

Focal nodular hyperplasia of the liver – in our experience

Ogniskowy guzkowy rozrost wątroby – doświadczenia własne

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Słowa kluczowe: ogniskowy guzkowy rozrost wątroby, diagnostyka ogniskowego rozrostu guzowego wątroby, biopsja wątroby, techniki obrazujące.

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Abstract

Introduction: Focal nodular hyperplasia (FNH) is a tumour-like lesion of the liver.

Aim: The purpose of the study was to find out if there were any hints from the medical histories or additional investigations which would suggest FNH later confirmed by liver biopsy.

Material and methods: The clinical data of 28 patients with FNH hospitalized in the Department of Gastroenterology, MU of Lublin in the period 1st January, 2002 – 31st October, 2007 were analyzed retrospectively.

Results: Liver biopsy diagnosed FNH in 28 patients (92.86% women) from a total of 667 hospitalized in the Gastroenterology Department, Medical University of Lublin for focal lesions in the liver. In the group of 26 women 16 patients were on oral contraceptives, 5 were taking hypotensives; the men did not receive any medication. All 28 showed normal values of ALT, AST and AFP while each having a single focal lesion 24–121 mm in diameter found in USG. Their medical histories revealed that the FNH was asymptomatic and incidentally detected in USG. A central scar was detected in 9 of 28 patients on USG and in 14 of 23 patients on CT.

Conclusions: In our study FNH was a relatively rare pathology and constituted 4.20% of all cases with focal liver lesions. FNH prevailed in women (particularly who were oral contraceptive users), and did not differentiate in laboratory results. It manifested as a single focus being incidentally detected by imaging techniques with a central scar visualized in 32–60% of patients depending on the techniques applied. Scar absence accounts for the lack of features specific for FNH and then biopsy is the best option to diagnose the lesion.

Streszczenie

Wprowadzenie: Ogniskowy rozrost guzkowy (ORG) jest kwalifikowany jako niezłośliwy nowotwór wątroby typu *tumour-like lesion*.

Cel: Celem niniejszej pracy było określenie, czy istnieją typowe cechy z wywiadu medycznego i w badaniach dodatkowych, które mogłyby sugerować ustalenie rozpoznania ORG, potwierdzonego następnie biopsją zmiany ogniskowej wątroby w celu uzyskania niepodważalnego rozpoznania.

Materiał i metody: Retrospektywnie analizowano dane kliniczne 28 osób z ORG hospitalizowanych w Klinice Gastroenterologii Uniwersytetu Medycznego w Lublinie od 1 stycznia 2002 r. do 31 października 2007 r.

Wyniki: Wśród 667 pacjentów hospitalizowanych w analizowanym czasie z powodu zmian ogniskowych w wątrobie za pomocą biopsji wątroby wyodrębniono 28 chorych (92,86% kobiet) z ORG. Wśród 26 kobiet 16 z nich stosowało doustne środki antykoncepcyjne, natomiast 5 – leczenie hipotensyjne. Dwóch analizowanych mężczyzn nie przyjmowało żadnych leków. Średnie stężenia transaminaz alaninowej, asparaginianowej i α -fetoproteiny u wszystkich badanych pozostawały w granicach normy. Ogniskowy rozrost guzkowy u wszystkich analizowanych pacjentów miał postać pojedynczej, bezobjawowej zmiany ogniskowej o średnicy 24–121 mm wykrytej przypadkowo w czasie badania ultrasonograficznego jamy brzusznej. Za pomocą ultrasonografii wykazano obecność blizny centralnej u 9 z 28 pacjentów, natomiast za pomocą tomografii komputerowej u 14 z 23 poddanych badaniu.

Wnioski: Ogniskowy rozrost guzkowy jest rzadką patologią, w materiale własnym stanowił 4,20% wszystkich przypadków osób hospitalizowanych z powodu zmian ogniskowych wątroby w analizowanym czasie. Dotykał w większości kobiet (zwłaszcza stosujących doustną antykoncepcję) i nie wykazywał zmian

Introduction

Focal lesions developing in the liver pose serious problems for many medical specialists. The detection and characterization of them is one of the most important clinical problems due to their high incidence in the population. Obtaining a precise diagnosis is particularly difficult. Among them there is detection of solid focal masses in the liver in young or middle-aged women as they are more susceptible to developing oestrogen-dependent lesions.

