FOCAL NODULAR HYPERPLASIA FROM THE SURGERY TO THE FOLLOW-UP. CHANGE OF THERAPEUTIC APPROACH

GAETANO BERTINO[1], SHIRIN DEMMA[1], ANNALISA ARDIRI[1], ADRIANA TORO[2], STEFANO GIUSEPPE CALVAGNO[1], GIULIA MALAGUARNERA[3], NICOLETTA BERTINO[4], MICHELE MALAGUARNERA[3], MARIANO MALAGUARNERA[3], ISIDORO DI CARLO[2]
[1]Hepatology Unit, Department of Medical and Pediatric Sciences, University of Catania - Catania - [2]Department of Surgical Sciences, Organ Transplantation and Advanced Technologies, University of Catania - Catania - [3]Research Centre 'The Great Senescence', University of Catania - Catania, Italy

ABSTRACT

Aim: *Focal nodular hyperplasia is the second common benign tumor of the liver after hemangioma The aim of the present review is to point out the current approach for the differential diagnosis especially with fibrolamellar hepatocellular carcinoma, with a further look to the changes in therapeutic approach, from the surgery to the follow-up.*

Materials and methods*: An electronic search of the literature was made using cancer literature, the PubMed, Scopus and Web of Science database.*

Results*: We included studies published from 1997 to 2014 inclusive, these were excluded case reports, abstracts, non-english and not relevant studies. Were included fifty-six studies.*

Conclusion*: Although Focal Nodular Hyperplasia is managed conservatively in the majority of cases, it can albeit pose a difficult diagnostic dilemma. This tumour was once often resected because it was difficult to distinguish from hepatic adenoma, but with modern multiphase imaging it is now diagnosed strictly by imaging criteria and not resected.*

Key words*: hepatic benign tumors, focal nodular hyperplasia, vascular malformation, oral contraceptives.*

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Introduction

Focal nodular hyperplasia (FNH) is a benign lesion of the liver, usually asymptomatic and with indolent course, that rarely is involved in complications as rupture and hemorrhage. The malignant potential is still not known. It seems to grow up from a preexisting arterial malformation and usually it is found occasionally as an incidental finding because of the large use of imaging. Management options are evolving because of the recent developments in the understanding of molecular processes and subtypes of FNH. After haemangiomas, FNH is the most common benign liver cancer. Actually, in a large autopsy study, the incidence is of 0.31%[(1)]. Even if it can affect both male and female of all ages, its incidence in females is reported to be eight times higher than in males and is weakly associated with reproductive age and use of oral contraceptives[(2,3)]. Rarely it's a pediatric diagnosis[(4)].

Materials and methods

Literature search strategy

This is a narrative review.

An electronic search of the literature was made using cancer literature, the PubMed, Scopus and Web of Science (WOS) database for the following keywords: "focal nodular hyperplasia, "hepatic benign tumors", vascular malformation", "oral contraceptives". The search was performed for the period 1997 to 2014 inclusive using and was limited to English-language publications. All titles and abstracts were reviewed and appropriate papers

assessed for inclusion. The reference sections of all papers initially included were also assessed to ensure the identification of all relevant studies.

Exclusion and inclusion criteria

Case reports, editorials, unpublished data from conference abstracts, non-english and not relevant studies were excluded. Studies were included if they described pathogenesis, clinical manifestations, diagnostic methods used, imaging and therapeutic management of FNH.

Characteristics of included studies

Prospective, controlled studies, reviews or meta-analisis studies with a relevant number of patients, all series satisfying these criteria were included regardless.

Results

We included studies published from 1997 to 2014 inclusive, these were excluded case reports (n = 203), abstracts (n = 409), non-english studies (n = 138) and not relevant studies (n = 313). In the review were included fifty-six studies. The characteristics of excluded and included studies are shown in Fig. 1.

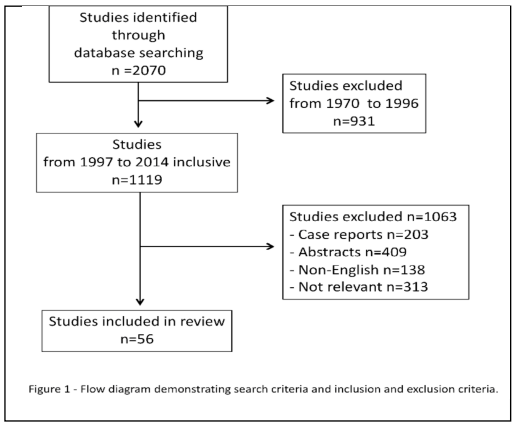

Figure 1 - Flow diagram demonstrating search criteria and inclusion and exclusion criteria.

