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To what extent can diverse types of liver lesions mimic hemangiomas? A retrospective quantitative analysis of masses found to be positive in SPECT/CT with labeled blood cells – a preliminary report

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Summary

Background: Although specificity of SPECT/CT examination using technetium-99m radiolabeled red blood cells (Tc-99m-RBC) for detection of liver hemangiomas is very high, it is still not perfect. It is possible to overlook a malignancy. Moreover, the difference in accumulation of RBCs between a hemangioma and uninvolved liver remains unknown.

The aim of the study is to determine the quotients of accumulation of Tc-99m-RBC in hemangiomas and in normal liver parenchyma (HEM/liv), and to verify, whether the quotient could be potentially helpful in distinguishing hemangiomas from other RBC-accumulating liver masses.

Material/Methods: 34 liver lesions larger than 1.5 cm classified scintigraphically (qualitatively) in our Department as either typical or suspicious of hemangioma 1.5–4 years earlier were enrolled in this retrospective study. Their SPECT/CT images were acquired 1 hour after *in vivo* labeling of RBCs with Tc-99m. In reconstructed images, ellipsoidal regions of interest (ROIs) with diameters of about 1.5 cm were created in the assessed lesions (HEM) and in the uninvolved liver parenchyma (liv). The HEM/liv quotients were calculated for each mass. The results were compared with radiological data.

Results: 31 lesions were found to be clinically and radiologically typical for hemangiomas, their HEM/liv ratios were at least 1.6 (smaller masses) or 1.8 (larger masses). One lesion with HEM/liv ratio equal to 1.21 was classified as metastasis. Two lesions with HEM/liv 1.42 and 1.46 were classified as benign foci other than hemangioma.

Conclusions: The quantitative analysis can be preliminarily proposed as a helpful tool in the assessment of possible liver hemangiomas.

Key words: liver hemangioma • SPECT/CT • quantitative analysis • Tc-99m • labeled red blood cells

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Background

Hemangioma is one of the most common benign focal liver lesions [1–4]. Its differentiation from other masses is frequently a challenge. In ultrasonography (US), hemangioma is usually: (I) well demarcated, (II) hyperechoic, (III) homogenous and (IV) lacks internal blood flow in color/power Doppler. In contrast-enhanced computed tomography (CE-CT), the mass is typically: (I) well demarcated, (II) hypodense and (III) homogenous before contrast agent administration, and exhibits (IV) contrast enhancement in portal phase, the enhancement is (V) peripheral, globular and centripetal ("fill-in") [4]. Unfortunately, sensitivity and specificity of both imaging methods is about 80%, which is less than satisfactory. Magnetic resonance imaging (MRI) [2,4] and contrast-enhanced ultrasonography [5] can also contribute to the diagnosis, but their accuracy is limited as well.

Contrary to radiological techniques, scintigraphy with technetium-99m-labeled patient's own red blood cells (Tc-99m-RBC), especially SPECT and SPECT/CT (single photon emission computed tomography/computed tomography), seems to possess very high sensitivity and specificity [1–3,6]. Typical findings include lack of perfusion (early phase, scintigraphically evaluable only in some lesions) and markedly enhanced RBC accumulation in delayed phase (phenomenon referred to as "perfusion/blood-pool mismatch"). However, false positive findings are also known, which makes possible to overlook a malignancy. Additionally, there are no quantitative data about the accumulation of RBCs in hemangiomas, i.e., it remains unknown by what factor RBC uptake within the lesions surpasses their accumulation in an uninvolved liver.

Data acquisition with a hybrid SPECT/CT scanner allows for acquisition of both emission (dependent on the radiotracer) and transmission (anatomical) tomograms. Reconstructed CT image, being actually an "attenuation map" of the scanned object, additionally allows for transformation of reconstructed SPECT images into a map of distribution of the radionuclide within the object. Thus, it makes possible to perform semi-quantitative comparisons of nuclide activities in different parts of the object [7].

