Contrast-enhanced ultrasound for multiple liver lesions after bone marrow transplant in a child with leukaemia: Multifocal focal nodular hyperplasia

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MV Verhagen¹ , O Ciocarlie², P Humphries¹ and T Watson¹

Abstract

We present a case of a two-year-old girl in which liver lesions were characterised on contrast-enhanced ultrasound as multifocal focal nodular hyperplasia. This child had previously undergone haematopoietic stem cell transplantation for juvenile myelomonocytic leukaemia and was suspected to have hepatobiliary graft versus host disease. Liver biopsy was performed to confirm the unexpected focal nodular hyperplasia and look for concurrent graft versus host disease. Focal nodular hyperplasia was histologically confirmed on a background of diffuse liver damage in keeping with polypharmacotherapy, steatosis and sepsis. An element of graft versus host disease was not excluded but was not confidently shown in the sample of the lesion. This case report describes and illustrates how contrast-enhanced ultrasound may be of use to further assess hepatic lesions in a complex case of multifactorial hepatic pathology. Radiologists, haematologists and pathologists should be aware that multifocal focal nodular hyperplasia is part of the differential diagnosis of liver lesions in a child with liver damage due to complex disease and treatment. Biopsy remains the gold standard, if there is a concurrent clinical suspicion of graft versus host disease.

Keywords

Graft versus host disease, contrast-enhanced ultrasound, focal nodular hyperplasia, Haematopoietic stem cell transplantation, post-transplant lymphoproliferative disease

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Introduction

Haematopoietic stem cell transplantation (HSCT) as leukaemia treatment is associated with hepatic complications such as graft versus host disease (GVHD), veno-occlusive disease (VOD), post-transplant lymphoproliferative disease (PTLD) and (fungal) infection.¹ The initial work-up of such liver diseases consists of physical examination, bloodwork and ultrasound. Making a conclusive diagnosis can be difficult and there is often a multifactorial aetiology of liver dysfunction to take into account, such as prolonged parenteral feeding and polypharmacotherapy.

GVHD occurs in approximately 20–50% of children undergoing allogeneic HSCT depending on the type of

transplant and remains a major cause of morbidity and mortality. The pathophysiology consists of an alloimmune process mediated by donor T cells interacting with recipient and donor antigen presenting cells that trigger hyper inflammation through cytokine release, resulting in donor T-cell proliferation, inflammation and tissue damage.² The skin is most commonly

¹Radiology Department, Great Ormond Street Hospital, London, UK
²Haematology Department, Great Ormond Street Hospital, London, UK

Corresponding author:

MV Verhagen, Great Ormond Street Hospital, Great Ormond Street, London WC1N 3JH, UK.
Email: martijn.verhagen@gosh.nhs.uk

involved (80%), with the upper and lower gastrointestinal tract affected in 54% of patients and hepatobiliary system in 50%.³

Hepatobiliary GVHD presents with rising conjugated bilirubin and alkaline phosphatase⁴ but may also have increased serum aminotransferases,⁵ thereby mimicking hepatitis. The differential diagnosis consists of VOD and hepatotoxicity with cholestasis.⁶ Imaging findings supporting GVHD may consist of biliary tract enhancement, gallbladder wall thickening, biliary duct dilatation and sludge, hepatomegaly and a high resistive spectral trace in the hepatic artery.⁶ Multiple liver lesions representing GVHD have been described on one occasion in magnetic resonance imaging (MRI).⁷ There is no specific imaging finding, and liver biopsy is the gold standard.⁵ Histopathology findings consist primarily of bile duct injury, with changes in biliary epithelial cells, lymphocytic infiltrate and, in more advanced stages, fibrosis and loss of bile ducts.³

The differential diagnosis of multiple liver lesions in a patient with prior HSCT depends on the immune recovery status and level of immunosuppression, and, in addition to GVHD, it includes (fungal) infection and PTLN.^{1,4} PTLN is associated with Epstein-Barr virus (EBV) reactivation.⁴ Ultrasound is often not specific, and clinical history takes priority over imaging.³ Nevertheless, modalities such as ultrasound and MRI may be the first to detect or support the clinical diagnosis.

