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Natural course of hepatic focal nodular hyperplasia from childhood to adulthood and review of the literature

Cemil Gürses, Feyzan Seher Okşar, Bekir Erol, Mustafa Yalçın, Nevfel Kahvecioğlu, Ahmet Şükrü Alparslan

Department of Radiology, Antalya Training and Research Hospital, Antalya, Turkey

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ABSTRACT

Focal nodular hyperplasia (FNH) is the second most common benign tumor of the liver and constitutes 4% of all primary hepatic tumors in pediatric population. Imaging characteristics of FNH in adults are well known, but those in children have rarely been reported. Here we describe the natural course of a giant hepatic FNH, which was followed up from childhood to adulthood for 12 years using computed tomography (CT) imaging and liver enzyme tests (LET). Differences in CT imaging characteristics were demonstrated. Changes were found in the FNH size in CT images and they were correlated with LET findings. The regression of FNH in our case was compared with the findings in the literature. Hepatic capsular retraction was observed in a benign focal liver lesion in the medical literature for the first time.

Keywords: Focal nodular hyperplasia, apoptosis, gamma-glutamyltransferase, alanine transaminase, prognosis

Case Report

INTRODUCTION

Focal nodular hyperplasia (FNH) is rare in children. Although imaging characteristics of FNH in adults are well defined, there is no knowledge on the natural course of biopsy-proven FNH and long-term changes in computed tomography (CT) findings from childhood to adulthood. Here we report the changes in imaging characteristics of FNH, which was diagnosed incidentally during childhood. Correlations of changes in findings of CT imaging and liver enzymes tests (LET) of aspartate aminotransferase (AST), alanine transaminase (ALT) and gamma-glutamyltransferase (GGT) were investigated.

CASE REPORT

11-year-old boy was referred to the radiology department for determining the etiology of the right upper quadrant pain and a palpable mass.

Gray-scale ultrasound (US) in 2003 demonstrated a big heterogeneous solid mass with ill-defined borders, and a specific diagnosis could not be made.

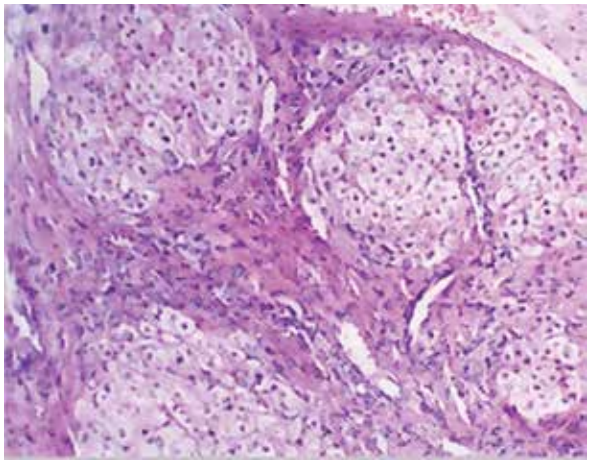

Figure 1. Pathological specimen

Dynamic CT scan was performed and in non-enhanced phase (NP), the mass lesion was slightly hypodense to the surrounding liver and the central scar was deeply hypodense. In arterial phase (AP), the lesion was homogenously enhanced, with exception of the central scar and pseudocapsule. A tortuous enlarged feeding

Address for Correspondence: Cemil Gürses E-mail: cemilgurses@hotmail.com
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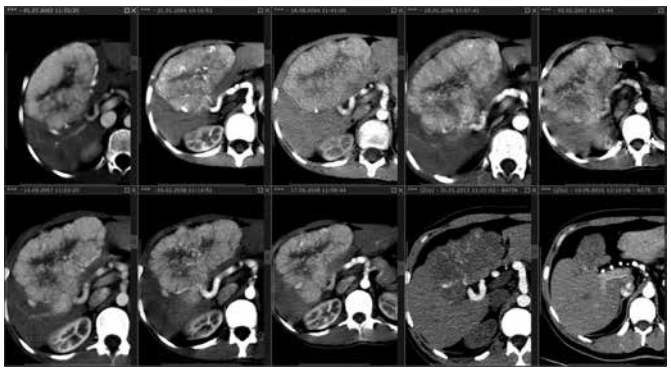