Material and Methods

Thirty-four liver lesions found in 21 patients were included in the retrospective study. The inclusion criteria were the following: positive result of SPECT/CT examination with Tc-99m-RBC (i.e. described as either typical or suspicious of hemangioma), diameters of at least 1.5 cm, location not adjacent to foci of markedly enhanced technetium accumulation (i.e. stomach), accessibility of results of CE-CT and US examination (performed and described by radiologists), and a period of patient observation (which ranged from 1.5 to 4 years) after the SPECT/CT study.

The patients' own red blood cells were labeled with Tc-99m *in vivo* according to the procedure described earlier in details [8–10]. Summing up, each patient received intravenous injection of stannous pyrophosphate. It was followed by injection of 500–750 MBq of Tc-99m pertechnetate 30 minutes thereafter.

Data was acquired with a hybrid, double-head, one-row SPECT/CT Symbia T device (Siemens). Each acquisition begun with dynamic anterior and posterior images of the liver (not taken into consideration in this study). Sixty minutes later each patient underwent SPECT/CT study of the lower thorax and upper abdomen, so that the heart and the liver were in the field of view (FOV). Parameters of SPECT acquisition were as follows: collimator: LEHR (low energy high resolution), number of images: 64 (32 detector positions in 25 seconds), matrix: 128×128, detector FOV: 53.3×38.7 cm. CT acquisition parameters were as follows: voltage: 130 kV, product of current and time – about 17 mAs (adjustable for each patient during the acquisition, resulting in additional radiation burden of about 1.7 mGy). No contrast agent was administered. Each reconstructed CT slice was 5-mm thick.

Before being analyzed by a physician, images were subjected to iterative reconstruction, CT-controlled attenuation correction and scatter elimination. Finally, analysis of the corrected SPECT images, CT images, and fusion (SPECT/CT) images was possible.

Qualitative analysis was performed directly after each examination. It was a simple visual assessment of presence or absence of foci of increased accumulation of the nuclide within the examined mass as compared to uninvolved liver parenchyma. Each mass was then classified either as typical/suspicious or not typical of hemangioma.

Quantitative analysis of radionuclide uptake was performed 1.5–4 years after the examination. For this purpose, ellipsoid-shaped (almost spherical) regions of interest (ROI) with diameters of about 1.5 cm (volume of about 1.7 ml) were created. The ROIs were located in:

1. Uninvolved liver tissue (marked as "liv"): distant from the lesion and from blood vessels, in peripheral parts of the organ, but at least 2 cm from its external border and not directly under the diaphragm;
2. Center of the left heart ventricle ("heart");
3. Lesion suspicious of hemangioma ("HEM") – in its central part or, in case of big (>5 cm) masses, in the place of maximal radiotracer uptake.

The number of counts per volume unit was determined for each ROI (liv, heart and HEM) in each patient.

Subsequently, a quotient of counts per volume unit (HEM divided by liv) was calculated for each lesion (further abbreviated as "HEM/liv"), HEM/ heart quotients were calculated in a similar manner.

CT images were assessed together with the scintigraphic data. Elliptical ROIs were created for each lesion and for the liver in each patient. Mean radiological density (Hounsfield units) was measured within each ROI and the difference between the radiological density of the liver and each lesion was determined ("liv-HEM").

Scintigraphy and SPECT/CT with Tc-99m-MBrIDA, an iminodiacetic acid (IDA) derivative, was additionally performed in one patient due to diagnostic doubts

Results

Thirty-four masses fulfilled the inclusion criteria and were processed in the course of further (quantitative) analysis.

Based on the calculated quotients and review of accessible medical documentation, two types of lesions were identified in our group (Table 1): typical hemangioma lesions (THL) and non-typical hemangioma lesions (NTHL).

