World Journal of Pediatric Surgery

Congenital focal nodular hyperplasia-like lesion mimicking hepatoblastoma: anecdotal but plausible

Alessandra Gatto ,[1] Chiara Natale,[1] Alessandra Preziosi,[1] Michela Casanova,[2] Rita Alaggio,[3] Maurizio Cheli,[4] Francesco Macchini,[1] Andrea Zanini[1]

To cite: Gatto A, Natale C, Preziosi A, *et al*. Congenital focal nodular hyperplasia-like lesion mimicking hepatoblastoma: anecdotal but plausible. *World Jnl Ped Surgery* 2025;**8**:e000980. doi:10.1136/wjps-2024-000980
► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/wjps-2024-000980).

Received 11 December 2024
Accepted 16 February 2025

[1]Department of Pediatric Surgery, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
[2]Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[3]Pathology Department, Ospedale Pediatrico Bambino Gesù IRCCS, Roma, Italy
[4]Department of Pediatric Surgery, ASST Papa Giovanni XXIII Hospital, Bergamo, Italy

Correspondence to
Dr Alessandra Gatto;
gattoalessandra97@gmail.com

ABSTRACT

Focal nodular hyperplasia (FNH)-like lesions of the liver are rare in the pediatric population and are seldom reported as congenital lesions. The differential diagnosis between these lesions and pure-fetal hepatoblastoma (HBL) is challenging. We present a case of a congenital FNH-like hepatic lesion, managed with a right hepatectomy due to suspected fetal HBL. Additionally, a review of all published cases of congenital FNH-like lesions of the liver was carried out.MRI

INTRODUCTION

Liver tumors in children are rare, with the most common malignant tumors being metastasis from Wilms tumor, lymphoma, and neuroblastoma. Conversely, primary hepatic tumors account for only 1%–4% of all solid tumors in children and 5%–6% of abdominal tumors. The most common primary liver tumors in the first 2 years of life are hepatoblastoma (HBL) and infantile hepatic hemangioma, while hepatocellular carcinoma and focal nodular hyperplasia (FNH) are more commonly found after 5 years of age.[1–3]

Congenital neoplasms account for only 1.5%–2.0% of all pediatric tumors, occurring at a rate of about 1 in 12 500 to 27 500 live births. Hepatic tumors comprise about 5% of all congenital tumors. The three main types of primary congenital hepatic tumors are hemangioma, mesenchymal hamartoma, and HBL.[4 5] The differential diagnosis of congenital liver tumors can be challenging. Therefore, awareness of all possible differential diagnoses for a congenital liver mass is crucial. Congenital FNH-like lesions of the liver are seldom reported in the literature.

In this short report, we present a case of a congenital FNH-like lesion of the liver, which was misdiagnosed as an HBL, leading to a potentially avoidable liver resection. Additionally, a review of all published cases of congenital FNH-like lesions of the liver was carried out.

CASE PRESENTATION

A 3-day-old newborn was transferred to our center because of a liver lesion detected antenatally. A routine ultrasound examination during pregnancy revealed the presence of a fetal liver abnormality, described as a round hyperechoic vascularized liver mass within the right hepatic lobe, measuring 3×3 cm. Initially, a hepatic hemangioma was suspected. Postnatal ultrasonography revealed a liver span at the upper reference limit and a focal area of increased echogenicity within the VII–VIII segment, with polylobate contours and maximum axial diameters of 3 cm, suggestive of a hepatic hemangioma. However, some solid components and a small anechoic component were evident within the mass, prompting further investigation. Blood tests showed normal liver function and alpha-fetoprotein (AFP) levels within the age-appropriate range (46 758 ng/mL; normal range until 6 months: 25 000–50 000 ng/mL). MRI (Magnetic resonance imaging) with a hepatospecific contrast agent confirmed the presence of a polylobate nodular mass measuring 30×28 mm, characterized by a non-homogeneous hyperintense signal on T2-weighted sequences and a mild hypointense signal on T1-weighted sequences. These findings could not be considered conclusive for diagnosis, as they could either indicate a hepatic hemangioma or a fetal HBL (figure 1).