Clinical manifestations

Rarely FNH causes symptoms. In fact[3], it may lead to vague abdominal pain if the lesion is responsible of a stretching of Glisson's capsule or of the displacement of other organs[5]. It is necessary, for first, to exclude other causes of pain.

Focal nodular hyperplasia may become very large and present with hepatomegaly or as an abdominal mass[2,3]. Usually serological parameters of liver function are normal but a mildly elevated serum gamma-glutamyl transferase can occur if the mass is large enough to cause extrinsic intrahepatic biliary duct compression. In order to differentiate those cases of atypical FNH from Hepatocellullar Carcinoma (HCC), the determination of serum α-fetoprotein (AFP) levels may be useful to detect HCC at an earlier stage. AFP, however, is a marker characterized by poor sensitivity and specificity[6,7,8,9,10,11,12].

A rare complication is represented by intratumoral hemorrhage and subsequent haemoperitoneum[13,14]. Patients that are more often involved are those with multiple FNH masses or with exophytic tumors[15].

Histopathology and pathogenesis

Focal nodular hyperplasia lesions are usually solitary. In 20 % of cases they can be multiple[1,2]. Focal nodular hyperplasia is subdivided into two types: classic (80%) and non-classic (20%)[2].

FNH is typically void of any formal portal triads[1]. It's a non-encapsulated nodule with a central fibrous body and with septa radiating from the center that divides nodules of hyperplastic hepatocytes. The central region contain abnormal vessels, as well as proliferating bile ductules.

Nguyen et al. describe three "non classical" histological subtypes: the telangiectatic FNH (tFNH) characterized by dilated sinusoids similar to adenoma, the mixed hyperplastic and adenomatous forms that are formed by separate regions similar to tFNH or adenoma but with some parts that are the result of morphological features between the two and the FNH with cytological atypia. This group is marked by atypical hepatocytes with irregular contours and enlarged hyperchromatic nuclei[2] (Fig. 2,3).

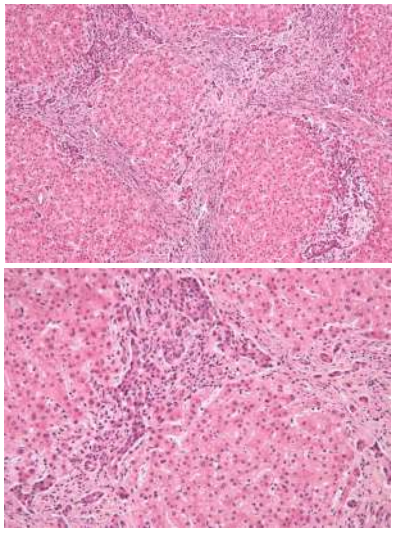

Fig. 2: Focal nodular hyperplasia histological "classic" lesions.

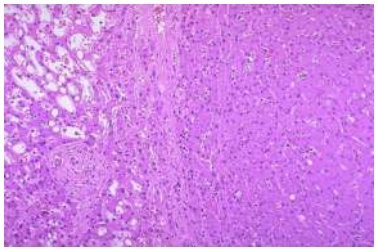

Fig. 3: Focal nodular hyperplasia histological subtypes "non-classic" lesions.

Etiology is still not known but it seems that the trigger event is usually a vascular malformation. Due to an arterial hyperperfusion, an hiperoxic condition can activate hepatic stellate cells and VEGF, activated by increate oxygen tension, may influence the proliferation of abnormal vessels[16].

Numerous reports suggest that oral contraceptives are involved in the development of FNH, especially in the long-term use[17,18] even if the debate about the hormone role in the growth of FNH is still ongoing. In the past oral contraceptives formulations contained much higher doses of estrogen that at present and radiological diagnosis was not accurate as today, so more prospective studies with histopathological confirmation should be undertaken. Most of the recent literature seems to refute the argument for an association[19,20,21].

Just few cases are described about the effect of pregnancy, usually with no complications[19,22].

Now attention is focused on the molecular pathogenesis of FNH, with a particular attention on clonal analysis. Recent literature deal with the polyclonal origin of the lesion[23,24], according to the most accepted theory that is an hyperplastic lesion. Others studies have described a lack of somatic genes mutations supporting the theory that it is a non-neoplastic lesion[24,25,26]. However monoclonal FNH are described, suggesting a partial neoplastic transformation[27,28].

