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SHORT REPORT

Focal nodular hyperplasia of the liver after intensive treatment for pediatric cancer: is hematopoietic stem cell transplantation a risk factor?

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Abstract Focal nodular hyperplasia (FNH) is a benign hepatic lesion very rarely described in the pediatric population. It has been reported more frequently in patients treated for pediatric cancers with chemotherapy or hematopoietic stem cell transplantation. The use of high dosage of alkylating agents, the occurrence of venous occlusive disease, graft-versus-host disease, and other variables linked to the hematopoietic stem cell transplantation procedure can represent risk factors for the development of FNH in the pediatric age. The discovery of hepatic nodules in the follow-up of patients treated for malignancies suggests recurrence of disease and raises a diagnostic dilemma. Here we describe possible risk factors, clinical and radiological findings of eight pediatric patients who developed focal nodular hyperplasia after hematopoietic stem cell transplantation. The aim of this report is to provide useful diagnostic tools to facilitate accurate diagnosis of FNH and suggest a correct management of this benign lesion during postcancer follow-up.

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Introduction

Focal nodular hyperplasia (FNH) is an uncommon, nonmalignant neoplasia of the liver rarely described in the pediatric population, the etiological origin of which is poorly understood [19, 20]. It is defined as a nodular lesion composed by benign-appearing hepatocytes measuring <5 cm in diameter, with a stellate fibrous scar, within a histologically normal or nearly normal liver parenchyma [3, 22]. In the general pediatric population, an annual incidence of FNH of 0.02% has been approximately estimated [3]. FNH has been reported more frequently in children with a history of malignancy after treatment for cancer [3, 10]. In children who have received hematopoietic stem cell transplantation (HSCT) both allogeneic (allo) and autologous (auto), only case reports are signaled [3, 21]. We here describe the clinical and radiologic features of FNH of eight pediatric patients who developed FNH after HSCT (two allo and six auto).

Patient presentation

Eight pediatric patients (four male, four female) affected by malignancies (Table 1) after front line chemotherapy according to the relevant treatment protocols underwent HSCT (six auto, two allo) at a median age of 9.7 years (range 4–15.1). Characteristics of the patients and of the HSCT procedure have been resumed in Table 1. During the HSCT, none of the patients presented evidence of venous occlusive disease (VOD). Both of the patients who received

Table 1 Case series data

Variable	Case no.							
	1	2	3	4	5	6	7	8
Sex	M	F	F	F	M	M	M	F
Disease	ALL	AML	ES	AML	AML	ES	ES	NB
Radiotherapy	TBI	–	TLI	TBI	TBI	–	TLI	–
Age at HSCT (years)	12.1	8.8	15.1	14.6	10	5.4	7.6	4
Disease risk at HSCT	HR	LR	LR	LR	LR	LR	LR	LR
Type of HSCT	ALLO	ALLO	AUTO	AUTO	AUTO	AUTO	AUTO	AUTO
Donor	MUD	MFD	–	–	–	–	–	–
Preparative conditioning regimen	TBI + TT + CPM	BU + CPM + MEL	BU + MEL	TBI + MEL	TBI + MEL	BU + MEL	BU + MEL	BU + MEL
Acute GVHD	2° (skin)	2°(skin, GI)	–	–	–	–	–	–
Chronic GVHD	Liver, lung	No	–	–	–	–	–	–
VOD	No	No	No	No	No	No	No	No
Age at Dx of FNH (years)	19.8	15.4	19.5	23.3	20.6	14.2	12	13.2
Years from HSCT to FNH	7.7	6.6	4.4	8.7	10.6	8.8	4.4	9.2
N of nodules	1	Multiple	3	4	3	4	3	2
Size (mm)	12	Max 60	15, 16, 17	7, 24, 28, 43	26, 27, 28	15, 17, 22, 25	20, 16, 8	15, 8
GOT at Dx of FNH (U/L)	40	25	13	37	22	16	15	27
GPT at Dx of FNH (U/L)	70	19	14	37	31	20	17	24
ALP at Dx of FNH (U/L)	190	505	140	239	179	163	156	170
Gamma GT at Dx of FNH (U/L)	27	26	17	39	13	18	19	24
Oral contraception	–	Yes	Yes	Yes	–	–	–	Yes
US reason	Elevated transaminases	Hypergonadotropic hypogonadism	Own choice	Recurrent abdominal pain	Follow-up	Own choice	Follow-up	Follow-up
SonoVue-enhanced US	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Other diagnostic imaging	CT	CT, PET	CT	CT, PET	CT	CT, MRI	CT	CT
Liver biopsy	No	Yes	Yes	No	No	No	No	No