Therefore, a percutaneous tru-cut biopsy with an 18G needle was performed under ultrasound guidance. The pathological analysis supported the suspicion of a well-differentiated fetal HBL with low mitotic activity. The immunophenotype was CK-8-18+, HepPar-1+, glypican-3+, glutamine-synthetase+, INI-1+, β-catenin+ (membrane pattern) and CK7–. A centralized revision confirmed the morphological aspect of pure fetal HBL.

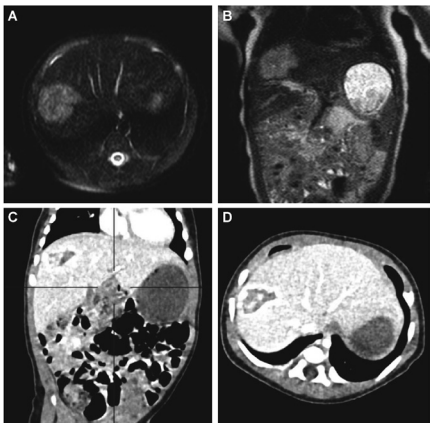

Figure 1 MRI with a hepatospecific contrast agent showing polylobate nodular mass measuring 30×28 mm characterized by a non-homogeneous hyperintense signal on T2-weighted sequences (A transverse; B coronal) and a mild hypointense signal on T1-weighted sequences (C coronal, D transverse).

A staging chest CT (computed tomography) ruled out lung metastases. Abdominal CT confirmed the known hepatic mass, demonstrating peripheral enhancement in the arterial phase and a subsequent non-homogeneous contrast enhancement pattern. The lesion occupied Couinaud's segment VIII with minimal cleavage plan with the middle hepatic vein. No involvement of the portal or caval vein was observed, nor were any pathological lymph nodes detected. No additional focal hepatic lesions were identified (figure 1). According to the Pretreatment Extent of Disease system developed by the European International Society of Pediatric Oncology,[6] the patient was classified as a PRETEXT 2 without additional criteria. The mass was considered resectable, and after multidisciplinary discussion, an upfront resection was opted for. The 2-month-old patient then underwent a right hepatectomy. The definitive pathological analysis allowed the conclusive diagnosis of an FNH-like lesion. The lesion was described as a non-capsulated mass with non-definite margins, consisting of hepatic cell proliferation with monolayered or bilayered trabeculae (preserved reticulum). A marked dilatation of the sinusoids, defined as a "peliotic" appearance, was observed, along with endothelialization confirmed by CD34 positivity. Small foci of extramedullary hematopoiesis were also identified. Moreover, some minor ductal proliferation was also identified in the peripheral region within the fibrous septa. The portal spaces presented physiological triads and were easily recognizable even within the lesion. Small foci of necrosis with no atypia and some mitosis with low proliferation index, assessed using anti-Ki67 antibodies, could also be distinguished. The resection was complete and margin negative (R0). Immunophenotype analysis confirmed β-catenin membrane positivity, along with diffuse mild positivity for glypican-3 and glutamine synthetase. Other markers included SAA–, CD34+ (attributable to the endothelization of the sinusoids in the nodular region), ERG–, and GLUT1–. The pathological analysis of the resected specimen was crucial for establishing a definite diagnosis. The presence of normal portal spaces and the absence of architectural abnormalities, together with the negative nuclear beta-catenin staining, ruled out HBL. These findings were highly suggestive of FNH, despite the absence of typical vascular characteristics. Moreover, although the sinusoidal endothelization and dilatation were unusual, they are described in the telangiectatic variant of FNH.

LITERATURE REVIEW

A literature review was conducted using PubMed with the following keywords: "congenital liver lesion," "focal nodular hyperplasia-like," "neonatal telangiectatic focal nodular hyperplasia," and "congenital liver tumor." We analyzed the available papers and included those presenting cases of congenital liver lesions that were diagnosed as FNH-like lesions. We then extrapolated demographic data, biopsy results (if performed), surgical treatments, and definitive pathological diagnoses. Articles that were not in English were excluded from the review.

