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RESEARCH ARTICLE

A RETROSPECTIVE STUDY EVALUATING FOCAL NODULAR HYPERPLASIA AND REGENERATIVE NODULAR HYPERPLASIA IN PEDIATRIC MALIGNANCIES

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ABSTRACT

Introduction: Primitive liver tumors represent 0.3-2% of all pediatric tumors, of which malignancies account for approximately 75%. Benign liver neoplasms include, though rare, focal nodular hyperplasia (FNH) and nodular regenerative hyperplasia (NRH). In recent years, a growing number of cases of FNH and NRH have been incidentally diagnosed during the follow-up of patients undergoing chemotherapy and/or radiotherapy for non-hepatic primitive tumors, representing a differential diagnosis with metastatic relapse of the primitive disease. Methods: Our paper represent a retrospective review of children 16< years of age with diagnosis of NRH and FNH performed at our Department (Radiology Unit- Santobono Pausllipon), discovered during routine examination. Results: 12 patients had a diagnosis of FNH and NRH. in 10 (83%) patients were diagnosed with FNH, while in 2 (17%) of NRH. In 11 cases (91%) imaging was concluded. In only one case (9%) it was necessary to perform biopsy in order to diagnose FNH. Conclusion: In our experience, according to reports in the literature to date, CT and MRI were the most appropriate imaging techniques for the characterization of these liver lesions. A regular follow-up with US and MRI is recommended to monitor the evolution of liver diseases.

INTRODUCTION

Primitive liver tumors represent 0.3-2% of all pediatric tumors, of which malignancies account for approximately 75%, with a higher incidence of hepatoblastoma below 5 years (Mueller *et al*., 2006). Benign liver neoplasms include infant hemangioendothelioma, adenoma, mesenchymal hamartoma, focal nodular hyperplasia, regenerative nodular hyperplasia and benign biliary tumors. In recent years, a growing number of cases of FNH and NRH have been incidentally diagnosed during the follow-up of patients undergoing chemotherapy and / or radiotherapy for non-hepatic primitive tumors, representing a differential diagnosis with metastatic relapse of the primitive disease. We reported a case series of FNH and NRH discovered in children after the treatment for malignancies at a single istitute (Radiology Unit at Santobono Pausllipon).

MATERIALS AND METHODS

Our paper represent a retrospective review of children < 16 years of age with diagnosis of NRH and FNH performed from 2010-2016 at our Department, discovered during routine examination with adbominal US or CT. All children had been treated with chemotherapy and / or radiotherapy for extraepathic malignancies: 3 neuroblastoma, 2 Ewing sarcoma, 4 Nefroblastoma, 1 Rhabdomyosarcoma, 1 Lymphoma, 1 small bowel sarcoma. 8 patients were female, and 4 patients were male. During the follow up, all patients underwent US, TC and in selected cases, MRI was performed.

RESULTS

12 patients had a diagnosis of FNH and NRH. In 10 cases (83%) patients were diagnosed as FNH, while only 2 cases (17%) of NRH. In 11 patients (91%) imaging was conclusive. In one case (9%) it was necessary to perform biopsy in order to diagnose FNH. None of the patients had clinical, laboratory and other radiographic signs of primitive disease progression (Table 1). All patients present multiple focal liver lesions, small in size. Adominal Doppler Ultrasound showed different echo patterns (hypoechoic, isoechoic, hyperechoic lesions), no calcifications and it not provide a definitive diagnosis.