Bioulac-Sage at al. compared several cases of tFNH to classical FNH and to adenomas showing that hepatic adenoma was the most similar to tFNH[25]. 100 % of tFNH was monoclonal.

The natural history of FNH

Nowadays a conservative approach is recommended because of the stability of most FNH lesions, the lack of potential for malignant transformation and the very low risk of hemorrhage and rupture. Moreover a regression of the lesion with the age is possible, also as a result of thrombosis of the feeding artery[1].

A study of 54 FNH, followed for 32 months, demonstrated that a minority of lesions can increase in size[29]. Many studies describe long-term follow up imaging of FNH, proving no malignant transformation[29,30].

Imaging of FNH

Differentiate FNH from other hepatic lesions that may require surgery or systemic therapies[31] like HCC or hepatic adenoma can be difficult because of the similarity on imaging and if FNH shows atypical characteristics it might be necessary additional invasive diagnostic measures.

Ultrasound

In cases of FNH, Ultrasound findings are variable. The lesion may appear as a homogeneous mass that is isoechoic, hypoechoic, or hyperechoic. FNH has a mass effect that may displace intrahepatic blood vessels. In only 18% of cases is a central scar present[32,33,34].

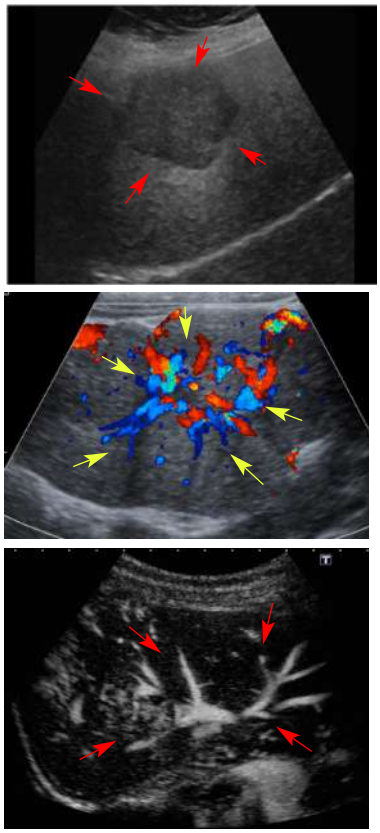

Fig. 4: Focal nodular hyperplasia, Ultrasound Imaging (A), Doppler sonograms (B), Dynamic contrast-enhanced (C) - (arrows).

Doppler sonograms demonstrate an enlarged afferent blood vessel with central arterial hypervascularity and centrifugal filling to the periphery in a spoke-like manner. Large draining veins may be

seen at the periphery of the mass. High-velocity Doppler signals with arterial pulsatility may be recorded from arteriovenous shunts. Echo-enhanced Doppler US has a high sensitivity for detection of the feeding artery and for depiction of the radial vascular architecture in FNH lesions, especially for the ones located in the liver's left lobe. Power Doppler US has increased sensitivity for FNH and may help distinguish FNH from hepatocellular carcinoma.

Dynamic contrast-enhanced US is increasingly being used to diagnose FNH. According to Ungermann et al, contrast-enhanced US may be the final diagnostic method for lesions that are larger than 3 cm and have a typical spoke-wheel structure; however, they concluded that if the spoke-wheel pattern is not present and if there is no central scar, the diagnosis of FNH cannot be made specifically on the basis of contrast-enhanced US alone[25] (Fig. 4).

Computed Tomography (CT)

Sensitivity and specificity of this kind of imaging are respectively 75% and 92%[35,36]. The typical finding is a well-circumscribed lesion appearing iso- or hypodense on the non-contrast studies (37). A hypodense scar is visible in a minority of cases. In the arterial phase there is a rapid homogenous intense enhancement due to the feeding arteries. During the portal venous phase the lesion becomes iso-hypodense because of the presence of large sinusoids and draining veins while the central scar gradually acquires enhancement as the contrast diffuses into the fibrous tissue, especially in the larger lesions. In the 40% of cases it's possible to recognize a discontinuous peripheral vascular rim[24].