Abbreviations: *ALL* acute lymphoblastic leukemia, *ALP* alkaline phosphatase, *AML* acute myeloid leukemia, *ALLO* allogeneic transplantation, *AUTO* autologous transplantation, *BU* busulphan, *CPM* cyclophosphamide, *CT* computed tomography, *ES* Ewing's sarcoma, *F* female, *FNH* focal nodular hyperplasia, *GI* gastrointestinal tract, *GOT* glutamic oxaloacetic transaminase, *GPT* glutamic pyruvic transaminase, *GT* glutamyltransferase, *GVHD* graft-versus-host disease, *HR* high-risk included patients in second complete remission at HSCT, *HSCT* hematopoietic stem cell transplantation , *LR* low-risk included patients in first complete remission at HSCT, *M* male, *MEL* melphalan, *MFD* matched family donor, *MRI* magnetic resonance imaging, *MUD* matched unrelated donor, *N* number, *NB* neuroblastoma, *PET* positron emission tomography, *TBI* total body irradiation, *TLI* total lung irradiation, *TT* thiotepa, *US* ultrasound, *VOD* veno-occlusive disease

allo HSCT experienced a grade 2 hepatic and gastrointestinal acute graft-versus-host disease (GVHD) and one patient developed hepatic and pulmonary chronic GVHD. After HSCT, all of the transplanted patients have been routinely screened with an annual abdominal ultrasound follow-up. The diagnosis of FNH was incidentally made during the follow-up, after a median time of 7.6 (4.4–10.6) years from the HSCT. All the patients were asymptomatic except one case with positive anamnesis for recurrent abdominal pain. Physical examination did not reveal any pathologic diagnostic findings. None of the patients were serologically positive for hepatitis B or C, and only one presented high levels of AST and ALT at FNH diagnosis. No other peculiar laboratory findings were observed. Ultrasound (US) revealed multiple hypoechoic liver nodules located in both hepatic lobes in seven patients, whereas one case presented a single liver lesion. Nodule size was 7–60 mm. Color Doppler US showed signals of vascularization both in the central and in the peripheral zone (coin-like figuration), with Doppler spectral trace characterized by high frequency (3 kHz) and low systo-diastolic variation (low resistive index) [7]. SonoVue-enhanced US has been done in six cases to analyze the enhancement features of the arterial and portal venous phases of FNH: liver lesions during the arterial phase looked like hypervascular masses (Fig. 1) and on a portal venous phase lesions showed enhancement equal to liver. Abdominal computerized tomography (CT) was performed in all the patients in order to better characterize the nature of the hepatic lesions: FNH typically resulted in a diffuse, homogeneous hypodense lesion. Contrast-enhanced CT images confirmed the hypervascularity of FNH on arterial phase and the sustained enhancement of the lesions on portal venous phase (Fig. 2). In one case, liver nodules revealed a rapid washout during the portal venous phase. Central scars have been demonstrated with CT in two of eight cases. One patient also had a magnetic resonance imaging (MRI) of the liver which showed a hypointense signal on T1 and a hyperintense signal on T2-weighted sequences. Gadolinium-enhanced MRI revealed hyperintensity of liver nodules on the arterial phase and a sustained enhancement on the portal venous phase, and the presence of a characteristic central scar with enhancement that increased on the late phase. Furthermore, in two cases, a positron emission tomography (PET) was performed and it showed hypercaptation of C-acetate and a normal captation of 2-fluoro-2-deoxy-D-glucose by liver lesions. A liver biopsy was obtained in two patients to exclude the presence of malignant masses: the histological examination revealed the regenerative benign nature of the nodules, characterized by an abnormal nodular architecture surrounded by fibrous septa, vessel malformation, and cholangiolar proliferation, confirming the diagnosis of FNH. The median follow-up time of observation after FNH diagnosis was 2.8 years, consisting in an abdominal US performed every 3–6 months. No malignant transformation was observed, and only in two patients the number of nodules mildly increased (from four to six and from three to five, respectively cases 3 and 4), whereas size and radiologic characteristic of nodules remained the same.