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Table 1. Description of main features evaluated in children after treatment for malignancies

Primitive tumor	Sex	Major symptoms	Time interval after treatment (months)	Diagnostic tool	Diagnosis	Follow up
Neuroblastoma	F	None	48	Radiology	FNH	Stable
S.Ewing	F	None	48	Biopsy	FNH	Stable
Wilms tumor	M	None	36	Radiology	NRH	Stable
Lymphoma	M	None	48	Radiology	FNH	Stable
rhabdomyosarcoma	F	None	94	Radiology	FNH	Stable
Wilms tumor	F	None	94	Radiology	FNH	Regression
Wilms tumor	F	None	72	Radiology	NRH	Stable
Wilms tumor	F	None	36	Radiology	FNH	Stable
Small Bowel Sarcoma	M	None	48	Radiology	FNH	Stable
Neuroblastoma	M	None	48	Radiology	FNH	Stable
Neuroblastoma	F	None	58	Radiology	FNH	Stable
S.Ewing	F	None	24	Radiology	FNH	Stable

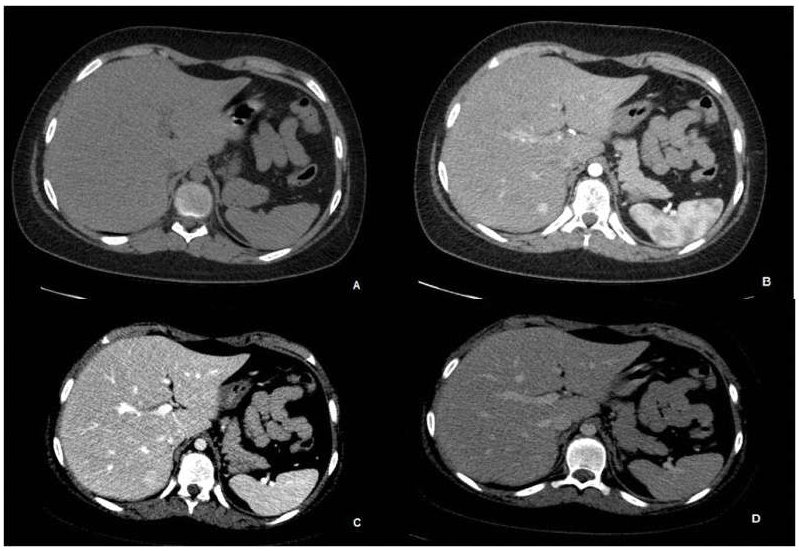

Fig. 1. Abdominal CT axial scan images (A-B-C-D): a hepatic lesion not visible on unenhanced image, but it has intense enhancement on the arterial phase, becoming isodense in portal venous and delayed phase

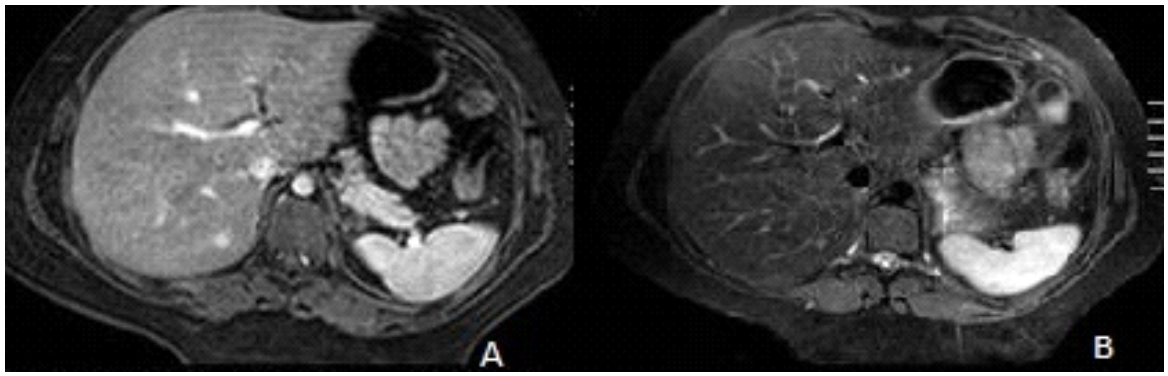

Fig. 2. Abdominal MRI axial images (A -THRIVE, B- STIR RT after contrast agent injection): the lesion shows a slight high signal intensity on early images and isosignal on delayed phase

On CT evaluation, frequent findings which contributed to diagnosis of FNH were: iso-hypodense nodular lesions on basal scan, with an enhancement homogeneous in arterial and early portal phase, becoming isodense in the delayed phases (Fig. 1). On MRI, we found the preponderance of multiple isointense/ slightly hypointense lesions on T1 weighted images, weakly hyperintense in T2 weighted images. After contrast agent injection they appeared homogeneous hyperintense compared to the liver parenchima on arterial images and slightly hyperintense / isointense on portal and delayed phases. None of the lesions, given its small size, had the central scar (Fig. 2).

