Case Report

Identification of secondary splenic lymphoma with contrast-enhanced ultrasound in the pediatric population. A case report

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Abstract

Contrast-enhanced ultrasound scan (CEUS) is the application of ultrasound contrast agents (UCAs) to traditional ultrasound. Our aim is to report the use of CEUS for a prompt assessment of a suspected secondary splenic lymphoma in a child, which, in our experience, has allowed an accurate description of the parenchymal perfusion and vascularization pattern, leading to a confident diagnosis. We suggest that CEUS will replace Magnetic resonance imaging (MRI) or Computed tomography (CT) as standard imaging option for differential diagnosis of spleen lesions in pediatric population. As a result this will lead to decreasing the overall use of ionizing radiation and reducing the time interval to a certain diagnosis.

Keywords:
Secondary splenic lymphoma
Contrast-enhanced ultrasonography
CEUS- Malignant Solid Lesion
Spleen
non-Hodgkin’s lymphoma

Introduction

Microbubble-based CEUS, a low-risk and reliable technique for extensive examination of organs widely used in the adult population, has recently received the approval for assessment of focal liver lesions in children and for some “off-label” uses in pediatric practice, as indicated by the European Federation of Societies in Ultrasound and Medicine (EFSUMB) guidelines [1]. Apart from trauma, indeed, CEUS may be used in children with current its advantages. The CEUS is a non-invasive, non-ionizing modality, which in our experience, especially in the pediatric population, offers a prompt and confident diagnosis.

∗ Competing interests: We confirm that this work is original and has not been published elsewhere nor is it currently under consideration for publication elsewhere. Publication is approved by all authors and by the responsible authorities where the work was carried out. Each author has participated sufficiently in any submission to take public responsibility for its content. The authors have no conflicts of interest.

∗∗ Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Data obtained in this study did not interfere with course of treatment for patients included.

∗ Availability of data and material: material and data are all available

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https://doi.org/10.1016/j.radcr.2021.11.027

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to confirm the presence of anatomical anomalies (e.g., aberrant splenic nodules) and to characterize focal solid benign splenic lesions (hemangiomas or hamartomas) from malignant ones, especially if isoechoic or hypoechoic on conventional B-mode US. [2] CEUS has shown several gains including its low cost and the fact that it doesn’t require general anesthesia. It requires instead the injection of a second-generation Ultrasound contrast agents (UCAs). SonoVue (Braaco SpA, Milan, Italy) is the most commonly used UCAs and it contains sulphur hexafluoride gas. The addition of sodium chloride to a lyophilized powder followed by vigorous shaking results in the production of microbubbles of sulphur hexafluoride which are exhaled via the lungs with an excellent safety-profile [1–5]. The assessment of CEUS in spleen disease is poorly documented especially compared to liver examination. Splenic traumas are nowadays a common indication for the use of UCA in pediatric population, however different diagnoses of splenic focal lesions (abscess, complex cyst, lymphoma, haemangioma) have been comprehensively described only in few publications, but they seem to be strong suitable indications [2, 6, 7]. Herein we describe a 6-year-old male case of splenic secondary lymphoma, diagnosed with CEUS, which was performed as integration of US.

General consideration and patient preparation

The administration of the UCA is still “off-label”, and written consent for UCA administration was obtained according to the hospital requirement and permission. Written and informed verbal consent was obtained from parents as legal guardians prior to the examination for contrast examinations and UCA administration.

Patients are not required to fast before taking the examination, however, examination after abundant meals should be avoided. A large-bore venous indwelling catheter is required for both contrast-medium administration and saline flush. Monitoring of vital parameters is not mandatory. UCAs are extremely safe so it is not necessary to perform any laboratory tests to assess organs function prior to their administration. To date, as to the authors’ knowledge, no severe adverse event occurred in children in our center prompting intensive care arrangements [8].

Case description

A 6-year-old boy was admitted to our Pediatric Emergency Department with acute abdominal pain and a history of 7 days mild fever and fatigue. Clinical history showed no weight loss, night sweats or itching. Relevant risk factors for viral or bacterial infection, such as travel, pets, low socioeconomic status, poor oral hygiene, autogenic or sinus infections as well as immune dysfunction were investigated.

Upon admission, blood laboratory tests showed an important anemia, high WBC 14.000 and a mild increased C-reactive protein. Other laboratory test parameters appeared to be normal.