Teleangiectatic Focal Nodular Hyperplasia (tFNH) has different characteristics. Usually it is multiple, heterogeneous, without a central scar and with a persisting enhancement on delayed phase imaging[38,39,40]. In consideration of new evidence that make this lesion closer to hepatic adenoma instead of classic FNH, CT masses with these characteristic should be approached with suspicion.

Other hepatic lesions as fibrolamellar subtype of HCC and hepatocellular adenoma need to be considered in differential diagnosis as they share some similar aspects to FNH, especially in the atypical forms, at the CT scan[41,42,43].

Nonetheless, the fact that FNH and Fibrolamellar hepatocelllular carcinoma (FL HCC) occur in the same age groups and in those patients with no underlying liver disease may lead to confusion if the lesions have atypical appearance[44] (Fig. 5).

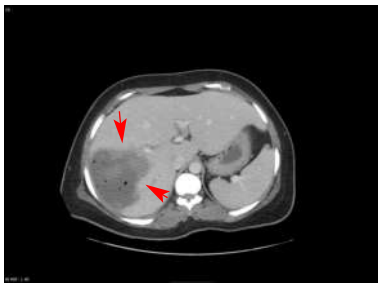

Fig. 5: Focal nodular hyperplasia, Computed Tomography Imaging (arrows).

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is both sensitive (70%) and specific (98%). At the MRI the FNH appears as an homogenous lesion, isointense or lightly hypointense on T1-weightened images and isointense of lightly hyperintense on T2-weighted images. The scar is hypointense on T1 and hyperintense on T2.

In contrasted MRI, Gadolinium enhancement is similar to CT contrast medium. During arterial phase a typical FNH appears homogenous hyperintense, during the portal phase it returns to isointensity. On delayed phase images FNH is either isointense or lightly hyperintense. The central scar is hypointense during the arterial phase and retains contrast on delayed scans[45,46].

tFNH has different features on the MRI compared to the classical FNH. It is usually heterogeneous, hyperintense on T1, strongly hyperintense on T2 and with no central scar[40].

If atypical features appear on MRI, diagnosis may be difficult and it can require biopsy, resection or a period of observation to exclude other hepatic lesions as fibrolamellar HCC and hepatic adenoma (Fig. 6).

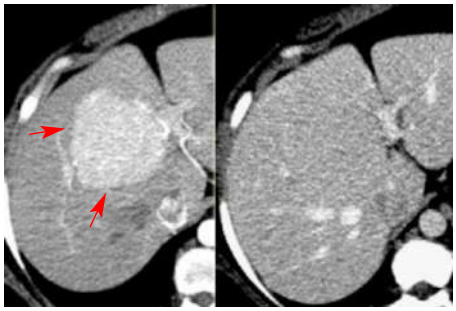

Fig. 6: Focal nodular hyperplasia, Magnetic Resonance Imaging (arrows).

Nuclear Medicine

The presence of Kupffer cells in FNH allows these lesions to take up technetium (Tc) 99m sulphur colloid. P\A positive scans is seen in 80% of lesions, and is helpful in distinguishing them from hepatic adenomas, HCC and hepatic metastases which do not contain Kupffer cells[47] (Fig. 7).

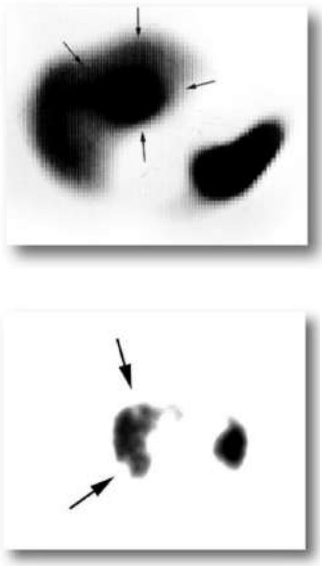

Fig. 7: Focal nodular hyperplasia, liver scan with technetium (TC) 99m sulphur colloid.
a)Focal nodular hyperplasia: "hot spot" liver scan (arrows); b) Focal nodular hyperplasia: "multiple defects" (arrows)

Biopsy

Biopsy may be appropriate in those cases with an unclear imaging[48]. It is important to evaluate risks and benefits of this procedure, including bleeding or seeding of malignant cells if the lesion is not benign. Literature data suggest that there is still a need for consensus about diagnostic criteria regarding needle biopsy features of FNH. An alternative management of patients with atypical lesions is observation for a period of 3-4 months. After that it is necessary to repeat CT or MRI to exclude changes in size or other characteristics of the suspicious lesion.