Contrast-enhanced ultrasound (CEUS) is a technique in which sulphur hexafluoride microbubbles (SonoVue, Bracco, Italy) are given intravenously allowing the dynamic enhancement pattern of a lesion to be assessed on modified B-mode imaging.⁸ Advantages include: real-time assessment of the enhancement and perfusion pattern, no ionising radiation exposure or sedation is necessary, and there is no renal toxicity as it is a purely blood pool agent. Because of these advantages, CEUS is advocated as an additional child-friendly, problem solving tool, for which the extent of clinical applications in children are still being explored.⁹ CEUS has been shown to be of use as a complementary tool for the detection of acute intestinal GVHD,¹⁰ and for characterising liver lesions in both children and adults.^{8,11}

We present the case of a two-year-old girl who had undergone an HSCT for juvenile myelomonocytic leukaemia (JMML) on a background of neurofibromatosis type 1 (NF1). The child was suspected to have reactivation of hepatobiliary GVHD. We describe, illustrate and discuss how CEUS helped characterise the B-mode ultrasound finding of multiple liver lesions as focal nodular hyperplasia (FNH) in the setting of complex liver disease.

Case report

A two-year-old girl with a history of juvenile myelomonocytic leukaemia on a background of NF1 was seen at the bone marrow transplantation clinic. She had undergone allogeneic bone marrow transplantation 12 months before (10/10 matched unrelated donor bone marrow transplant with myeloablative conditioning and GVHD prophylaxis) and had been off immunosuppression for one month. She had had a previous episode of GVHD post-HSCT. GVHD reactivation was suspected clinically because of fever, skin rash, high C-reactive protein (CRP) and pancytopenia. A complete work-up was performed. Blood cultures grew micrococcus and she received broad antibiotic coverage. Viral PCR demonstrated a high EBV viral load of 62,944 copies/ml. She received prophylactic anti-fungal treatment after a chest computed tomography (CT) was normal. On physical examination, there was hepatosplenomegaly and rising liver enzymes (bilirubin 75 $\mu\text{mol/L}$, alanine aminotransferase 362 U/L, gamma-glutamyl transferase 845 U/L). A multifactorial aetiology was considered most likely with possible contributors consisting of polypharmacotherapy, long-term parenteral feeding, (fungal) infection, GVHD, VOD, PTLN and biliary duct obstruction.

An ultrasound was performed to assess general liver size and appearance, the biliary tree and for focal lesions. This demonstrated hepatomegaly and multiple sharply delineated echoic lesions throughout the liver, the largest lesion measured 1.3 cm in diameter (Figure 1). Apart from the hepatomegaly, no specific imaging features of hepatobiliary GVHD or VOD were found. The differential diagnosis consisted of multiple adenomas, regenerative nodules/FNH, fungal

Figure 1. B-mode appearance of the focal liver lesions (arrows). The lesions are variable in size, with the largest measuring 1.3 cm in diameter (which was later biopsied). They are sharply demarcated, round and mostly echoic with an isoechoic centre.

infection, multifocal fatty infiltration, PTLN and (unlikely) focal GVHD.

CEUS was performed to further assess the lesions without the need for general anaesthesia. A target lesion was identified in the left lobe of the liver (segment 4A). This was selected because it was the largest and most obvious on B-mode imaging. SonoVue (1 ml) was injected via the indwelling right-sided double lumen central venous catheter. The target lesion demonstrated early arterial uptake of contrast within the centre of the lesion (Figure 2), followed by centrifugal filling of the periphery. Additional lesions, some identifiable on B-mode and others not, were also identified in the imaged volume and demonstrated identical characteristics. The lesions retained contrast slightly above that of normal background liver for the first 30 seconds before becoming isoechoic with background liver. There was no abnormal washout and a late portal phase sweep through the liver did not show washout in any of the other lesions. This centrifugal perfusion pattern reflected a benign process such as FNH⁸ and was unlikely to represent (fungal) infection as these do not typically enhance. However, in light of the unexpected finding of FNH, the differential diagnosis of PTLN, and the high clinical suspicion of concurrent hepatobiliary GVHD, biopsy was performed of a focal lesion and the liver parenchyma. Pathology confirmed FNH and showed regenerative hyperplasia on a background of

diffuse liver damage in keeping with polypharmacotherapy, steatosis and sepsis. An element of GVHD was not excluded but was not confidently shown in the sampled lesion. The skin biopsy supported the diagnosis of skin GVHD. She was treated with tacrolimus, topical and systemic steroids (methylprednisolone/prednisolone). She fully recovered from her pancytopenia and EBV viral load markedly reduced. On follow-up, ultrasound the liver lesions became less conspicuous over the subsequent months.