Thirty-one lesions were classified into the first group (THL). The HEM/liv quotients ranged from 1.61 to 4.95. The liv-HEM differences ranged from 11 to 33 H.u. In this series: THLs were radiologically less dense than the surrounding liver tissue, and therefore could be easily delineated after proper adjustment of the image. In the majority of lesions, HEM/heart quotient (data not shown in Table 1)

Table 1. Lesions described qualitatively as typical or suspicious for hemangioma.

Number	Patient	Age	Gender	Location	Diameters [cm]	Liv-HEM [H.u.]	HEM/liv [cts/cts]
1	1	87	f	4a	1.5×2×1.5	20	2.18
2	1			4a	2×2×2	18	2.59
3	1			3	1.5×2×1.5	17	2.44
4	3	47	f	8	8×7.5×8	22	4.95
5	4	54	m	8	8×7×4	25	3.06
6	4			3/2	7×11x7	24	2.88
7	7	66	f	8	2×2×1.5	15	2.71
8	9	51	m	6 / 5	2×2×2	12	3.22
9	10	50	m	5	2.5×2.5×2.5	33	3.53
10	11	54	m	5 / 6	2×2×2.5	21	3.99
11	12	33	f	8	2×1.5×1.5	28	1.61
12	12			L (ped.)	6×7×6	33	1.98
13	13	56	f	2	3×3×3	24	2.20
14	14	51	m	3 / 4a	3.5×3.5×3	17	2.41
15	15	40	f	7 / 8	4×4×5.5	25	4.16
16	15			7 / 8	5×6.5×6.5	26	2.77
17	15			4a	3×3×2	21	1.87
18	17	44	f	2	2×2×2	11	2.03
19	17			7	2×2×2	13	2.00
20	17			7	2×2×2	12	2.27
21	19	60	m	6	6×4×5	18	2.74
22	19			3	3×2×2	11	1.87
23	20	29	f	6	2×2×1.5	23	1.73
24	22	47	f	Hilus	2.5×2.0×1.5	31	1.61
25	25	45	m	7	2.5×3×3	12	2.38
26	30	42	f	7	3.5×3×2.5	19	3.17
27	30			4a	3×2.5×2.5	20	3.03
28	30			2	2.5×2×2	18	2.30
29	31	50	f	4a	2×2×2	24	1.84
30	31			8	2×2×2	26	1.73
31	33	55	f	L (giant)	8×7×6	30	2.86
!1	32	36	F	6	8×7	8	1.46
!2	32			7	4×3	9	1.42
!3	6	64	m	4	About 4	10	1.21

Column "Number" – simple-numbered lesions – THL (see text), numbers with exclamation mark – NTHL. Column "Patient" – number of the patient. Columns "Age" and "Gender" – demographical data of the patients (m – male, f – female). Location: number of the segment, in which the lesion was found (abbreviations: L – left lobe; ped. – peduncled). Column "Diameters" – diameters of the lesions given in centimeters. Column "Liv-HEM [H.u.]" – liv-HEM expressed in Hounsfield units. Column "HEM/liv [cts/cts]" – HEM/liv quotients.

ranged from 0.48 to 0.92; however, in two lesions it was close to 1 (number 15: 0.99 and number 31: 1.01) and as high as 1.48 in one lesion (number 4). Multiple lesions (more than one lesion in one patient) showed diversity of their HEM/liv quotients, although a slight tendency for similar liv-HEM ratios could be observed.

From the THL-group, only one person died within the period of observation (patient 1, aged 88, stroke). The rest showed neither clinical nor radiological signs of deterioration, especially due to a tumor. In all of these patients (including the patient 1) result acquired with at least one of the two imaging techniques, US or CE-CT, was typical for hemangioma in all of the 5 CE-CT or (and) all of the 4 US features. There were no lesions, exhibiting less than 3 (of 5) features in CE-CT or less than 2 (of 4) features in US considered typical for hemangioma.