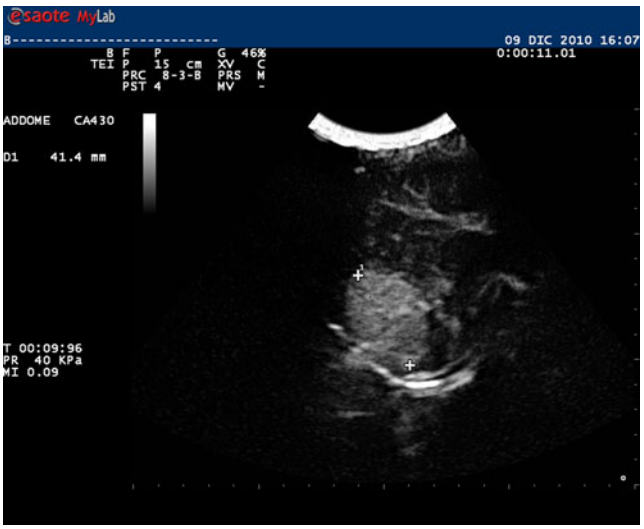


Fig. 1 Arterial phase CEUS shows a hyperintense 41.4-mm lesion of the liver found in a 23-year-old patient

Discussion

FNH of the liver is an uncommon, solid and nonmalignant neoplasia in children, rarely described in literature as a posttransplant late effect [1, 3, 21]. Its real incidence is difficult to be determined, since it is mostly incidentally detected during diagnostic procedures performed for other disease. The etiology of FNH is subject of discussion. The most widely accepted theory is that FNH could be a reaction to a localized vascular injure primed by chemotherapy. Stating this hypothesis, both auto and allo HSCT represent procedures at risk for the development of FNH. The use of high doses of alkylating agents such as busulfan and melphalan [3, 6] in myeloablative regimen before HSCT [3, 21], the total body irradiation (TBI) administered in some preparative regimen [21], the occurrence of VOD, and the occurrence of hepatic chronic GVHD in the allo HSCT setting [21] are described as possible risk factor for the development of FNH. Many discussions about the hypothetic role of oral contraception in the pathogenesis of FNH have been conducted in the past [16, 18] but no significant influence has been confirmed [13]. In our case series, five of eight patients received a busulfan-based and three of eight a TBI-based preparative regimen before