Figure 2. Arterial phase serials

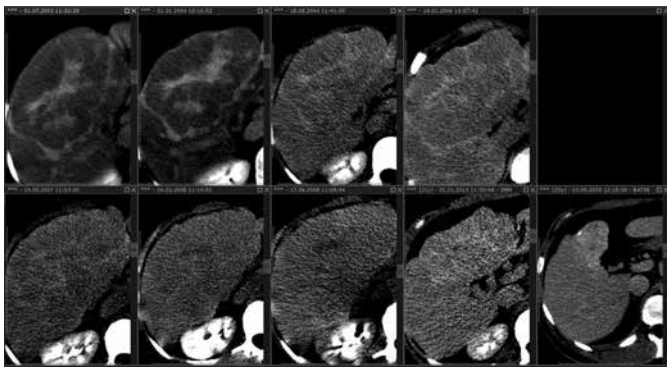


Figure 3. Equilibrium phase serials

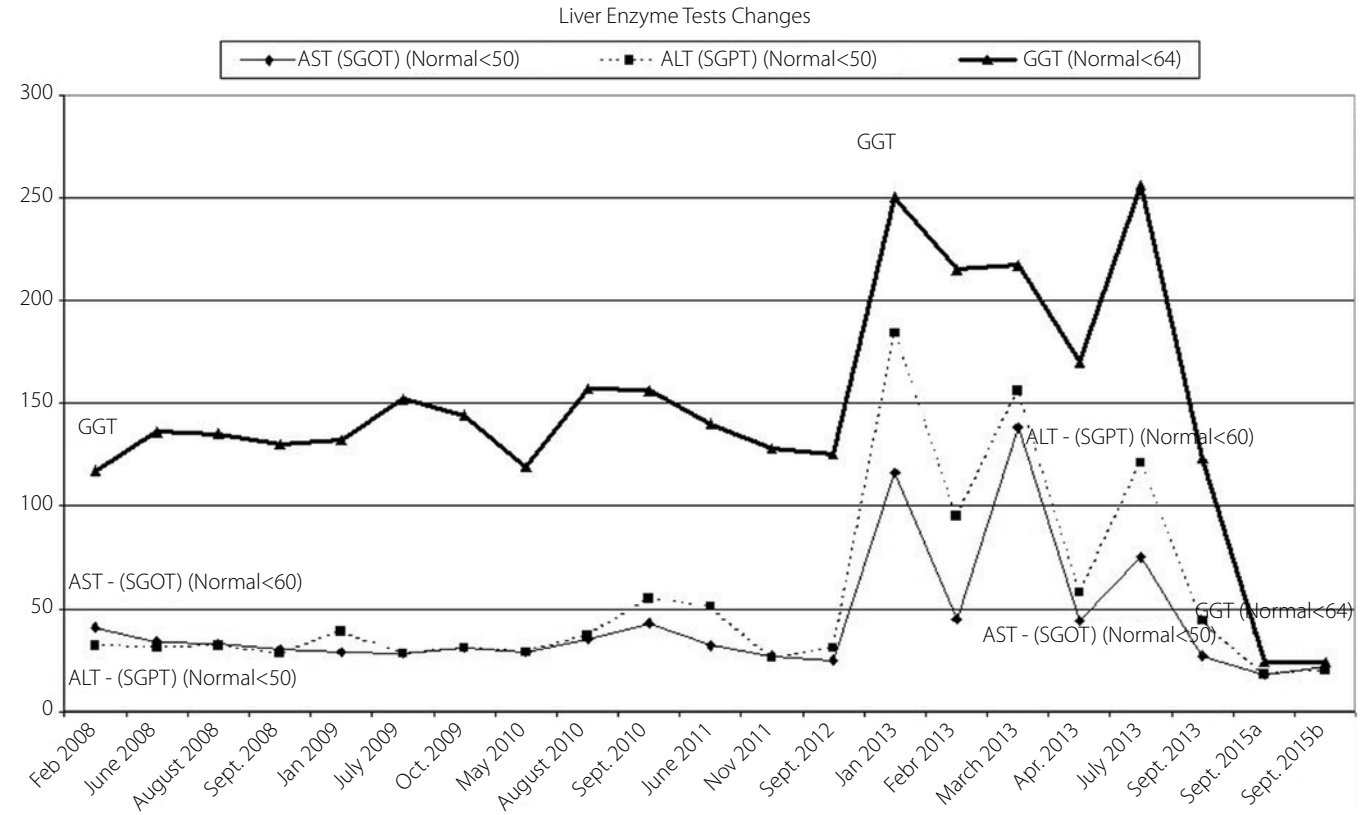


Figure 4. Changes in liver enzyme test findings

artery was prominent. In venous phase (VP), the lesion was isodense and the central scar was hypodense similar to those in AP. In equilibrium phase (EP), the lesion was isodense; however, the central scar and pseudocapsule were hyperdense.

Gray-scale ultrasound-guided core-needle biopsy was performed in the operation room, and FNH was pathologically confirmed (Figure 1).

After the pathological confirmation of FNH, the patient was followed up using periodic CT scanning (Figure 2,3), US, and LETs (Figure 4) every 6-8 months in the first 5 years of the follow-up period. After 2008, CT scanning was not performed for 5 years because LET findings were normal (Figure 4,5) and no significant change was detected in US examinations.

After 2008, US and LETs were used for follow-up, and CT imaging was performed in case of changes in LET findings or abdominal discomfort.

For CT imaging, ProntoSE CT scanner (Hitachi, Tokyo, Japan) with a single detector was used from 2003 to 2008 and Brilliance 64-channel multidetector CT systems (Philips, Koninklijke, Netherland) were used in 2013 and 2015. A low-dose CT protocol was used for examining the pediatric abdomen in the first half of the follow-up period.

Dynamic CT examinations with four phases were performed using low-dose pediatric protocol: NP and AP with 25-s delay, VP with 60-s delay, and EP with 10-min delay times after administering 100-mL nonionic iodinated contrast media with