The NTHL group consisted of three lesions in two patients. One patient (number 6, male, aged 64) was referred for further assessment of three liver masses. Two of them could be found neither in non-contrast CT nor in SPECT. Detection of the third focus was relatively difficult in CT (liv-HEM=10), but possible in SPECT (HEM/liv=1.21). Subsequently performed CE-CT showed a vivid enhancement in the early arterial phase in all three foci. In US examination, they presented as heterogeneous, rather hyperechoic and ill-defined masses with calcifications. A control US showed progression lesion sizes. This patient died due to a metastatic disease of unknown origin.

The next patient (number 32, female, aged 36) was referred for assessment of two masses incidentally detected in US. Prior to our examination, we knew only locations of the lesions. Both presented as ill defined, slightly hypodense foci in non-contrast enhanced CT (liv-HEM values were 8 and 9). The SPECT study showed two foci of accumulation of labeled RBCs (HEM/liv were 1.46 and 1.42, respectively), locations of which corresponded to the US findings, but their diameters were smaller (compared to further acquired data). They were ill defined, heterogeneous, rather hypoechoic, with weak but preserved blood flow. In CE-CT study they both showed weak, homogenous (not peripheral) enhancement in an early phase. During four years of observation the patient presented with neither clinical nor radiological signs of deterioration. Because of the dubious findings, particularly the radiological-scintigraphic discrepancies, a scintigraphy with Tc-99m-MBrIDA was performed. It showed weak uptake of the tracer in both masses.

Discussion

Although some differences in management of benign liver masses were proposed, the most important issue is to differentiate them from malignant ones. Numerous scintigraphic techniques have been employed to solve the problem. Accumulation of radiolabeled colloids (specific for phagocyte cells) and IDA-derivatives (specific for hepatocytes) is considered indicative rather for benign tumors [11], but there are also reports on uptake of IDA by cancers (HCC) [12]. A standard F-18-fluoro-deoxyglucose (FDG) tumor marker, which is useful for diagnostics of many malignancies including lung cancer [13], was reported not to accumulate in hemangiomas [14], although a pathological entity known as "sclerosing hemangioma" can be FDG-avid [15,16]. Moreover, FDG was shown not to be sensitive in HCC [17], especially in well-differentiated cases, but can be helpful, if compared to the uptake of C-11-acetate [18] or C-11-choline [19]. Radiolabeled somatostatin analogs are highly sensitive and specific for liver metastases of neuroendocrine tumors [20], which are, however, relatively rare. Occasionally, liver foci can unexpectedly take up other tracers, as bone seekers [21].

Scintigraphy with Tc-99m-RBC is widely accepted as a sensitive and specific method of detection of liver hemangiomas [1–4,6,22,23]. SPECT and, especially, SPECT/CT improved the sensitivity particularly for smaller lesions and those with location unfavorable for planar imaging, i.e., close to heart, kidney and large vessels.

A precise determination of the value of SPECT/CT with Tc-99m-RBC is difficult. The majority of studies, especially those with a higher number of lesions, involve comparison to other imaging techniques, even though their accuracy is also limited. Histological verification, an invasive and potentially risky procedure, may not be suggested in each clinically healthy subject with only a liver lesion, which is most likely associated with little or no risk. Therefore, no lesion in our study underwent a biopsy.

False negative results of the study are rare, although even a histologically proven case of a giant hemangioma with preserved perfusion in an early phase and absent RBC accumulation in delayed phase is known [24]. In such case, the patient could be subjected to further diagnostics and/or surgery of a potentially harmless lesion. It was proposed that thrombosis could occasionally occur in hemangiomas [25,26] and thereby diminish the uptake of labeled RBC.

On the other hand, numerous false-positive cases have been reported. They include benign masses such as adenoma [27] and malignant tumors such as hemangiosarcoma [26], hepatocellular carcinoma (HCC) [28,29], metastases of colon carcinoma [30,31] and small-cell lung carcinoma [32]. It must be emphasized, however, that no quantitative analysis was performed in any of these cases. Positive predictive value of the examination for hemangioma is accepted to be above 90%, reaching 98% in some studies [3]. It means that as much as a few percent of RBC-positive foci can be wrongly interpreted as hemangiomas, although they might require an urgent therapy. Thus, it seems necessary to identify such false-positive cases.