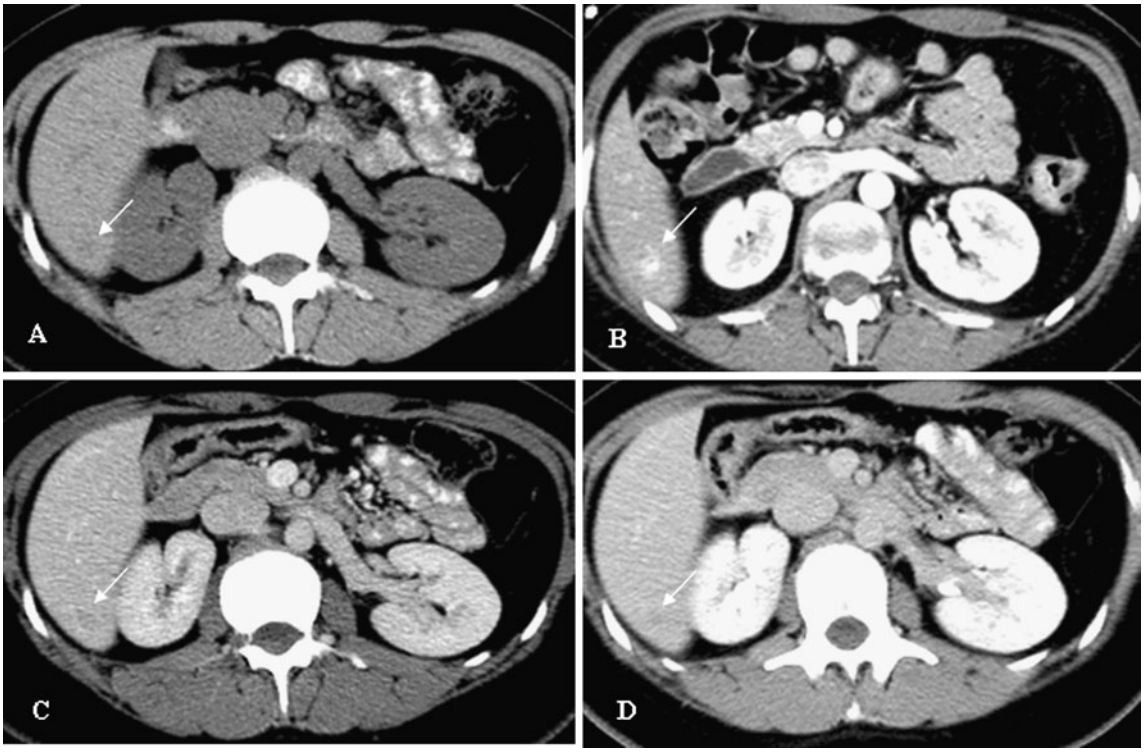
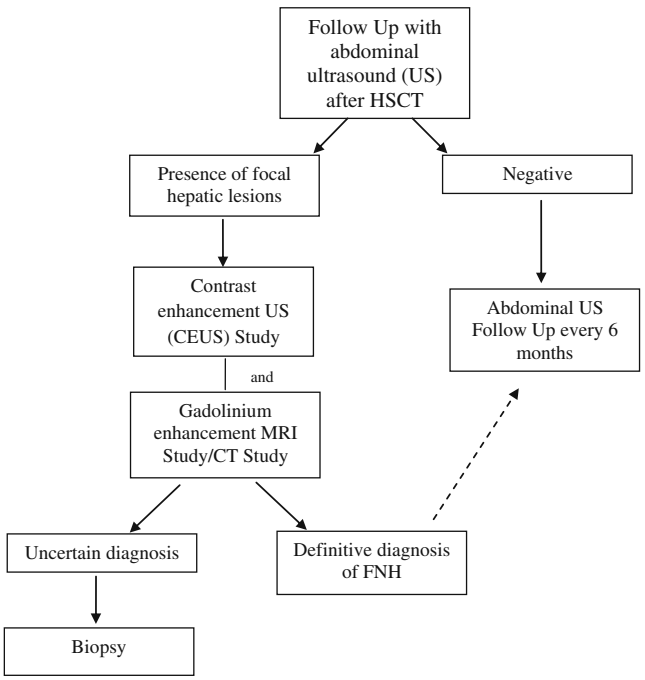


Fig. 2 CT findings of focal nodular hyperplasia in 14-year-old woman. **a** Unenhanced CT scan shows lesion of liver which is slightly hypodense to remainder of liver. Note more hypodense central scar (*arrow*) **b** Arterial phase contrast-enhanced CT scan shows strong enhancement of lesion, caused by arterial vascular supply (*arrow*) **c** Contrast-enhanced CT scan during the portal venous phase shows lesion being hypoattenuating compared with surrounding liver because of rapid contrast material washout (*arrow*). **d** Delayed phase contrast-enhanced CT scan shows isoattenuation of the lesion

HSCT, none has been diagnosed with VOD, and both of the two allo-transplanted patients experienced hepatic acute GVHD. Notably, three of three female patients had used oral contraception in the past. Especially for patients previously treated for neoplastic disease, it is important to offer diagnostic tools to rule out differential diagnosis such as other benign hepatic tumors, metastases, or a potentially threatening tumor [3, 12]. When considering the possible differential diagnosis, the specific age group of the respective patient has to be kept in mind. The infantile hemangioendothelioma, or the infantile hepatic hemangioma, is a benign vascular tumor, characteristic of the pediatric age group. The mesenchymal hamartoma occurs mainly in young children. Nodular regenerative hyperplasia, a multiacinar nodular lesion, is a rare pediatric condition, and often associated with portal hypertension, which may be evident at imaging [4]. Metastases or recurrence of disease has to be first excluded in the diagnostic process of hepatic lesions discovered in the post-HSCT follow-up of a child. To do this, a correct radiological diagnostic investigation has to be conducted and a consequential follow-up management of FNH has to be planned as proposed in the following algorithm. The