Fig. 1 – (A and B) Focal splenic lymphoma involvement in a 6-years-old male patient with non-Hodgkin’s lymphoma. B-mode US image demonstrates multiple different shapes hypoechoic masses through the spleen (yellow arrows). The nodules range varies between 3 mm to 15 mm, the bigger on the medial face of the spleen (calipers). Color version of figure is available online.

Fig. 2 – Grey scale sonogram of the neck: A detailed showing of multiple hypoechoic malignant lymphomatous nodes with intranodal reticulation (yellow arrows). Color version of figure is available online.

In our case the clinical presentation was non-specific, but at physical examination several palpable bilateral neck lymph nodes not associated with pain were depicted. So, real time sonographic examination was performed as the first-line method to investigate abdomen and lymphatic stations. There was no evidence of free fluid in the abdomen. Intestinal loops and others organ were also normal. But, at spleen examination, B-Mode US showed an homogeneous splenic texture of regular size with multiple irregularly delineated hypoechoic focal lesions (Fig. 1A and B). The nodules range varies between 3 mm to 15 mm, the bigger on the medial face of the spleen. There was no alteration of the splenic vessels on color-Doppler imaging.

At neck examination, on grayscale sonography there was a huge lymphadenopathy with enlarged bilateral lymphomatous nodes in latero-cervical region (Fig. 2). They appeared hypoechoic, round, with and/or without echogenic hilus and an anarchic vascularization. Some of them showed intranodal reticulation with a micronodular appearance (Fig. 3) [9].
Based on clinical suspicion and for possible mediastinal involvement, US evaluation was also extended to other lymphatic stations, as the chest, where similar lymphadenopathies were identified in the mediastinum (Fig. 4). All these findings, basing on conventional B-mode, were highly suspicious for malignancy. Differential diagnosis included splenic lymphoma, metastatic splenic lesions or also abscesses. Therefore, depending on the indication and in absence of clinical contraindications, the sonographic investigation was completed with a CEUS, performed by a skilled and trained pediatric radiologist (F.E.) [10].

CEUS examination allowed real-time recording and evaluation of the wash-in and wash-out phases of the UCA over several minutes. Using the B-mode image for guidance, the use of a dual-image display format allowed the operator to keep the lesion in the imaging plane.

The injection of the SonoVue TM was administered via catheter as a bolus injection with a concentration of 0.1 ml solution per patient age in years, given at about 1-2ml/s, immediately followed by a 5-10 ml of physiologic saline solution at about 2 ml/s.

The mechanical index (MI) was the way to measure part of the US waves on the tissue and the contrast medium bubbles and it was set at value below 0.1.

All lesions detected by standard B-Mode US were also seen on CEUS, even some not showed in US (Figs. 5-7). In the arterial phase (5-40 s) of CEUS the lesions showed iso-enhancement, before having a rapid washout followed by a marked persistent hypoenhancement in the parenchymal phase (1 up to 5 minute) being clearly delineated from the surrounding splenic tissue compared to standard B-Mode US (Figs. 3 and 4). The continuity of the splenic vessels was respected. The young patient was kept under strict medical supervision for about 30 minutes following the administration of the UCA. Then a physical examination was carried out to verify the occurrence of any adverse reactions (such as erythema, nausea or emesis) [2, 8, 11] before discharging the patient from the Radiology Department.

According to medical history and clinical characterization, this pattern led us to a diagnosis of secondary splenic lymphoma, (non-Hodgkin’s lymphoma in this case), which ensured consistently accurate staging and therefore stage-adapted oncological therapy after histological confirmation.

Discussion

To date, only 10%-30% of Hodking Lymphomas exhibits spleen’s involvement. Although rare, lymphoma is the most common secondary pediatric tumor reported.

Real Time US represents the first-level imaging modality employed in the evaluation of the spleen, but categorization of either focal or diffuse lesions is challenging comparing to those of other parenchyma [2, 6].