Focal nodular hyperplasia (FNH) is a tumour-like lesion of the liver which occurs in otherwise normal liver parenchyma. It is relatively rare, occurring in 0.3% of adults, and its prevalence appears to have been increasing in recent years. It is the second most common focal lesion in the liver after haemangioma and like haemangioma most frequently detected incidentally by ultrasonography [1]. Focal nodular hyperplasia can coexist with adenoma, haemangioma, and vascular anomalies in the brain [2]. In 76% of cases it has the form of a single mass. More rarely it occurs as multiple foci [3]. Focal nodular hyperplasia is a stationary lesion and only a few casual studies report on its progressive form [4]. It is usually asymptomatic with sporadic abdominal pains. In 2-3% of cases bleeding into the peritoneal cavity can develop [5-7]. Aetiopathogenesis of FNH is not well known, but focal nodular hyperplasia is probably due to abnormal arterial vascularization, congenital or caused by injury, and focal ischaemia associated with it. Some hypotheses emphasize the involvement of oestrogens in development of this pathology [8-11]. However, its nature and pathogenesis are still controversial.

Accurate diagnosis of FNH based on clinical presentation and radiological studies is difficult and usually histological confirmation is required. If diagnosed correctly, no treatment is needed in asymptomatic patients. The potential for complications is extremely low. The main difficulty in management derives from the frequent difficulty in differentiating FNH from adenoma and fibrolamellar hepatocellular carcinoma [2].

The authors of this study asked the question what percentage of focal lesions in the liver were FNHs in the group of patients hospitalized in the Department

w badaniach laboratoryjnych. Manifestował się jako stwierdzone przypadkowo pojedyncze ognisko w wątrobie, z obecnością centralnej blizny uwidocznionej u 32–60% pacjentów, zależnie od zastosowanej techniki obrazowania. Brak centralnej blizny sprawia, że nie znajduje się innych w pełni swoistych cech typowych dla ORG w badaniach obrazujących. Podstawą rozpoznania pozostaje wówczas biopsja wątroby.

of Gastroenterology, Medical University in Lublin. They also wondered if in case of no clinical symptoms the disease produced typical imaging pictures that enabled a decisive diagnosis of FNH and whether it was possible to avoid invasive biopsy of the focal lesion in the liver to obtain unquestionable findings.

Material and methods

The patients hospitalized in the Department of Gastroenterology, Medical University of Lublin in the period 1st January, 2002 – 30th October, 2007 were examined retrospectively: patients' case histories and medical discharge records were analyzed and used to select those whose hospitalizations were caused by focal lesions detected in the liver. All these patients underwent targeted USG or CT guided liver biopsy to evaluate morphological lesions in the suspected site. Afterwards the patients with FNH were selected and their cases were further analyzed. The investigated parameters included: age, gender, medicines used before – data from medical histories, lab results (alanine aminotransferase – ALT, aspartate aminotransferase – AST, α -fetoprotein – AFP) and scan results (ultrasonography – USG, computed tomography – CT, liver scintigraphy). The age of the patients, results of laboratory tests and the diameter of the lesions are presented as means and SD. The purpose of the study was to find out if there are any hints from the medical histories or additional investigations which would suggest FNH later confirmed by liver biopsy.

Results

In the period 1st Jan, 2002 – 31st Oct, 2007 a total of 667 patients were hospitalized in the Department of Gastroenterology, Medical University of Lublin for focal lesions in the liver. During that period 5777 patients were hospitalized in our clinic, so the patients with focal lesions in the liver made up 11.54% of all patients. Liver biopsy found 28 patients with FNH, constituting 4.20% of all patients with focal lesions in the liver and 0.48% of all those hospitalized during that period.

The group of patients analyzed consisted of 2 men (7.14%) aged 41 and 46 yrs and 26 women (92.86%)

aged 19-51 yrs; mean age of female patients was 42.2 ± 7.3 yrs. Mean values of ALT and AST determined on admission to the hospital were normal (24.4 ± 3.7 and 19.3 ± 2.5 IU/l respectively). Mean AFP was 3.7 ± 0.9 ng/ml and was within the normal range in all patients examined. In the group of 26 women 16 patients were on oral contraceptives, 5 patients were taking hypotensives and 5 received no medication; men did not receive any medication.