FNH's presentation on imaging techniques—US, CT, MRI, and PET—is quite well characterized, whereas the data have been found mainly on adult patients. Ultrasound is in most cases the first instrument detecting the predominantly asymptomatic lesion. The conspicuity of the lesions is the characteristic central scar; however, hepatic parenchyma may appear either hypoechoic, isoechoic, or slightly hyperechoic [8]. US Doppler technology can be used to increase the overall US diagnostic accuracy, by the detection of vascular signals of hepatic artery and its spectral analysis as well as quantitative parameters (i.e., peak frequency and resistive index) [7]. The low precision of the US technique may be overcome by the use of real-time contrast-enhanced ultrasonography (CEUS), showing a typical coin-like enhancement of contrast in the arterial phase (washin) and homogeneous vascular pattern in the parenchymal phase [17]. Real-time study of these lesions has been demonstrated to be useful for avoiding possible false-negative results [17]. CT represents an excellent tool for detection and characterization of focal liver lesions, such as FNH, but because of the radiation hazard, its use remains however limited.

At unenhanced CT, FNH appears hypodense or isodense as compared with liver parenchyma [14]. In the arterial phase, the lesions become hyperdense, whereas in the portal and later phases, FNH assumes isodense characteristics with parenchyma. Some enhancement may be observed in the central scar [18]. MR imaging has been shown to be the diagnostic tool with the highest sensitivity and specificity (70% and 98%, respectively) for FNH [14, 15]. FNH is typically isointense or hypointense on T1-weighted images and hyperintense on T2-weighted sequences. When gadolinium is used, a typical intense enhancement in the arterial phase followed by a slight enhancement of the central scar on the portal venous phase can be observed [15]. Positron emission tomography has also been shown to be useful in the differential diagnosis of hepatic neoplasms, particularly when performed with the use of ^{18}F-fluorodeoxyglucose (FDG) [2]. The FDG uptake in the FNH lesion is usually equal or even lower than in normal liver parenchyma, and an equal pattern has been registered in two of our patients having undergone PET in their diagnostic course. The use of ^{11}C-acetate (AC PET) has no additional diagnostic advantage as compared with the use of FDG only, as a recent study has been able to show [11]. The most difficult radiological differential diagnosis is represented by the hepatocellular adenoma, often consisting in a particular diagnostic challenge when differentiating both kinds of lesions [2]. Although FNH lesions are radiologically quite typical and show particular features in every single imaging method, their identification beyond any doubt is crucial, and it can spare invasive diagnostic measures to the patients. Should any doubt be present, mainly in oncologic patients, a histological diagnosis needs to be performed by means of percutaneous biopsy. Surgical biopsy should only be performed when percutaneous biopsy is nondiagnostic [5]. Moreover, in the few cases where even biopsy is not diagnostic, some immunological markers such as cytokeratins 7 and 19 and neuronal cell adhesion molecule can be useful to differentiate FNH from hepatocellular adenoma [9].

In conclusion, children who have received HSCT can be at risk for developing FNH due to many risk factors. Until now, most of the diagnoses of FNH during the post-HSCT follow-up have been casual, but an abdominal US follow-up every 6 months can be suggested in transplanted children, being this kind of sequela probably underdiagnosed. The main relevance of FNH at the moment is a secure diagnosis, possibly performed only by imaging techniques, thereby avoiding an invasive procedure such as percutaneous biopsy of this benign entity. Its differentiation from a metastatic or malignant lesion in the follow-up of pediatric patients, who underwent HSCT, is of crucial importance. Once diagnosed with maximal certainty, a conservative “wait and see” strategy is recommended.

Algorithm of diagnosis and management of focal hepatic lesions discovered during the post-HSCT follow-up in children.

Conflict of interest The authors disclose any conflict of interest. No sponsor(s) has been involved in any step of study design, collection, analysis, and interpretation of data, writing of the report, and decision to submit the paper for publication. No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

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