Only few data studies about CEUS and its role in observation and determination of this condition in pediatric population are currently available. Diagnosis is traditionally based on clinical signs and symptoms as well as laboratory tests and second-level imaging such MRI and CT-scan or Pet-Ct.
Fig. 5 – Pediatric patient with non-Hodgkin’s lymphoma. Split-screen ultrasound image (grayscale image on left and contrast image on right) in early enhancement phase CEUS demonstrates the typical zebra pattern of the spleen (white arrows). The splenic lesions are not clearly identified during this early enhancement phase. Then, there is a nearly isoechoic enhancement followed by a persistent homogeneous hypoechoic enhancement during the parenchymal phase (early washout of the masses) (red arrowheads). Pattern of enhancement of target lesion in arterial phase of CEUS examination at 20, 40 and 60 seconds after contrast administration. Color version of figure is available online.

Fig. 6 – Split-screen ultrasound image (grayscale image on left and contrast image on right) in parenchymal phase (1 up to 5 minute) shows persistent hypoechoic enhancement of the masses (black arrows), even on those not clearly detected on B-mode (white arrows).

Differential diagnoses should include metastasis, abscess, vascular or lymphatic malformation, splenic cyst or pseudocyst, infarct, hamartoma [2, 12]. Splenic lymphoma’s usually appear with three possible sonographic patterns on standard B-Mode US: a homogenous splenic texture, a diffuse inhomogeneous splenic texture, and focal lesions of different sizes [12–13].

In our case, on conventional B-mode, the spleen shows numerous hypoechoic focal nodular lesions with no internal vascularity. These findings were highly suspected. However, dif-
Fig. 7 – Split-screen ultrasound image (grayscale image on left and contrast image on right) in parenchymal phase (1 up to 5 minute) shows persistent hypoechoic enhancement of the masses (black arrows), even on those not clearly detected on B-mode (white arrows).

Table 1 – Contrast-enhanced ultrasound (CEUS) findings for imaging of hypo-echoic spleen lesions.

| Spleen Diagnosis | Arterial Phase | Parenchymal Phase |
|------------------|----------------|------------------|
| Lymphoma         | Isoenhancement lesion | Rapid/progressive washout persistent hypoechoic enhancement |
| Metastasis       | Mostly hypoechoic lesion. Sometime hyper-/Isoenhancement | Progressive washout hypoenhancement lesion |
| Abscess          | Absent enhancement lesion ± perilesional hyperenhancement | Absent enhancement lesion ± perilesional hyperenhancement |

Differential diagnosis included metastatic splenic lesions or also abscesses, which are very rare in the pediatric population, but can have different US appearance depending on the immunologic status of the child [2].

CEUS accurately distinguished the lesions as lymphomas by highlighting features that were highly suspicious for malignancy: isoechoic enhancement pattern in arterial phase, and rapid washout with marked hypoechoic enhancement in the parenchymal phase. Determination of benign/malignant nature of the lesion has been fundamental to reduce the time interval to a certain diagnosis. Differentiation between benign and malignant splenic lesions is indeed evidenced at CEUS by the different dynamics of uptake and washout of UCA in the arterial and parenchymal phase (Table 1).

Malignant lesions show: inhomogeneous poor or peripheral or absent enhancement in the arterial phase, followed by a rapid progressive and complete washout in the parenchymal phase. In fact, elimination of microbubbles from malignant lesions is faster than from benign lesions.

Benign lesions mostly show: iso or high hyperenhancement in the arterial phase, whereas in the parenchymal phase there is only a modest washout. [14]

CEUS of the spleen has shown a remarkable ability to depict benign or malignant lesions with a relative low cost and an outstanding safety profile, demonstrating higher value in comparison to B-mode US in patients with focal splenic lesions [3-4, 15-16].

In conclusion, our case shows the use of intravenous microbubbles CEUS to characterize a spleen malignant solid lesion, especially in the parenchymal phase, with CT scan results confirmation, making the diagnosis of splenic lymphoma involvement easier. CEUS represents a useful tool for an accurate characterization of focal nodular splenic lesion. We suggest that it will replace Magnetic resonance imaging (MRI) or Computed tomography (CT) as standard imaging option for differential diagnosis of spleen lesions in the pediatric population. As result this will lead to reducing the time interval to a certain diagnosis. Therefore, CEUS has been useful to gain diagnostic reliability in this young patient with non-Hodgkin’s lymphoma [13].

Its use will be increasing as contrast-enhanced ultrasound scan becomes available more widely, decreasing the overall use of ionizing radiation and representing an ideal potential indication in children.