All patients had USG of the abdomen performed which found a single focal lesion 24-121 mm in diameter, mean 53 ± 3.2 mm. Their medical histories revealed that the findings in the liver were asymptomatic and incidentally detected on USG examination performed for other reasons. USG was performed on the patient's request in 21 cases (75%) as a part of follow-up, without any clinical symptoms, 5 patients had USG for suspected urolithiasis confirmed by the findings and 2 patients for unspecific abdominal pain. USG images varied: in 9 patients the lesion was hypoechogenic, in 8 cases isoechogenic and in the remaining 11 cases it showed higher echogenicity in comparison to the parenchyma of the liver. In 9 patients the scan found a scar present in the central part of the lesion, confirmed by Doppler as a site of arterial blood flow. None of the USG scans determined a capsule surrounding the focal lesion. In all patients the detected FNH had the form of a single lesion.

Computed tomography was performed in 23 patients. The mean density of the liver was 50 j. H. and was lower in comparison with normal density of the liver parenchyma. Venous injection of dye strengthened the nodule density up to 96 j. H. in the arterial phase. In 14 patients CT found a scar located centrally in the lesion. After 5 min on average the central scar was strengthened, but the remaining parts of the nodule presented normal density.

In 1 patient ^{99m}Tc labelled colloid scintigraphy was performed. The scans confirmed a tumour 32 mm in diameter with excessive isotope concentration.

All patients had targeted biopsy of the liver: in 27 cases it was USG guided biopsy and in 1 patient it was CT guided as it was difficult to access the focal lesion visualized on a USG scan. In all cases analyzed FNH was diagnosed on the basis of histological evaluation. Microscopic pictures revealed extensive fibrosis in the form of septa intersecting the parenchyma into nodules accompanied by biliary duct proliferation with unevenly distributed lymphocytes, penetrating parenchyma at sites focally with neutrophils present. In most of the patients the examination revealed blood vessels with thickened walls. Figures 1-3 present a microscopic picture of FNH

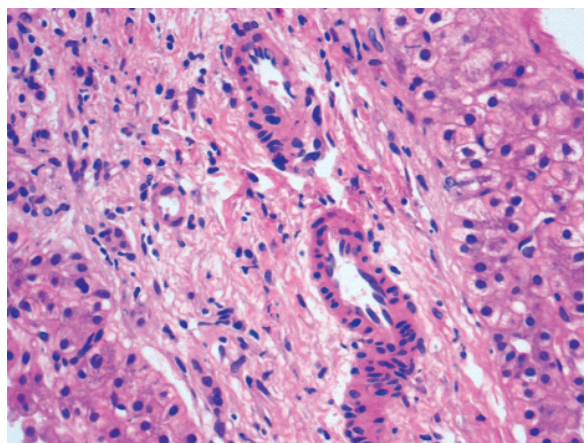


Fig. 1. Fibrous septa with thick-walled blood vessels and scant inflammatory infiltrate. Steatosis present in a few hepatocytes. H + E. Orig. magn. 200×

Ryc. 1. Włókniste przegrody ze ścięńczatą ścianą naczyń krwionośnych i skąpym naciekiem zapalnym. Stłuszczenie obecne w nielicznych hepatocytach. Barwienie H + E. Powiększenie 200×

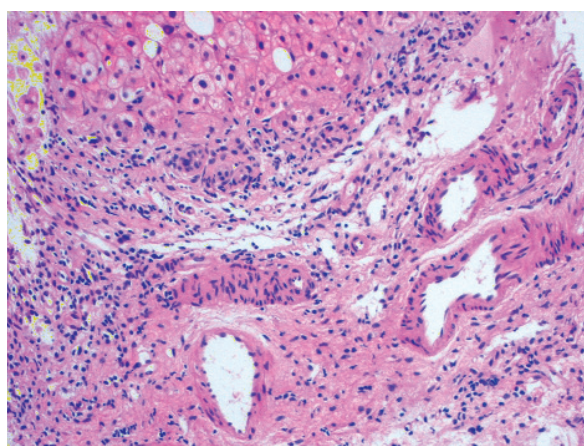


Fig. 2. Fibrous septum with thick-walled vessels and moderate inflammatory infiltrate focally penetrating parenchyma. Steatosis present in some hepatocytes. H + E. Orig. magn. 200×