In the cases of NRH, CT showed nodular lesions small in size, hypoattenuating to the normal liver, remaining isodense or hypodense in both arterial and portal venous phases. On MRI they were slightly hyperintense on T1 weighted images, weakly hypointense in T2 weighted images. After contrast agent injection they showed the absence of arterial enhancement and a portal enhancement similar to normal parenchyma (Fig. 3). Only in one case it was necessary to perform biopsy to make a diagnosis of FNH, because the lesion showed a rapid washout on enhanced CT images in delayed phases, placing doubts on the possible presence of liver metastases.

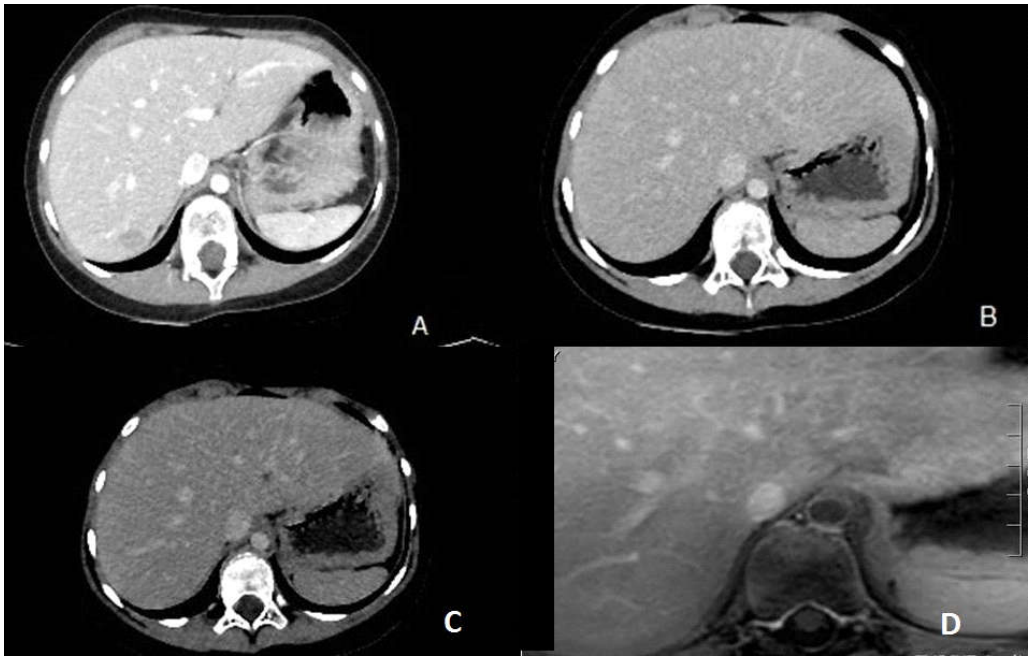

Fig. 3. A-B-C abdominal CT axial scan images : on CT images lesion regenerative nodule appears hypoattenuating and it remains isodense in both arterial and portal venous phased. D: abdominal MRI axial images (THRIVE after contrast agent injection) the nodule presents enhanced similar to normal liver parenchima on delayed image

During the follow up, no alteration of hepatic function and no modifications of lesions were seen in 11/12 children. In one case of FNH diagnosis, the regression of the lesions was observed.