Out of the 2216 screened papers, 4 met the inclusion criteria, describing a total of 8 cases (online supplemental table). There were five male and three female patients, with gestational ages at birth ranging between 32 and 40 weeks. Five cases were discovered incidentally, while two were symptomatic—one with abdominal distension and another with a palpable abdominal mass. One case was identified during an autopsy.

Six patients underwent CT and/or MRI. The average AFP level was about 40 000 ng/mL. The liver mass was in the right liver in six cases and in the left liver in two cases, with an average size of 3.7 cm. Out of these eight patients, one was stillborn, one underwent upfront resection without previous biopsy, and for another case undergoing hepatectomy, it was not specified whether a preoperative biopsy was performed. The remaining five neonates underwent lesion biopsy: one case was first diagnosed as HBL-fetal type at biopsy but then established to be FNH-like on the resection specimen. The other four biopsies were accurately diagnosed as FNH-like lesions. At follow-up, there was no significant progression of the disease (online supplemental table).

To the best of our knowledge, our case is only the ninth reported instance of a hepatic FNH-like lesion in infancy described in the literature. Moreover, it is only the second case to be detected prenatally. In the online supplemental tables, we summarize some characteristics of the other described cases.

Case 2 is an 11-month-old boy whose abdominal mass was detected at birth, and the authors considered it the first reported telangiectatic FNH of congenital origin.[7] Case 3 is a boy whose parents noticed abdominal distension about 2 weeks after birth: an ultrasound revealed a large hepatic mass, and he underwent a right hepatectomy. Okamura *et al.* considered it as the third case of congenital telangiectatic FNH.[8] In fact, Okayasu *et al.*

documented an autopsy case of a congenital liver cell tumor initially thought to be an HBL but was later found to have features corresponding to telangiectatic FNH. Therefore, this case seems to be the first telangiectatic FNH described in the literature.[9] Berklite *et al.* presented a series of five cases (cases 4, 5, 6, 7, and 8) of FNH-like lesions arising in infants aged 2 weeks to 6 months with glypican-3 expression.[10] Case 9 refers to our case.

All these articles highlight the significant challenges in distinguishing fetal HBL from FNH-like lesions. Most of these patients underwent biopsy; however, despite the difficulty in reaching a conclusive diagnosis from the limited biopsy samples, the authors successfully identified the benign nature of the lesion without requiring a liver resection in four out of seven cases.

DISCUSSION

FNH is rare in children, accounting for 2%–7% of pediatric liver tumors. Its etiology is not certain, but it is considered to be a hyperplastic reaction secondary to a vascular abnormality, either congenital or acquired. The lesion typically features a single feeding artery with no bile ducts or veins, causing a hyperperfused area of the parenchyma which subsequently develops some regenerative nodules separated by fibrous bands around the artery. Predisposing factors include chemotherapy and radiation therapy in children treated for malignancies (incidence in long-term survivors estimated to be around 5%), portal deprivation because of congenital or surgical portosystemic shunts, and biliary atresia. In cases without predisposing factors, the occurrence of FNH is around 0.5%. It tends to affect females more than males and is typically diagnosed between the ages of 6 and 10 years, with a median age of 8.7 years.[3 10–12] However, although rare, some cases have been reported in early infancy as well.[13 14] Because of its infrequency in childhood, FNH can be challenging to diagnose. Moreover, in our case, the infant age and male gender, together with the absence of underlying hepatic conditions, made it extremely difficult to suspect an FNH-like lesion. From a clinical perspective, FNH is typically asymptomatic and often found incidentally during imaging performed for other reasons, as in our case where it was identified during prenatal screening. Rarely, FNH presents with non-specific symptoms such as abdominal pain, hepatomegaly, weight loss, or a palpable mass.[10–12 15]

On radiological examinations, FNH typically appears as a single mass measuring less than 5 cm in diameter and presenting with a central scar. However, the central scar, which is the well-known characteristic feature of FNH, may be absent in smaller lesions or in patients with underlying hepatic conditions.[15] On ultrasound, it appears as a relatively homogeneous isoechoic mass with hypervascularity, presenting radiating vessels in a spoke-wheel pattern.[15–17] In our patient, the absence of the typical central scar with a spoke-wheel pattern, together with the presence of a small solid component, did not point toward the suspicion of an FNH lesion. Therefore, further evaluation was required to rule out a malignant lesion.