Management

A conservative approach is to prefer for that patients with asymptomatic FNH, due to the no potential for malignant changes and to the rare acute complications.

Over 40 years of age benign lesions can present atypical features on imaging and this may reflect hormonal fluctuations in women when menopause occurs. In patients with atypical characteristics, but with benign features, observation for 3-4 months is a reasonable opportunity, if other worrying characteristics are no present. If the lesion changes, enlarges significantly or become symptomatic surgery should be considered both to treat and to diagnose[49].

Patients that usually require surgery have large and subcapsular lesions.

Indications for resection include: persistent symptoms, atypical features in lesions that have increased in size or changed and symptoms onset after an observation period. If a malignant lesion is suspected, an immediate resection should be performed.

Pregnant women or women that are trying to be pregnant don't need any resection. Observation is sufficient. Oral contraceptives should be stopped in patients under observation even if only limited data are available supporting an association between low-dose oral contraceptives and FNH.

No randomized controlled trials studying the befit of elective surgery for any benign liver tumor versus conservative management are available[50].

Laparoscopic resection may have more benefits in term of post-operative hospital stay and return to normal activities compared to open surgery[51].

Angiographic embolization has tried sporadically in those cases where resection was contraindicated but no controlled studies comparing the two procedures are available[30,52].

Conclusions

Although different pathological subtypes that may explain the heterogeneous presentation of FNH are now described, frequently requiring a differential diagnosis[53,54,55] FNH history is still not completely understood. Modern imaging is very useful in characterizing most of the suspicious lesions, avoiding the need of needle biopsy and surgical intervention.

The role of hormonal milieu is still strongly supported in influencing the development of FNH, confirmed by the fact that the diagnosis is extremely rare in postmenopausal women[56].