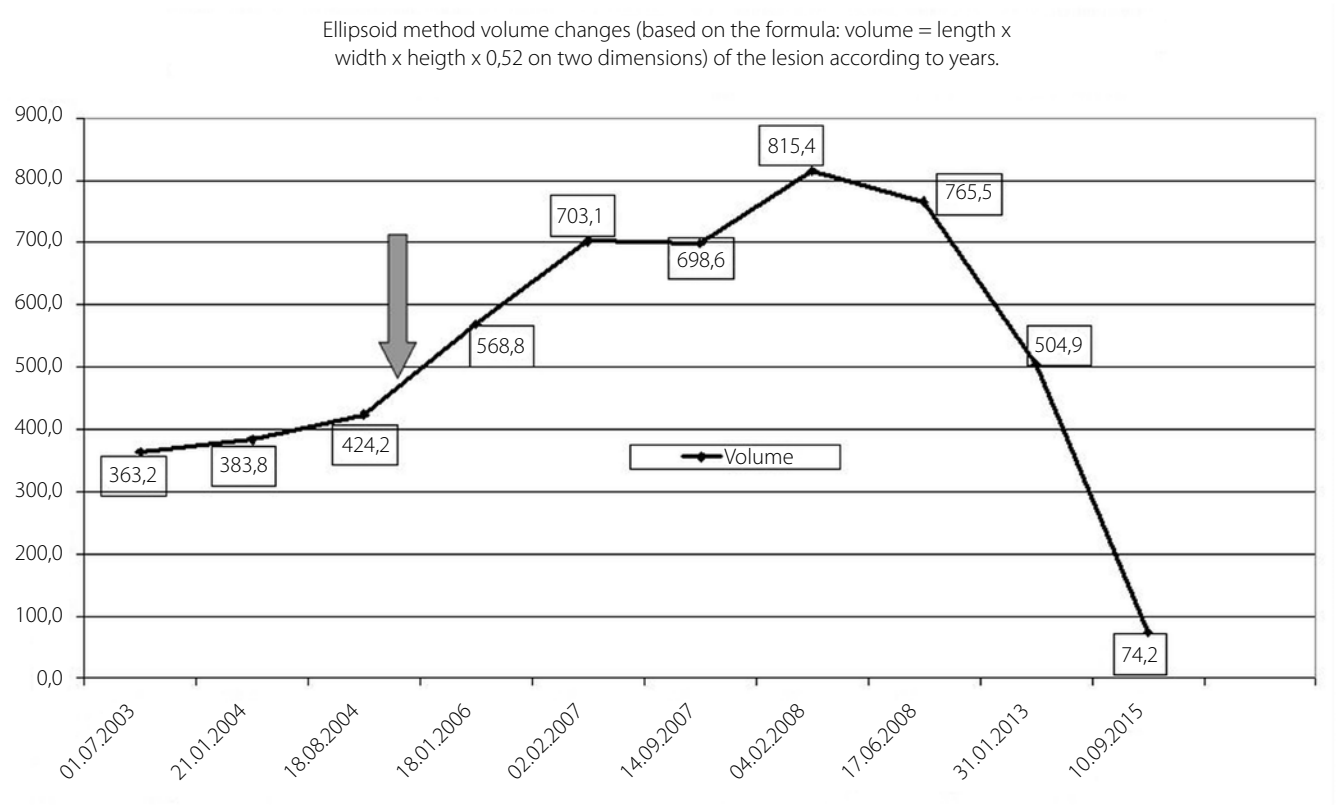


Figure 5. Changes in lesion volume. The thick gray arrow indicates the attempt of embolization

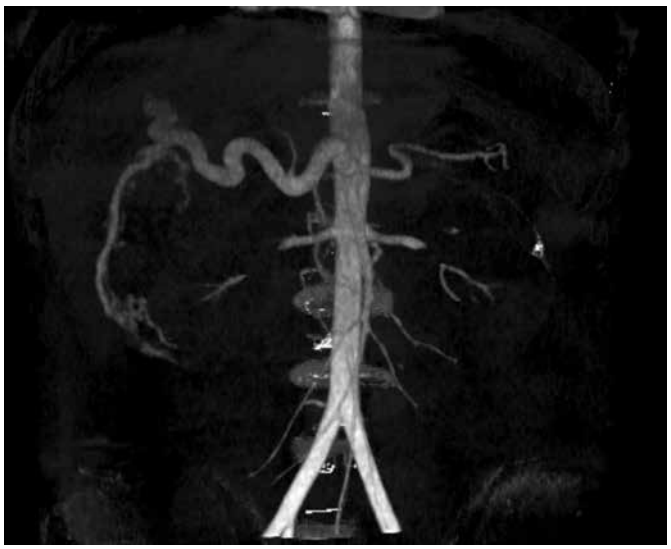


Figure 6. Coronal 3D computed tomography angiography of the feeding artery in 2013