CT features of FNH include homogeneity, the absence of a capsule, the presence of a central scar, and intense arterial enhancement suggestive of hypervascularity with subsequent isodensity to the surrounding liver parenchyma on the delayed phase. On MRI, FNH typically appears hypointense on T1-weighted sequences and isointense to slightly hyperintense on T2-weighted sequences. The central scar, which is present in 85% of cases, should appear hyperintense compared with the mass and may enhance in the later phases. In our case, neither the homogeneity nor the central scar could be seen. Moreover, the non-homogeneous appearance and signal intensity patterns on the MRI sequences were suspicious for an HBL, which usually presents as T2-hyperintense, T1-hypointense, and heterogeneous because of areas of necrosis, hemorrhage, and calcification.[3 16 18 19] Therefore, these radiological findings not only were not interpretable as an FNH but also strengthened the suspicion of a malignant lesion. In addition, the absence of the typical arterial-phase discontinuous nodular enhancement with centripetal fill-in over time[18] allowed for the exclusion of a congenital hemangioma.

Immunophenotypically, FNH is characterized by an increased “map-like” glutamine synthetase expression. This typical pattern is a useful tool for diagnosis, as this enzyme is a downstream target of the Wnt/β-catenin pathway. In normal livers, glutamine synthetase expression is limited to the hepatocytes adjacent to the central vein, while in FNH it is overexpressed, resulting in a pathognomonic distribution.[3 10] However, this increased expression may also occur in hepatocellular adenoma and HBL, complicating the differential diagnosis, especially in small biopsies.[10]

Several studies have described three non-classical categories of FNH: telangiectatic, mixed hyperplastic, and adenomatous, and a variant with cytologic atypia.[7 8 20–23] The features in our case were found to correspond to telangiectatic FNH, a lesion characterized by marked vascular disorders, including sinusoidal dilatation and peliosis, without significant fibrosis.[20] It is described as an ill-defined and unencapsulated lesion with no central scar and less prominent lobular architecture. Thin fibrous septa with enlarged arteries drain into sinusoids, causing dilation. Sinusoids are congested with red blood cells, giving a telangiectatic appearance. Portal tracts are dispersed within the tumor, containing proliferating bile ductules. Hepatic cords are typically one cell thick, and sinusoids separate hepatic plates, sometimes with marked ectasia.[7–10 24] Immunophenotypically, the endothelial cells lining the dilated sinusoids are strongly positive for CD34 staining. Mild bile ductular proliferation can be noted with CK19, and the reticulin is preserved within the lesion.[7–10] Notably, β-catenin staining appears to be membranous only,[10] as opposed to the nuclear staining pattern that can be observed in a well-differentiated fetal

HBL.[25] Ki-67 may be higher than in the surrounding tissues.[9] CRP and SAA are usually negative, while glutamine synthetase staining may be variable.[10] Glypican-3 expression is frequently employed as a discriminating marker to distinguish between neoplastic and non-neoplastic liver tissue. Positivity for glypican-3 can be suggestive of malignancy, such as HBL or hepatocellular carcinoma,[10 26] though it is also expressed in "fetal" liver, indicating hepatic immaturity.[10]

The pathological analysis ultimately is the definitive tool in clarifying the diagnosis. In our case, the percutaneous tru-cut biopsy was not representative enough, and the expression of glypican-3 supported the malignant nature of the lesion. Moreover, the diagnosis of an HBL with a well-differentiated fetal histology could not be conclusively made from the small biopsy samples and would require the evaluation of the complete resection specimen.[25]