References

1) Dimitroulis D, Charalampoudis P, Lainas P, Papanikolaou IG, Kykalos S, Kouraklis G. *Focal nodular hyperplasia and hepatocellular adenoma: current views*. Acta Chir Belg. 2013 May-Jun; 113(3): *162-9*. Review.
2) Nguyen BN, Flejou JF, Terris B, Belghiti J, Degott C. *Focal nodular hyperplasia of the liver: a comprehensive pathologic study of 305 lesions and recognition of new histologic forms*. Am J Surg Pathol 1999; 23: *1441-1454*.
3) Luciani A, Kobeiter H, Maison P, Cherqui D, Zafrani ES, Dhumeaux D, Mathieu D. *Focal nodular hyperplasia of the liver in men: is presentation the same in men and women?* Gut 2002; 50:*877-880*.
4) Cha DI, Yoo SY, Kim JH, Jeon TY, Eo H. *Clinical and imaging features of focal nodular hyperplasia in children*. AJR Am J Roentgenol. 2014 May; 202(5): *960-5*.
5) Fujiwara H, Sekine S, Onaya H, Shimada K, Mikata R, Arai Y. *Ring-like enhancement of focal nodular hyperplasia with hepatobiliary-phase Gd-EOB-DTPA-enhanced magnetic resonance imaging: radiological-pathological correlation*. Jpn J Radiol. 2011 Dec; 29(10): *739-43*.
6) Bertino G, Ardiri A, Malaguarnera M, Malaguarnera G, Bertino N, Calvagno GS. *Hepatocellualar carcinoma serum markers*. Semin Oncol. 2012; 39: *410-33*.
7) Di Carlo I, Mannino M, Toro A, Ardiri A, Galia A, Cappello G, Bertino G. *Persistent increase in alpha-fetoprotein level in a patient without underlying liver disease who underwent curative resection of hepatocellular carcinoma. A case report and review of the literature*. World J Surg Oncol. 2012 May 6; 10: *79*. Review.
8) Bertino G, Neri S, Bruno CM, Ardiri AM, Calvagno GS, Malaguarnera M, Toro A, Malaguarnera M, Clementi S, Bertino N, Di Carlo I. *Diagnostic and prognostic value of alpha-fetoprotein, des-γ-carboxy prothrombin and squamous cell carcinoma antigen immunoglobulin M complexes in hepatocellular carcinoma*. Minerva Med. 2011 Oct; 102(5): *363-71*. Review.
9) Bertino G, Ardiri AM, Calvagno GS, Bertino N, Boemi PM. *Prognostic and diagnostic value of des-γ-carboxy prothrombin in liver cancer*. Drug News Perspect. 2010 Oct; 23(8): *498-508*. Review.
10) Bertino G, Ardiri AM, Santonocito MM, Boemi PM. *Some patients with HCC haven't abnormal des-gamma-carboxy prothrombin and alpha-fetoprotein levels*. Panminerva Med. 2009 Jun; 51(2): *133-4*.
11) Biondi A, Malaguarnera G, Vacante M, Berretta M, D'Agata V, Malaguarnera M, Basile F, Drago F, Bertino G. Elevated serum levels of Chromogranin A in hepatocellular carcinoma. BMC Surg. 2012;12 Suppl 1:S7.
12) Malaguarnera G, Paladina I, Giordano M, Malaguarnera M, Bertino G, Berretta M. *Serum markers of intrahepatic cholangiocarcinoma*. Dis Markers. 2013; 34(4): *219-28*. Review.
13) Rahili A, Cai J, Trastour C, Juwid A, Benchimol D, Zheng M, Bourgeon A. *Spontaneous rupture and hemorrhage of hepatic focal nodular hyperplasia in lobus caudatus*. J Hepatobiliary Pancreat Surg. 2005; 12(2): *138-42*.
14) Hardwigsen J, Pons J, Veit V, Garcia S, Le Treut YP. *A life-threatening complication of focal nodular hyperplasia*. J Hepatol 2001; 35: *310-312*.
15) Demarco MP, Shen P, Bradley RF, Levine EA. *Intraperitoneal hemorrhage in a patient with hepatic focal nodular hyperplasia*. Am Surg 2006; 72: *555-559*.
16) Sato Y, Harada K, Ikeda H, Fijii T, Sasaki M, Zen Y, Nakanuma Y. *Hepatic stellate cells are activated around central scars of focal nodular hyperplasia of the liver-a potential mechanism of central scar formation*. Hum Pathol 2009; 40: *181-188*.
17) Scalori A, Tavani A, Gallus S, La Vecchia C, Colombo M. *Oral contraceptives and the risk of focal nodular hyperplasia of the liver: a case-control study*. Am J Obstet Gynecol 2002; 186: *195-197*.
18) Kapp N, Curtis KM. *Hormonal contraceptive use among women with liver tumors: a systematic review*. Contraception. 2009 Oct; 80(4): *387-90*.
19) Mathieu D, Kobeiter H, Maison P, Rahmouni A, Cherqui D, Zafrani ES, Dhumeaux D. *Oral contraceptive use and focal nodular hyperplasia of the liver*. Gastroenterology 2000; 118: *560-564*.
20) Durczyński A, Hogendorf P, Szymański D, Sporny S, Strzelczyk J. *Synchronous occurrence of multiple focal nodular hyperplasia and huge hepatic perivascular epithelioid cells tumor (PEComa) in young woman after oral contraceptive use is there a common pathogenesis?* Pol Przegl Chir. 2012 Sep; 84(9): *457-60*.
21) Kapp N, Curtis KM. *Hormonal contraceptive use among women with liver tumors: a systematic review*. Contraception 2009; 80: *387-390*.
22) Rifai K, Mix H, Krusche S, Potthoff A, Manns MP, Gebel MJ. *No evidence of substantial growth progression or complications of large focal nodular hyperplasia during pregnancy*. Scand J Gastroenterol. 2013 Jan;48(1): 88-92.
23) Gong L, Li YH, Su Q, Li G, Zhang WD, Zhang W. *Use of X-chromosome inactivation pattern and laser microdissection to determine the clonal origin of focal nodular hyperplasia of the liver*. Pathology. 2009; 41(4): *348-55*.
24) Chen YW, Jeng YM, Yeh SH, Chen PJ. *P53 gene and Wnt signaling in benign neoplasms: beta-catenin mutations in hepatic adenoma but not in focal nodular hyperplasia*. Hepatology 2002; 36: *927-935*.
25) Bioulac-Sage P, Rebouissou S, Sa Cunha A, Jeannot E, Lepreux S, Blanc JF, Blanche H, Le Bail B, Saric J, Laurent-Puig P, Balabaud C, Zucman-Rossi J. *Clinical, morphologic, and molecular features defining so-called telangiectatic focal nodular hyperplasias of the liver*. Gastroenterology 2005; 128: *1211-1218*.
26) Chen YJ, Chen PJ, Lee MC, Yeh SH, Hsu MT, Lin CH. *Chromosomal analysis of hepatic adenoma and focal nodular hyperplasia by comparative genomic hybridization*. Genes Chromosomes Cancer 2002; 35: *138-143*.
27) Cai YR, Gong L, Teng XY, Zhang HT, Wang CF, Wei GL, Guo L, Ding F, Liu ZH, Pan QJ, Su Q. *Clonality and allelotype analyses of focal nodular hyperplasia compared with hepatocellular adenoma and carcinoma*. World J Gastroenterol 2009; 15: *4695-4708*.
28) GongL, LiYH, SuQ, LiG, ZhangWD, ZhangW. *Use of X- chromosome inactivation pattern and laser microdissection to determine the clonal origin of focal*