DISCUSSION

Focal nodular hyperplasia (FNH) and nodular regenerative hyperplasia (NRH) are benign liver lesions, which may be rarely found in children. Edmondson was the first to describe FNH in 1958 (Edmondson, 1958); it represented 2-7% of all pediatric hepatic neoplasms, with a female predominante (Tomlinson and Finegold, 2002; Luciani *et al*., 2002). The pathogenesis is still largely unknown, depending in part by a hyperplastic response of liver cells to local vascular disorders (thrombosis, vasculitis, increased blood flow after chemotherapy) (Rebouissou *et al*., 2008). The majority of children are asyntomatic; possible clinical manifestastions are non specific, such as palpable abdominal mass and abdominal pain. According to literature, multiple FNH lesions are found in children with a history of malignancy, and often without central scars (Towbin *et al*., 2011).

Histological findings are: unusual architecture, bile duct proliferation and vascular malformations. On US, FNH appearance homogeneous mass with variable echogenicity and a stellate hyperechoic central scar, while on unenhanced CT scan it is iso/slightly hypodense mass to the surrounding liver parenchyma, and has a hypoattenuating central scar. Lesions have a characteristic pattern of enhancement, homogeneously in the arterial and early portal venous phases, thanks to its arterial supply, and becomes isoattenuating to the liver in the late portal venous and delayed phases. The stellate scar appearce hypoattenuating on early contrast-enhanced images and it has enhancement on delayed phases. On MRI images, FNH lesions are homogeneous and isointense/slightly hypointense to the liver on T1-weighted images and isointense/slightly hyperintense on T2-weighted images. The central scar appears most frequently hypointense on T1-weighted images and hyperintense on T2-weighted images.

On enhanced MRI the lesions are hyperintense to the liver in the arterial phase and rest slightly hyperintense or isointense to the liver in the portal venous phase. The central scar, in general, has enhancement during the delayed images. FNH lesions have a high signal intensity long after other liver lesions have washed-out allowing a differential diagnosis between FNH and metastases (Liliana Chiorean *et al*., 2015). Nodular regenerative hyperplasia (NRH) is first defined by Steiner in 1959 (Steiner, 1959). It is a rare benign lesion of the liver due to vascular alterations lead to atrophy, followed by compensatory re generation. NRH cases represented 2.1% of liver tumors from birth to two years of age (Stocker, 2001). Histopathological findings are diffuse regenerative micronodular transformation of the liver, without fibrosis or minimal in the perisinusoidal or periportal areas on reticulin staining. Nodules are usually between 1-3 mm in diameter, causing portal hypertension in non-cirrhotic young patients (Hartleb *et al*., 2011). On US evaluation, NRH lesions are homogeneous hypo-isoechoic often not visible, due to their small size or isoechogenicity. On CT images, regenerative nodules are usually hypoattenuating to the normal liver,rarely isoattenuating. After intravenous iodinated contrast administration, the lesions usually do not enhance, remaining isodense or hypodense in both arterial and portal venous phases. This important feature distinguishes NRH from FNH. On MRI pre-contrast images, regenerative nodules are frequently slightly hyperintense on T1- weighted images, while On T2-weighted images, the lesions are iso-hypointense to normal liver. The NRH lesions show contrast enhancement preferentially in the portal venous phase, similar to normal liver parenchyma (Chung *et al*., 2010; Zech *et al*., 2007). FNH has no probability of malignant trasformation, while complications are rare, such as rupture, necrosis and hemorrhage. It may have also spontaneous improvement or a complete remission (Okada *et al*., 2006; Di Stasi *et al*., 1996). Resection is indicated in cases of voluminous messes or symptomatic children (Weimann *et al*., 1997). In cases of NRH diagnosis, follow up is necessary due to possible complications as portal hypertension.

Conclusion

Children with a history of malignancy may develop FNH and NRH during follow-up in a time period varying from the cessation of therapy, thus imposing a differential diagnosis with liver metastatic recurrence of the primary disease. In our experience, according to reports in the literature to date, CT and MRI were the most appropriate imaging techniques for the characterization of these liver lesions, avoiding biopsy which, however, is not free of complications. A regular follow-up with US and MRI is recommended to monitor the evolution of liver diseases.

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