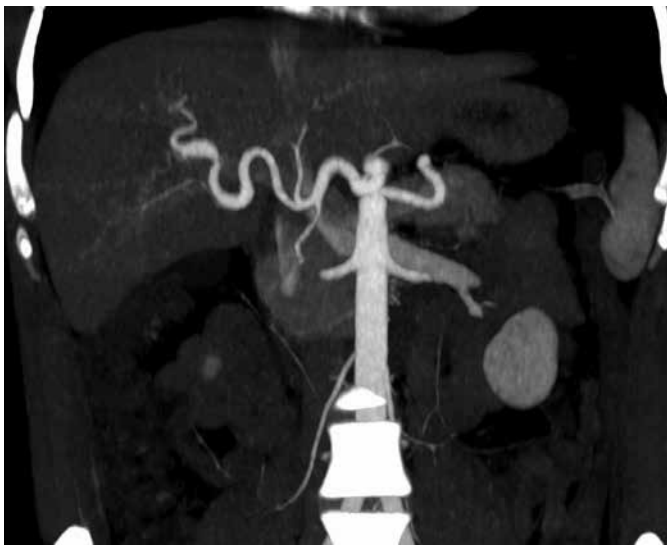


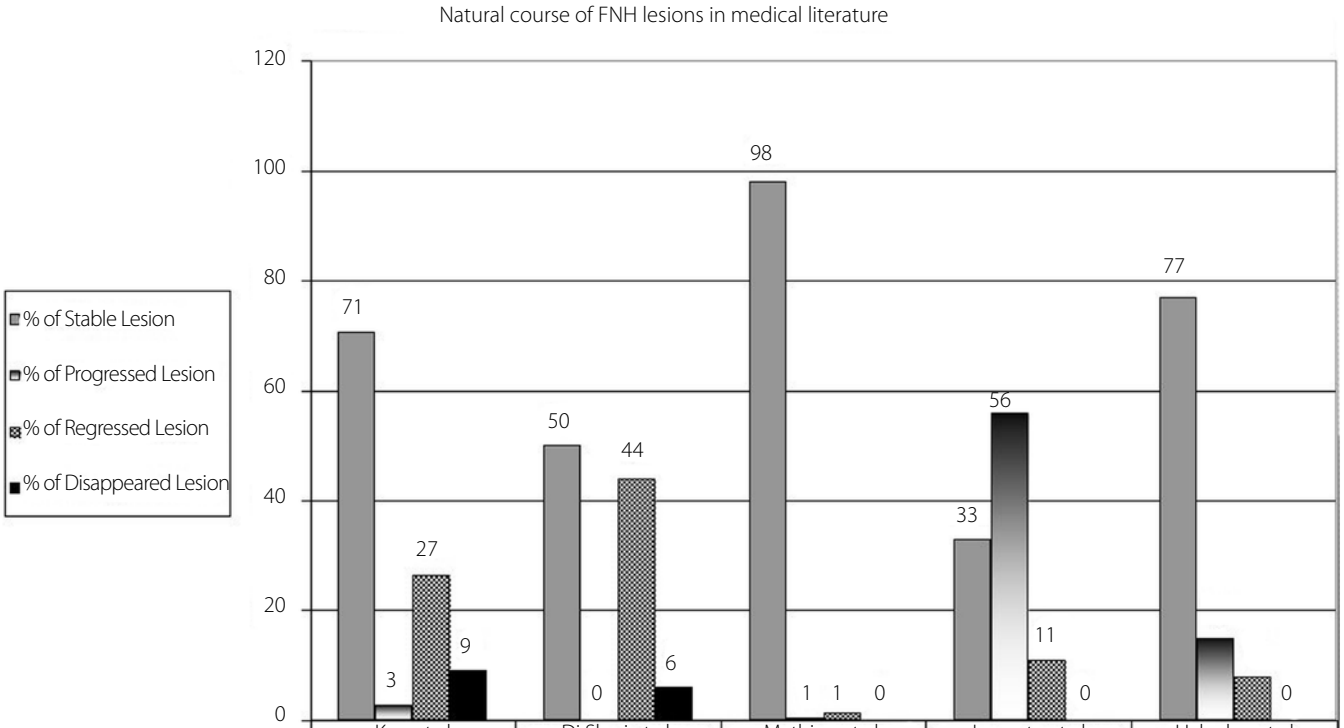
Figure 7. Coronal 3D computed tomography angiography of the feeding artery in 2015

power injector (Medrad). Injection rate was 2-4 mL/s, and slice thickness was 5 mm. In February 2, 2007, the EP scanning could not be performed missing because of technical reasons.