nodular hyperplasia of the liver. Pathology 2009; 41: *348-355*.

29) Weimann A, Ringe B, Klempnauer J, Lamesch P, Gratz KF, Prokop M, Maschek H, Tusch G, Pichlmayr R. *Benign liver tumors: differential diagnosis and indications for surgery.* World J Surg 1997; 21: *983-990*; discussion *990-981*.

30) Navarro AP, Gomez D, Lamb CM, Brooks A, Cameron IC. *Focal nodular hyperplasia: a review of current indications for and outcomes of hepatic resection*. HPB (Oxford). 2014 Jun; 16(6): *503-11*.

31) Bertino G, Di Carlo I, Ardiri A, Calvagno GS, Demma S, Malaguarnera G, Bertino N, Malaguarnera M, Toro A, Malaguarnera M. *Systemic therapies in hepatocellular carcinoma: present and future*. Future Oncol. 2013 Oct; 9(10): *1533-48*.

32) Kubaska S, Sahani DV, Saini S, et al. *Dual contrast enhanced magnetic resonance imaging of the liver with superparamagnetic iron oxide followed by gadolinium for lesion detection and characterization*. Clin Radiol. May 2001; 56(5): *410-5*.

33) Uggowitzer MM, Kugler C, Mischinger HJ, et al. *Echo-enhanced Doppler sonography of focal nodular hyperplasia of the liver*. J Ultrasound Med. Jul 1999; 18(7): *445-51*; quiz 453-4.

34) Lee IJ, Jeong SH, Choi JW, Park HS, Lee KH, Kim H. *Radiological findings in a case of multiple focal nodular hyperplasia associated with portal vein atresia and portopulmonary hypertension*. Korean J Radiol. Aug 2008; 9(4): *386-9*.

35) Dreizin D, Infante J, Tirada N, Raman SP, Madrazo B. *Focal nodular hyperplasia within accessory liver: imaging findings at computed tomography and magnetic resonance imaging*. J Comput Assist Tomogr. 2014 May-Jun; 38(3): *424-6*.

36) Valentino PL, Ling SC, Ng VL, John P, Bonasoni P, Castro DA, Taylor G, Chavhan GB, Kamath BM. *The role of diagnostic imaging and liver biopsy in the diagnosis of focal nodular hyperplasia in children*. Liver Int. 2014 Feb; 34(2): *227-34*.

37) Trillaud H, Bruel JM, Valette PJ, Vilgrain V, Schmutz G, Oyen R, Jakubowski W, Danes J, Valek V, Greis C. *Characterization of focal liver lesions with SonoVue-enhanced sonography: international multicenter-study in comparison to CT and MRI*. World J Gastroenterol. 2009 Aug 14; 15(30): *3748-56*.

38) Liu QY, Zhang WD, Lai DM, Ou-Yang Y, Gao M, Lin XF. *Hepatic focal nodular hyperplasia in children: imaging features on multi-slice computed tomography*. World J Gastroenterol. 2012 Dec 21; 18(47): *7048-55*.

39) Carlson SK, Johnson CD, Bender CE, Welch TJ. *CT of focal nodular hyperplasia of the liver.* AJR Am J Roentgenol 2000;174: *705-712*.

40) Attal P, Vilgrain V, Brancatelli G, Paradis V, Terris B, Belghiti J, Taouli B, Menu Y. *Telangiectatic focal nodular hyperplasia: US, CT, and MR imaging findings with histopathologic correlation in 13 cases*. Radiology 2003; 228: *465-472*.

41) Ganeshan D, Szklaruk J, Kundra V, Kaseb A, Rashid A, Elsayes KM. *Imaging features of fibrolamellar hepatocellular carcinoma*. AJR Am J Roentgenol. 2014 Mar; 202(3): *544-52*. doi: 10.2214/AJR.13.11117. Review. Erratum in: AJR Am J Roentgenol. 2014 Apr; 202(4): *933*.