Author contribution

Francesco Esposito: Conceptualization, Methodology, Divina D’Auria: Data curation, Writing- Original draft preparation. Gioconda Argenziano: Visualization, Investigation. Dolores Ferrari, Domenico Noviello and Anna Marcella Giugliano: Validation. Divina D’Auria and Gioconda Argenziano: Writing- Re-
viewing and Editing. All authors read and approved the final version of the manuscript.

**Patient consent**

Informed consent was obtained from all individual participants included in the study. Additional consent to participate was obtained from all individual participants included in the study. Additional consent for publication was obtained from all individual participants included in the study.

**Acknowledgments**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**References**

[1] Sidhu PS, Cantisani V, Deganello A, Dietrich CF, Duran C, Franke D, et al. Role of Contrast-Enhanced Ultrasound (CEUS) in Paediatric Practice: An EFSUMB Position Statement. Ultraschall Med. 2017;38(1):33–43. doi:10.1055/s-0042-110394.

[2] Franke D, Anupindi SA, Barnewolt CE. Contrast-enhanced ultrasound of the spleen, pancreas and gallbladder in children. published online ahead of print, 2021 Aug 24. Pediatr Radiol. 2021. doi:10.1007/s00247-021-05131-7.

[3] Squires JH, McCarville MB. Contrast-Enhanced Ultrasound in Children: Implementation and Key Diagnostic Applications. published online ahead of print, 2021 Apr 28. AJR Am J Roentgenol. 2021. doi:10.2214/AJR.21.25713.

[4] Görg C, Bert T. Second-generation sonographic contrast agent for differential diagnosis of perisplenic lesions. AJR Am J Roentgenol. 2006;186(3):621–6.

[5] Peddu P, Shah M, Sidhu PS. Splenic abnormalities: a comparative review of ultrasound, microbubble- enhanced ultrasound and computed tomography. Clin Radiol. 2004;59:777–92.

[6] Sidhu PS, Sellars ME, Deganello A. Contrast-Enhanced Ultrasound in Pediatric Imaging (Eds.) cap 13.

[7] Benedetti E, Proietti A, Miccoli P. Contrast-enhanced ultrasonography in nodular splenomegaly associated with type B Niemann. Pick disease: an atypical hemangiomatous enhancement pattern. J Ultrasound. 2009;12:85–92.

[8] Piskunowicz M, Back SJ, Darge K. Contrast-enhanced ultrasound of the small organs in children. published online ahead of print, 2021 Apr 8. Pediatr Radiol. 2021. doi:10.1007/s00247-021-05006-x.

[9] Trinci M, Piccolo CL, Ferrari R, Galluzzo M, Iannillo S, Miele V. Contrast-enhanced ultrasound (CEUS) in pediatric blunt abdominal trauma. J Ultrasound. 2019;22(1):27–40. doi:10.1007/s40477-018-0346-x.

[10] Stenzel M. Intravenous contrast-enhanced sonography in children and adolescents - a single center experience. J Ultras. 2013;13(53):133–44. doi:10.15557/joU.2013.0014.

[11] Ahuja AT, Ying M, Ho SY. Ultrasound of malignant cervical lymph nodes. Cancer Imaging. 2008;8(1):48–56 Published 2008 Mar 25. doi:10.1102/1470-7330.2008.0006.

[12] Görg C, Faoro C, Bert T, Tebbe J, Neesse A, Wilhelm C. Contrast enhanced ultrasound of splenic lymphoma involvement. Eur J Radiol. 2011;80(2):69–74. doi:10.1016/j.ejrad.2009.11.012.

[13] Stang A, Keles H, Hentschke S. Differentiation of benign from malignant focal splenic lesions using sulfur hexafluoride-filled microbubble contrast enhanced pulse-inversion sonography. AJR Am J Roentgenol. 2009;193:709–21.

[14] Caremamni M, Occhini U, Caremamni A. Focal splenic lesions: US findings. J Ultrasound. 2013;16(2):65–74 Published 2013 May 4. doi:10.1007/s40477-013-0014-0.

[15] Dhyani M, Anupindi SA, Ayyala R, Hahn PF, Gee MS. Defining an imaging algorithm for noncystic splenic lesions identified in young patients. AJR Am J Roentgenol. 2013;201:W893–9.

[16] Zavari J, Konstantatou E, Deganello A. Common and uncommon features of focal splenic lesions on contrast-enhanced ultrasound: a pictorial review. Radiol Bras 2017;50:395–404.