Both masses found in patient 32 (numbered !1 and !2) were primarily diagnosed as "probably hemangiomas" (CE-CT and detailed US results were not known to us). The comparisons with further radiological data as well as the quantitative analysis performed 4 years after the examination revealed the unexpected results. The criterion of time (no clinical signs of a disease, lack of progression in US) allows for excluding a malignancy with the highest probability. Although literature data regarding scintigraphy with IDA-derivatives in hemangiomas is scarce, typical hemangiomas – actually a combination of endothelium, blood and connective tissue – are not expected to accumulate them. The

etiology of both lesions remains unclear. On the basis of the findings, hepatic adenomas, teleangiectatic focal nodular hyperplasia (FNH) or smaller haemangiomas included in or mixed with other lesions can be considered.

The other NTHL (numbered !3, HEM/liv=1.21) was assumed to be a metastatic lesion on the basis of its distinct morphology, progression, and the diagnosis of a disseminated malignancy with fatal clinical outcome.

It is assumed that clinical observation justifies certain exclusion of malignancy in each THL (even in the patient 1). Radiological features, which are less sensitive and specific than scintigraphic ones as mentioned above, cannot be considered conclusive *per se*. However, each THL shared either all 4 US features and at least 3 (of 5) CE-CT-features or at least 2 US and all 5 CE-CT features considered typical for hemangioma. The NTHL significantly differed from the "typical" pattern. These qualitative radiological features, although somewhat prone to subjective interpretation, were described by radiologists working independently from us. It can be also noted that the liv-HEM differences are smaller for NTHL than for THL. Although this difference (in non-contrast enhanced CT) is not a widely accepted criterion in the differential diagnosis of liver masses and moreover, it was measured by us, it seems less prone to bias, since it can be measured and expressed as a number. Taken together, the THL group differed from NTHL not only due to higher HEM/liv ratios, but also due to their radiological appearance and clinical behavior. Positive predictive value of SPECT/CT with Tc-99m-RBC for hepatic hemangioma appeared to be 0.912 (31/34) in our series.

On the basis of the findings, estimation of a cutoff-value for the lesions could be attempted. All three non-hemangiomas, which were found to be hemangioma-like in qualitative assessment (NTHL), had HEM/liv ratios of 1.46 or less. On the other hand, all 31 masses assumed to be hemangiomas (THL), had HEM/liv ratios of 1.61 or more. It can be further noted that the THLs with the lowest HEM/liv ratios were also smallest in diameter (lesions no.: 11, 24, 23, 30 and 29), which were comparable to the diameters of the ROI. Hence, an appropriate correction for partial volume effect would even increase the values of HEM/liv for the smallest lesions in the THL-group. Since the correction is one of the most challenging and controversial issues in quantitative nuclear medicine [7], we did not perform it. In the bigger lesions from the THL-group (other than 11, 24, 23, 30 and 29), the HEM/liv ratios reached values of 1.87 or more.

Calculated HEM/heart quotients gave no additional diagnostic information regarding the masses. However, in lesions 15 and 31 HEM/heart was close to 1, which might suggest that they were composed of blood only. In the lesion number 4, the quotient was as high as 1.48, indicating that the (average) concentration of erythrocytes within the lesion was higher than in blood. This result supports the proposed model of RBC sedimentation in some hemangiomas, as suggested on the basis of MRI studies [4] – so called "hemangioma with fluid-fluid level".

Conclusions

The quantitative analysis in SPECT/CT can be proposed as a tool, which might potentially give additional information for differential diagnosis of liver masses. The HEM/liv ratio higher than 1.8 or 1.6 (depending on diameters of the lesion and the ROI) was found indicative for hemangioma. Our observations demonstrate that hemangioma should be considered unlikely and further verification should be strongly recommended if this ratio is lower than 1.5. These preliminary results need further studies with a higher number of lesions.

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