The term "neonatal telangiectatic " has more recently been redefined as "FNH-like lesion". The nomenclature variability reflects the rarity of the lesion. The absence of molecular studies limits the interpretation of its pathogenic mechanisms and its correlation with corresponding adult lesions, such as the FNH and inflammatory adenoma (previously considered as telangiectatic FNH). Paradis *et al.* analyzed the telangiectatic FNH from a molecular perspective and concluded that its molecular profile is much closer to that of hepatocellular adenomas than typical FNHs, while Bioulac-Sage *et al.* concluded that telangiectatic FNH should be considered a separate entity.[20 23]

These benign lesions generally have a favorable prognosis, with a slightly higher risk of spontaneous bleeding. There is no risk of malignant degeneration, although they may create diagnostic confusion. FNH is typically managed conservatively; however, some children may undergo surgical resection because of symptoms, increasing size, or the inability to definitively rule out malignancy, as was the case with our patient.[10 12 14 17 27]

In conclusion, our study aims to raise awareness of this rare differential diagnosis and highlights the difficulty of evaluating focal liver lesions in very young children. FNH-like lesions may have some radiologic, histologic, and immunophenotypic features which overlap with HBL, making it exceedingly difficult to distinguish a fetal HBL from FNH-like lesions. Therefore, it would be wise to consider FNH-like lesions should be considered in the differential diagnosis even in the scenario of congenital liver lesions. However, due to the challenges faced in establishing a histopathological diagnosis from a biopsy sample, it may be difficult in some cases to avoid liver resection in order to achieve a definite diagnosis.

Contributors AG, CN, AP, MC, RA, MC, FM and AZ declare that we have all actively contributed to the creation and development of this document. Each contributor played a vital role in the process, particularly during the literature review, ensuring a comprehensive understanding of the existing research in our field. Specifically, AG and CN took the lead in drafting the article, meticulously organizing and presenting the findings. They were supported by AP and AZ, who provided valuable insights and assistance throughout the writing process. The collaborative effort of all members was instrumental in shaping the final manuscript. Furthermore, MC, RA, MC, FM and AZ undertook the critical task of reviewing the manuscript. Their careful examination and feedback helped enhance the clarity, coherence and overall quality of the document. We are grateful for their constructive criticism and suggestions, which significantly contributed to the refinement of our work. We extend our heartfelt thanks to everyone involved in this project for their dedication and support throughout the development of this document.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval This study was approved by the insititutional review board and complies with the Helsiniki Declaration.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iD

Alessandra Gatto http://orcid.org/0009-0009-6634-5638

REFERENCES

1 Stocker JT. Hepatic tumors in children. *Clin Liver Dis* 2001;5:259–81.
2 Xing H, Yang C, Tan B, *et al*. Incidence trends and predictive model of hepatic malignant tumors in children: a population-based study. *Am J Transl Res* 2022;14:7268–89.
3 Lucas B, Ravishankar S, Pateva I. Pediatric Primary Hepatic Tumors: Diagnostic Considerations. *Diagnostics (Basel)* 2021;11:333.
4 Alamo L, Perrin L, Vial Y, *et al*. Prenatal imaging of congenital hepatic tumors: a report of three cases. *Clin Imaging* 2017;41:112–7.
5 Isaacs H Jr. Fetal and neonatal hepatic tumors. *J Pediatr Surg* 2007;42:1797–803.
6 Brown J, Perilongo G, Shafford E, *et al*. Pretreatment prognostic factors for children with hepatoblastoma-- results from the International Society of Paediatric Oncology (SIOP) study SIOPEL 1. *Eur J Cancer* 2000;36:1418–25.
7 Kim HS, Kim YA, Kim CJ, *et al*. Telangiectatic focal nodular hyperplasia of the liver: a case detected at birth. *J Korean Med Sci* 2003;18:746–50.
8 Okamura N, Nakadate H, Ishida K, *et al*. Telangiectatic focal nodular hyperplasia of the liver in the perinatal period: case report. *Pediatr Dev Pathol* 2005;8:581–6.
9 Okayasu I, Mori W, Hatanaka M. An autopsy case of congenital hepatic cell tumor. *Acta Pathol Jpn* 1974;24:387–92.
10 Berklite L, Shenoy A, Hollowell M, *et al*. Focal Nodular Hyperplasia-Like Lesions With Glypican-3 Positivity in Infancy. *Pediatr Dev Pathol* 2023;26:30–8.
11 Franchi-Abella S, Branchereau S. Benign hepatocellular tumors in children: focal nodular hyperplasia and hepatocellular adenoma. *Int J Hepatol* 2013;2013:215064.
12 Lautz T, Tantemsapya N, Dzakovic A, *et al*. Focal nodular hyperplasia in children: clinical features and current management practice. *J Pediatr Surg* 2010;45:1797–803.
13 Petrikovsky BM, Cohen HL, Scimeca P, *et al*. Prenatal diagnosis of focal nodular hyperplasia of the liver. *Prenat Diagn* 1994;14:406–9.
14 Ma IT, Rojas Y, Masand PM, *et al*. Focal nodular hyperplasia in children: an institutional experience with review of the literature. *J Pediatr Surg* 2015;50:382–7.