Ryc. 2. Włókniste przegrody ze ścięńczatą ścianą naczyń krwionośnych i obecnością umiarkowanego nacieczenia zapalnego ogniskowo wnikaającego do miąższu. Stłuszczenie obecne w kilku hepatocytach. Barwienie H + E. Powiększenie 200×

in liver biopsy in examined patients. In 1 case, i.e. in a 19-year old woman, left-sided lobectomy was performed due to the large size of the lesion (121 mm in diameter). All the patients with FNH discussed here are still being followed up on an ambulatory basis.

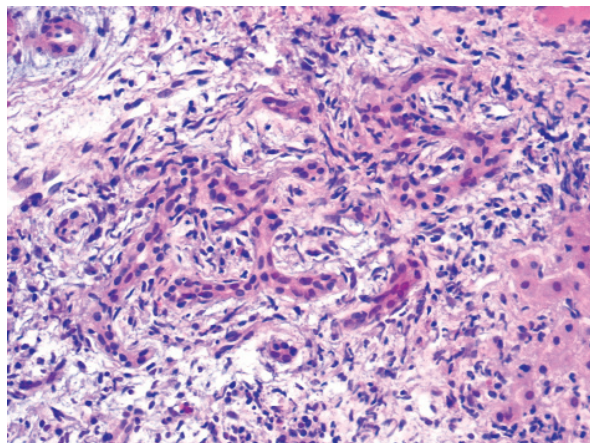


Fig. 3. Fibrous septum with proliferating bile ductules and more intensive inflammatory infiltrate penetrating parenchyma. H + E. Orig. magn. 200×

Ryc. 3. Włókniste przegrody z proliferacją przewodników żółciowych i stosunkowo intensywnym naciekiem zapalnym penetrującym miąższ. Barwienie H + E. Powiększenie 200×

Discussion

Focal nodular hyperplasia of the liver is a rare benign focal lesion detected more and more frequently. It is more prevalent among women (80-95%) than in men [3]. In our study 92.86% of patients were women. FNH usually occurs between 30 and 50 years of age (mean age of our patients was 42.0 ± 7.4 yrs), though some casual studies reported it in children as well [12, 13]. The studies emphasize the probability of FNH associated with oestrogen therapy. Long-term use of oral contraceptives and anabolic androgenic steroids can induce a benign hepatocellular lesion, among them FNH [8-11]. 50-75% of women with FNH are oral contraceptive users [11]. In our study 61.54% of females in whom FNH was detected have used oral contraceptives. In the majority of patients biochemical parameters of the liver remain within the normal range, and any detected deviations from the norm are insignificant. Alpha-fetoprotein concentrations are normal [6], which was also confirmed by our results. It has to be remembered though that normal biochemical scores can silence diagnostic alertness, especially as morphologically similar fibrolamellar carcinoma does not produce α -fetoprotein either and occurs in basically healthy liver in young people. Fibrolamellar carcinoma grows slowly; thus it can be interpreted as a stationary lesion as well.

In the majority of cases FNH is asymptomatic and is detected incidentally (35-90%) [3]. Only large lesions

may be associated with significant symptoms. Focal nodular hyperplasia's main manifestations include abdominal pains, loss of body weight, and weak appetite. Only a few patients developed the symptoms of spontaneous nodule rupture and bleeding into the peritoneal cavity [5, 7]. In our study all cases of FNH were asymptomatic and discovered incidentally on USG examination performed for other reasons.