Discussion

A child who has undergone HSCT and presents with multiple liver lesions warrants further investigation. The differential diagnosis is broad but differentiating benign lesions from infection, PTLN and GVHD will impact treatment. B-mode ultrasound may detect focal lesions but is usually insufficient to characterise them. Although biopsy is the gold standard, it is invasive and not without risk especially in sick or unstable children. MRI would traditionally be the modality to further characterise liver lesions in children, but this may require general anaesthesia, which can pose risks in this subset of children who often have multi-organ impairment. We have shown that CEUS can characterise liver lesions found after HSCT, with the advantage of being a bedside technique which avoids general anaesthesia.

Figure 2. CEUS injection of microbubbles was performed via a peripheral venous cannula. CEUS at 6, 7 and 8 seconds demonstrates early arterial centrifugal enhancement of multiple lesions (arrows). These become isoechoic to the liver at 12 seconds and remain isoechoic, with lack of washout noted at 30 seconds and 3 minutes.

CEUS use in children is considered safe and has recently been Food and Drug Administration (United States) approved in children.⁹ In the UK, SonoVue is used as an off-label drug, which should be discussed with and consented by the child's parent prior to the procedure. The FDA recommends a dose of 0.03 ml/kg SonoVue; in our case, this would have resulted in 0.36 ml instead of 1 ml. Our case was performed before the recommendation came out and appropriate dose usage in our practice is being reviewed. Based on experience and given the impracticality of administering fractions of 1 ml, a minimum of 0.6 ml is suggested in children <6 years old,⁸ and we prefer 1 ml to ensure diagnostic images with one injection. CEUS can readily be applied for the characterisation of liver lesions in children¹¹ and may replace CT or MRI in some cases. This may be especially relevant in babies and young children, in which B-mode ultrasound provides higher resolution than any other imaging. Our case serves as an example for this. Another example of CEUS successfully characterising a liver lesion was that of a four-month-old with a hepatic haemangioma,¹² in which case further imaging (MRI) was no longer necessary.

CEUS in our case demonstrated an enhancement pattern in keeping with FNH in multiple liver lesions. The enhancement pattern of FNH on CEUS, MRI and CT has been well established; however, these are usually solitary and incidental. Although the enhancement pattern of multiple assessed lesions was identical and in keeping with FNH,⁸ the finding of multiple lesions in a child with concurrent high clinical suspicion for GVHD prompted us to pursue a biopsy. This was done to confirm the unexpected finding of multiple FNH but also to assess for concurrent GVHD. Multiple FNH have been described by Pillon et al. on MRI.¹³ They found a significantly higher incidence of FNH in children who underwent HSCT compared to the overall paediatric population (5.2% versus 0.02%). Majority (11/17) of the children had multiple nodules with a median of two nodules/patient (range 1–7). Of these, six cases were biopsy proven to be FNH, and 16/17 had previously suffered from GVHD. They postulated that the FNHs were acquired and could be a result of stem cells from HSCT enhancing the regenerative response to liver injury. It is possible that the occurrence of multiple FNH in HSCT patients is underestimated and increased awareness may improve detection and characterisation of lesions. CEUS appears to be a useful tool for characterising lesions in this clinical setting.

Reactivation of GVHD was a major concern in our case. Literature on the appearance of hepatobiliary GVHD on CEUS is not available. Imaging of hepatobiliary GVHD is generally non-specific and not

associated with focal lesions; one study, however, reported biopsy proven hepatobiliary GVHD in a 21 year old six weeks after HSCT with multiple liver lesions. In that case, the nodules demonstrated only mild rim enhancement on MRI.⁷ Another concern in our case was EBV reactivation, which is associated with PTLN and also warrants a conclusive diagnosis in a case of multiple focal lesions.⁴ Liver biopsy was able to rule out infection and PTLN. No convincing features of GVHD were demonstrated, but it was noted that GVHD could not be excluded based purely on the biopsy of a single lesion; differentiating between GVHD and liver damage resulting from other causes may not be straightforward. We must also consider the possibility that although the biopsy site did not represent GVHD, there may have been hepatobiliary GVHD elsewhere.