DP-9900 (Mindray, Shenzen, China), HD11 (Philips Ultrasound, Bothell, WA), and Applio (Toshiba, Tokyo, Japan) ultrasound systems with a 2-6-MHz broadband convex transducer were used for US imaging.

Focal nodular hyperplasia was located in the Couinaud segments IVa, IVb, V, and VIII.

The FNH volume was calculated using the three-dimensional ellipsoid formula: length (L)×width (W)×anteroposterior diameter (APD)×0.523 (1). L was determined from the cephalocaudal axis; W and APD were measured in the axial plane slice which was showing the largest diameter of the lesion.



	Kuo et al (2009)* (4)**	Di Skasi et al (1996)* (5)**	Mathieu et al (2000)* (6)**	Leconte et al (2000)* (7)**	Halankar et al (2012)* (8)**
% of Stable Lesion	71	50	98	33	77
% of Progressed Lesion	3	0	1	56	15
% of Regressed Lesion	27	44	1	11	8
% of Disappeared Lesion9	6	0	0	0	0

Figure 8. Natural course of focal nodular hyperplasia lesions in medical literature

The lesion volume increased until 2008; AST and ALT levels, but the GGT level, were normal during this period. Between 2008 and 2013, the lesion volume kept decreasing while enzyme levels did not show a significant change.However, AST, ALT, and GGT levels peaked at the same time when the lesion volume decreased from 815.4 cm^3 to 504.9 cm^3 in 2013. (Figure 4,5).

Since liver enzyme levels began increasing in 2013, a CT scanning was performed again. However, all LET revealed normal findings in 2 weeks, which continued for 2 years (Figure 4).

After the third scanning, a selective feeding artery embolization was attempted to reduce the lesion volume in the autumn of 2004 (the thick gray arrow in Figure 5). However, the procedure could not be completed due to excessive pain despite administering sedoanalgesia.

The main change in the lesion observed in the scans during the consecutive years was enlargement of the lesion volume until 2008 (Figure 5).

Arterial phase enhancement pattern of the peripheral parts of the lesion were the most prominent in the initial CT scan in 2003 and was almost the same until 2013. In 2013, both of the central scar and pseudocapsule were isodense, and in 2015, all parts of the lesion were slightly and heterogeneously enhanced.

The central scar and pseudocapsule exhibited almost the same enhancement pattern in EP. The enhancement of the central scar and pseudocapsule decreased, and in 2008, the central scar started becoming hypodense and pseudocapsule was isodense in EP. The discrimination between the peripheral and central parts was possible in AP and VP; however, there was no discrimination in NP and EP in 2013 (Figure 3).

In 2015, the patient claimed that he noticed some changes in his abdomen while palpation. His abdomen was examined by using US and CT. Unexpectedly, caudal exophytic growth from segment 4b to segment 5 and distortion of the hepatic contour of the lesion were completely regressed and hepatic capsular retraction was detected for the first time in 144 months of follow-up (Figure 2,3,6,7).

The patient provided informed consent for publication.

DISCUSSION

Focal nodular hyperplasia is the second most common benign tumor of liver after hemangiomas and constitutes 4% of all primary hepatic tumors in pediatric population (2).

The patient was followed up by using not only CT and US, but also blood tests. US is an operator-dependent imaging modality and is difficult to standardize for measurements. In addition, the MRI scanner could not be used. Because installed MRI scanner in our radiology department was 0.35-T open-shield system and was not suitable for abdominal imaging. Therefore, we determined that CT was the most suitable among all the imaging modalities available in the department. In 2008, surgical treatment was planned because of voluminous increase in the mass. However, the patient refused surgery, and his LET findings were normal; therefore, "wait and see" approach was preferred.