Diagnostics of FNH uses imaging techniques such as USG of the abdomen, USG Doppler, CT and multiphasic CT [1, 6, 14, 15]. On a USG scan FNH presents itself as a single lesion; only in 5-20% of cases is it multifocal; sometimes it is well circumscribed and sometimes can be weakly demarcated from the surrounding parenchyma of the liver [3, 16]. A central scar is a fairly typical feature of FNH but can be found in about 50% of the lesions in the USG scan [17]. The central scar is formed by centrally located fibrous tissue along with the supplying artery, biliary ducts and inflammatory cells. Parametric imaging with contrast-enhanced sonographic examination could help less experienced sonologists diagnose FNH [18]. In CT scan FNH is characterized by hypervascularity, homogeneity, non-encapsulation and presence of a central scar, which occurs in 35-65% of cases according to the literature [15, 18, 19]. In our series USG was performed in all patients; however, in 9 cases only (32.14%) USG detected the presence of a central scar, which suggested FNH. In 14 of 23 patients (60.87%) CT scans found FNH on the basis of a central scar.

Technetium-99m labelled colloid scintigraphy is also useful in FNH detection. Focal nodular hyperplasia takes up radioactive colloid and presents as a hot focus or site of indifferent radioactivity from the rest of the liver parenchyma [20]. In our study one patient had ^{99m}Tc labelled colloid scintigraphy performed. It found a hot nodule of isotope hyperconcentration 30 mm in diameter.

Cherqui et al. [21] presented MRI as an alternative imaging technique with sensitivity and specificity of 70 and 98% respectively. In our study none of the patients had diagnostic MRI performed. Grazioli et al. [22] suggested MRI fast spin echo (FSE) with gadobenate dimeglumine (Gd-BOPTA) as a contrast agent used in the dynamic and delayed phase to achieve perfect morphological and functional characterisation of FNH. However, biopsy of the FNH site is the most essential and basic diagnostic tool.

Morphologically FNH is often classified into two types: classic (80% of cases) and non-classic (20%). Classical form consists of multiple nodules of hyperplastic parenchyma separated by fibrous septa with ductular proliferation. The non-classical form is divided into three subtypes: teleangiectatic FNH, FNH

with cytologic atypia and mixed hyperplastic and adenomatous FNH [17]. Histological assessment of biopsy of FNH reveals major diagnostic features: fibrous bands, thick-walled vessels, reactive ductules, nodularity; and minor features: sinusoidal dilatation, perisinusoidal fibrosis.

Roskams et al. [23] have found that progenitor cells are increased in FNH. This could be driven by transforming growth factor- α , which is overexpressed in FNH [24].

Most authors advocate an expectant attitude if radiology is unequivocal [22, 25]. If the differentiation against other focal liver lesions cannot be made, biopsy should be performed. Similarly, Fabre et al. [19] suggested that liver biopsy did not appear to be necessary in cases where imaging was typical. The absence of radiological diagnostic criteria of FNH does not preclude a positive diagnosis on liver needle biopsy. The presence of a central scar on scans argues in favour of FNH. However, it has to be remembered that it can also be an element of hepatocellular fibrolamellar carcinoma. Hence, it is necessary to differentiate between those two pathologies. In our material a central scar was noted in less than half of the patients; therefore the majority of those examined required the biopsy.

Recent studies have tried to find molecular features of FNH closely related to clinical and pathological characteristics. These findings may modify our clinical practice [26].

Focal nodular hyperplasia is a stationary lesion with good prognosis so there are no direct indications to operate on it [3]. Liver resection is performed in the case of doubtful diagnosis, for example if malignancy is suspected, to differentiate it from neuroendocrine carcinoma or fibrolamellar carcinoma, if the nodule has enlarged or its diameter is over 10 cm. In the presented paper one patient was operated on due to the large size of the tumour (12 cm in diameter). There are data in the literature reporting tumour recurrence after complete resection has been performed [4].

Our study showed that FNH is found as a relatively rare pathology. It concerned 0.48% of all admissions to the Department of Gastroenterology. Focal nodular hyperplasia constituted 4.20% of all cases with a focal liver lesion; thus statistically one 25th of patients with a focal liver lesion had FNH. It prevailed in women (particularly who were oral contraceptive users) and showed normal laboratory results. It was manifested as a single focus in the liver and was detected incidentally. The presence of a central scar, often detected by imaging techniques, was visualized in 32-60% of our

patients depending on the technique used. Scar absence accounts for the lack of specific features of FNH and then biopsy is the best option to diagnose the lesion and to rule out malignancy.

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