15 Cha DI, Yoo SY, Kim JH, *et al*. Clinical and imaging features of focal nodular hyperplasia in children. *AJR Am J Roentgenol* 2014;202:960–5.
16 Valentino PL, Ling SC, Ng VL, *et al*. The role of diagnostic imaging and liver biopsy in the diagnosis of focal nodular hyperplasia in children. *Liver Int* 2014;34:227–34.
17 LeGout JD, Bolan CW, Bowman AW, *et al*. Focal Nodular Hyperplasia and Focal Nodular Hyperplasia-like Lesions. *Radiographics* 2022;42:1043–61.
18 Shelmerdine SC, Roebuck DJ, Towbin AJ, *et al*. MRI of paediatric liver tumours: How we review and report. *Cancer Imaging* 2016;16:21.
19 Birkemeier KL. Imaging of solid congenital abdominal masses: a review of the literature and practical approach to image interpretation. *Pediatr Radiol* 2020;50:1907–20.
20 Paradis V, Benzekri A, Dargère D, *et al*. Telangiectatic focal nodular hyperplasia: a variant of hepatocellular adenoma. *Gastroenterology* 2004;126:1323–9.
21 Nguyen BN, Fléjou JF, Terris B, *et al*. Focal nodular hyperplasia of the liver: a comprehensive pathologic study of 305 lesions and recognition of new histologic forms. *Am J Surg Pathol* 1999;23:1441–54.
22 Wanless IR, Albrecht S, Bilbao J, *et al*. Multiple focal nodular hyperplasia of the liver associated with vascular malformations of various organs and neoplasia of the brain: a new syndrome. *Mod Pathol* 1989;2:456–62.
23 Bioulac-Sage P, Rebouissou S, Sa Cunha A, *et al*. Clinical, morphologic, and molecular features defining so-called telangiectatic focal nodular hyperplasias of the liver. *Gastroenterology* 2005;128:1211–8.
24 Attal P, Vilgrain V, Brancatelli G, *et al*. Telangiectatic focal nodular hyperplasia: US, CT, and MR imaging findings with histopathologic correlation in 13 cases. *Radiology* 2003;228:465–72.
25 López-Terrada D, Alaggio R, de Dávila MT, *et al*. Towards an international pediatric liver tumor consensus classification: proceedings of the Los Angeles COG liver tumors symposium. *Mod Pathol* 2014;27:472–91.
26 Zynger DL, Gupta A, Luan C, *et al*. Expression of glypican 3 in hepatoblastoma: an immunohistochemical study of 65 cases. *Hum Pathol* 2008;39:224–30.
27 Yang Y, Fu S, Li A, *et al*. Management and surgical treatment for focal nodular hyperplasia in children. *Pediatr Surg Int* 2008;24:699–703.