Our case has unique features. Firstly, it is the longest followed up FNH from childhood to adulthood in the literature, and secondly, imaging and blood LET findings were correlated. Changes in the FNH lesion volume and LET findings were inversely related, i.e., when the lesion volume increased, AST and ALT levels were almost normal, and when the volume decreased, AST, ALT, and especially GGT levels peaked. Thirdly, FNH was considered in the differential diagnosis of hepatic capsular retraction for the first time in the literature (Figure 2,3,6,7).

Bonney et al. (3) used persistence of pain as the main indication for surgery in FNH patients (3). However, pain is a subjective and relative symptom depending on personal tolerance of the patients. Their study could not clearly demonstrate how many patients with pain had elevated liver enzyme levels.

In the medical literature, the natural course of FNH has been reported to be variable, which is presented in Figure 8 (4-8). In their study, Kuo et al. (4) demonstrated that 9% (18% with regressed lesions) of FNH lesions disappeared, whereas Di Stasi et al. (5) reported that 6% of FNH lesions disappeared and found no progression of the lesions. However, we believe that the FNH lesion size can be seen increasing or decreasing depending on the follow-up duration time of the lesions, e.g, if this case was followed between 2004 and 2007, it could be decided as an enlarging space occupying lesion. On the other hand, if the follow-up period was taken into account between 2008 and 2013, it could be decided as regressing space occupying lesion. Volume changes figure supports that idea (Figure 5).

In our case, the lesion volume began decreasing in 2008 and regressed in 2015 (Figure 5). It is not well understood whether the FNH regressed due to embolization or spontaneously. We do not think that the regression occurred due to embolization because of the long time interval between embolization and reduction in volume. We considered apoptosis as the possible explanation for regression. Apoptosis is a process of programmed cell death (9,10). Apoptotic cells die in a controlled and regulated fashion; therefore, apoptosis is distinct from other uncontrolled cell death processes, such as necrosis, necroptosis, autophagy, and cornification (9). Apoptosis involves death of a single cell or small clusters of cells without inflammatory response (9).

The feeding artery was coursing through lateral side of the lesion, and we considered that it was gradually compressed between the enlarging lesion and normal hepatic parenchyma. The feeding artery was clearly visible in the CT scan performed in 2013 but not in the CT scan performed in 2015 (Figure 6,7). Therefore, we propose that regression of the FNH lesion occurs due to ischemia, which may trigger the apoptosis process, caused by the compression of the feeding artery. We also considered that increase in liver enzyme levels may be due to ischemia and cell apoptosis in FNH.

To the best of our knowledge, hepatic capsular retraction in the natural course of FNH has not been described in the literature; it should be kept in mind in the differential diagnosis of a liver lesion causing hepatic capsular retraction and of a liver lesion with exophytic growth and atypical enhancement and density pattern.

The surgical treatment of choice should be decided based on the findings of not only imaging modalities but also liver enzyme levels, especially GGT levels. If the lesion volume is increasing and there is no increase in the GGT level or if the lesion volume is decreasing and the GGT level is increasing, follow-up should be continued until a decrease is observed in both.

In conclusion, in addition to imaging modalities, it is logical to follow-up an FNH lesion using tests for AST, ALT, and especially GGT levels. Future studies involving more number of patients are needed.

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ORCID ID: Cemil Gürses: 0000-0003-2931-9309
ORCID ID: Feyzan Seher Okşar: 0000-0002-7519-0385
ORCID ID: Bekir Erol: 0000-0002-9444-3405
ORCID ID: Mustafa Yalçın: 0000-0002-8417-0909
ORCID ID: Nevfel Kahvecioğlu: 0000-0003-2641-5821
ORCID ID: Ahmet Şükrü Alparslan: 0000-0001-7083-5618

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