42) Teefey SA, Stephens DH, Weiland LH. *Calcification in hepatocellular carcinoma: not always an indication of fibrolamellar histology*. AJR Am J Roentgenol 1987; 149: *1173-1174*. J Gastrointest Surg (2011) 15: *2275-2283*.

43) Njei B, Konjeti VR, Ditah I. *Prognosis of Patients With Fibrolamellar Hepatocellular Carcinoma Versus Conventional Hepatocellular Carcinoma: A Systematic Review and Meta-analysis*. Gastrointest Cancer Res. 2014 Mar; 7(2): *49-54*.

44) Mavros MN, Mayo SC, Hyder O, Pawlik TM. *A systematic review: treatment and prognosis of patients with fibrolamellar hepatocellular carcinoma*. J Am Coll Surg. 2012 Dec; 215(6): *820-30*.

45) Cogley JR, Miller FH. *MR imaging of benign focal liver lesions*. Radiol Clin North Am. 2014 Jul; 52(4): *657-82*.

46) Dohan A, Soyer P, Guerrache Y, Hoeffel C, Gavini JP, Kaci R, Boudiaf M. *Focal nodular hyperplasia of the liver: diffusion-weighted magnetic resonance imaging characteristics using high b values*. J Comput Assist Tomogr. 2014 Jan-Feb; 38(1): *96-104*.

47) Lencioni R, Cioni D, Bartolozzi C. *Focal liver lesions, detection, characterization, ablation*. Springer Verlag. (2005) ISBN: 3540644644.

48) Fabre A, Audet P, Vilgrain V, Nguyen BN, Valla D, Belghiti J, Degott C. *Histologic scoring of liver biopsy in focal nodular hyperplasia with atypical presentation*. Hepatology 2002; 35: *414-420*.

49) Reddy KR, Kligerman S, Levi J, Livingstone A, Molina E, Franceschi D, Badalamenti S, Jeffers L, Tzakis A, Schiff ER. *Benign and solid tumors of the liver: relationship to sex, age, size of tumors, and outcome*. Am Surg 2001; 67: *173-178*.

50) Colli A, Fraquelli M, Massironi S, Colucci A, Paggi S, Conte D. *Elective surgery for benign liver tumours*. Cochrane Database Syst Rev. 2007 Jan 24; (1): CD005164. Review.

51) Bonney GK, Gomez D, Al-Mukhtar A, Toogood GJ, Lodge JP, Prasad R. *Indication for treatment and long-term outcome of focal nodular hyperplasia*. HPB (Oxford) 2007; 9: *368-372*.

52) Amesur N, Hammond JS, Zajko AB, Geller DA, Gamblin TC. *Management of unresectable symptomatic focal nodular hyperplasia with arterial embolization*. J Vasc Interv Radiol 2009; 20: *543-547*.

53) Bertino G, Ardiri A, Demma S, Giuseppe Calvagno S, Toro A, Basile E, Campagna D, Ferraro G, Frazzetto E, Proiti M, Malaguarnera G, Bertino N, Malaguarnera M, Malaguarnera M, Amaradio MD, Pricoco G, Di Carlo I. *Rare benign tumors of the liver: still rare?* J Gastrointest Cancer. 2014 Jun; 45(2): *202-17*.

54) Bertino G, Demma S, Ardiri A, Proiti M, Gruttadauria S, Toro A, Malaguarnera G, Bertino N, Malaguarnera M, Malaguarnera M, Di Carlo I. *Hepatocellular Carcinoma: Novel Molecular Targets in Carcinogenesis for Future Therapies*. Biomed Res Int. 2014; 2014: *203693*.

55) Bertino G, Demma S, Bertino N, Ardiri A. *Management of Hepatocellular Carcinoma: An Update at the Start of 2014*. J Gastroint Dig Syst 2014, 4: 2, 1-7 http://dx.doi.org/10.4172/2161-069X.1000178.

56) Nahm CB, Ng K, Lockie P, Samra JS, Hugh TJ. *Focal Nodular Hyperplasia A Review of Myths and Truths*. J Gastrointest Surg 2011; 15: *2275-2283*.

Corresponding Author
Prof. GAETANO BERTINO
Hepatology Unit, Department of Medical and Pediatric Sciences
University of Catania, Policlinic
Via S. Sofia n. 78
95123 Catania
(Italy)