useful anatomic information for assessing the number and size of tumors and the location of the tumor relative to the intrahepatic vasculature and biliary tract. The presence of an avascular central scar is highly supportive of FNH. Scintigraphy, if labeled colloid uptake is normal or increased, is highly specific for FNH (51). Important detail for diagnose the FNH is that it may be multifocal in 10%-20% of patients (52); it is seen with hemangiomas in 5% to 10% of patients (53) and rarely with hepatic adenoma (54).

According to histologic characteristic, FNH can be divided into two groups: the classic form accounts for 80.3% of the lesions and the nonclassical form (e.g., telangiectatic, atypia of large cell, and mixed hyperplastic and adenomatous forms) account for the rest (50). Nguyen et al considered three histologic features in a central scar (i.e., architectural perturbation, vascular lesions, and ductal proliferation) to be minimal criteria for the pathohistological diagnosis of FNH (55).

The management possibilities for FNH are a conservative approach, in which the lesion is monitored clinically and radiologically, excision of the tumor, or vascular intervention (embolization or ligation of the hepatic artery) (56,57,58). Some authors propose conservative approach for asimptomatic FNH lesions that included observation only by repeat ultrasound and discontinuation of use of the contraceptive pill in the OC users (30,32). On the

other hand, the typical small size and peripheral location of FNH lends itself to simple wedge excision or enucleation with minimal operative risk. (35,37). Surgical excision is also the treatment of choice for: (a) patients diagnosed incidentally during laparotomy for other indications, (b) young women of childbearing age given the unpredictable changes in the liver during pregnancy (59), the potential adverse effect from steroids (60) and the safety of resection, (c) in the case of complications such are: growth, rupture (30), portal hypertension (30), hemorrhage, and necrosis (14). The possible malignant potential of FNH lesions remains the central problem. To date, there have been no reports of histologically proven FNH presenting with a malignant evolution; however, cases of FNH lesions associated with hepatocellular carcinoma do exist (61).

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