GVHD is relatively common in the HSCT population,² and the imaging appearance on B-mode ultrasound is highly variable and non-specific. Our case showed that multifocal FNH should be in the differential diagnosis for focal liver lesions post-HSCT. Biopsy remains the gold standard if hepatobiliary GVHD is suspected; however, further understanding of CEUS application may make biopsy unnecessary for liver lesions when active GVHD is not suspected.

Summary/conclusion

Establishing the right diagnosis of multiple liver lesions in a child post-HSCT may be challenging, but it is essential in order to ensure the correct treatment. CEUS may be used as a low threshold tool to characterise focal lesions in this clinical setting and can provide further information that may make biopsy unnecessary. The occurrence of multifocal FNH in children with previous GVHD or other causes for liver damage may be underestimated and should be considered as a differential diagnosis in patients presenting with liver lesions following HSCT.

Take home messages

- Consider multifocal FNH in the differential diagnosis of multiple liver lesions after HSCT
- The occurrence of FNH after liver damage may be underestimated
- CEUS may help characterising liver lesions after HSCT without the need for general anaesthesia.

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Ethics Approval

Ethics approval is waived at our institution for retrospective case review.

Guarantor

TW.

Contributors

MV and TW researched literature and conceived the study. OC gained informed written consent from the patient's family. MV wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Informed Consent

Informed, written consent was obtained from the patient's family.

ORCID iD

MV Verhagen <http://orcid.org/0000-0001-9804-5781>

References

1. Levine DS, Navarro OM, Chaudry G, et al. Imaging the complications of bone marrow transplantation in children. *Radiographics* 2007; 27: 307–324.
2. Ferrara J, Levine J, Reddy P, et al. Graft-versus-host disease. *Lancet* 2009; 373: 1550–1561.
3. Lubner MG, Menias CO, Agrons M, et al. Imaging of abdominal and pelvic manifestations of graft-versus-host disease after hematopoietic stem cell transplant. *Am J Roentgenol* 2017; 209: 33–45.
4. Pandey T, Maximin S and Bhargava P. Imaging of complications from hematopoietic stem cell transplant. *Indian J Radiol Imaging* 2014; 24: 327.
5. Strasser S, Shulman H, Flowers M, et al. Chronic graft-versus-host disease of the liver: presentation as an acute hepatitis. *Hepatology* 2000; 32: 1265–1271.
6. Mahgerefteh SY, Sosna J, Bogot N, et al. Radiologic imaging and intervention for gastrointestinal and hepatic complications of hematopoietic stem cell transplantation. *Radiology* 2011; 258: 660–671.
7. Tomasian A, Sandrasegaran K, Elsayes KM, et al. Hematologic malignancies of the liver: spectrum of disease. *RadioGraphics* 2015; 35: 71–86.
8. Rafailidis V, Deganello A, Watson T, Sidhu PS and Sellars ME. Enhancing the role of paediatric ultrasound with microbubbles: a review of intravenous applications. *Br J Radiol* 2017; 90: 20160556.
9. Sidhu PS, Cantisani V, Deganello A, et al. Role of contrast-enhanced ultrasound (CEUS) in paediatric practice: an EFSUMB position statement. *Ultraschall Med* 2017; 38: 33–43.
10. Benedetti E, Bruno B, McDonald GB, et al. Prospective qualitative and quantitative non-invasive evaluation of intestinal acute GVHD by contrast-enhanced ultrasound sonography. *Bone Marrow Transpl* 2013; 48: 1421–1428.
11. Jacob J, Deganello A, Sellars ME, et al. Contrast enhanced ultrasound (CEUS) characterization of grey-scale sonographic indeterminate focal liver lesions in pediatric practice TT – Kontrastmittelultraschall (CEUS) in der Pädiatrie zur Charakterisierung von sonografisch nicht-differenzierbaren f. *Ultraschall Med* 2013; 34: 529–540.
12. Piorkowska MA, Dezman R, Sellars ME, et al. Characterization of a hepatic haemangioma with contrast-enhanced ultrasound in an infant. *Ultrasound*. Epub ahead of print 19 October 2017. DOI: 10.1177/1742271X17733298.
13. Pillon M, Carucci NS, Mainardi C, et al. Focal nodular hyperplasia of the liver: an emerging complication of hematopoietic SCT in children. *Bone Marrow Transpl* 2015; 50: 414–419.