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CHARACTERIZATION OF CONGENITAL VASCULAR MALFORMATION IN THE EXTREMITIES USING WHOLE BODY BLOOD POOL SCINTIGRAPHY AND LYMPHSCINTIGRAPHY

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ABSTRACT

The purpose of this study was to investigate the clinical usefulness of combined whole body blood pool scintigraphy (WBBPS) and lymphscintigraphy (LS) in the characterization of patients with congenital vascular malformations (CVMs) of the extremities. Subjects included 134 patients who underwent Tc-99m RBC WBBPS and Tc-99m filtered tin colloid (or antimony sulfur colloid) LS on initial diagnosis. Scintigraphic results were interpreted as arteriovenous malformations (AVMs), venolymphatic malformations (VLMs), lymphatic malformations (LMs), and venous malformations (VMs). Final diagnosis of the type of vascular malformation was determined by physical examination, magnetic resonance imaging (MRI), angiography, duplex ultrasonography, and/or biopsy results. The final diagnosis demonstrated that 14 of the study subjects had an AVM, 29 had a HLM, 20 had a LM, and 71 had a VM. The sensitivity of WBBPS and LS in the characterization of CVM was 85.7% (12/14) for AVMs, 96.6% (28/29) for VLMs, 95.0% (19/20) for LMs, and 88.7% (63/71) for VMs. The specificity was 100% for AVMs (120/120), 91.4% for VLMs (96/105), 99.1% for LMs (113/114), and 98.4% for VMs (62/63). The overall accuracy of WBBPS and LS was 91.0% (122/134). Our results show that combination of WBBPS with LS can characterize extremity CVMs in patients with high diagnostic accuracy, and may thus be useful for making optimal treatment decisions.

Keywords: whole body blood pool scintigraphy, Tc-99m red blood cells, lymphscintigraphy, congenital vascular malformation

Congenital vascular malformations (CVMs) are known as one of the most difficult and confusing diagnostic and therapeutic enigmas in the practice of medicine. The clinical presentations of CVMs are extremely variable, ranging from an asymptomatic birthmark to a life-threatening condition. These extremely variable findings have been a major challenge, even to the most experienced clinicians (1,2). Since the treatment plan and prognosis of CVMs depend on the type, extent, and location of the CVM, along with clinical features, accurate classification and characterization are important (3).

Currently, the most widely adopted classification of CVMs, proposed by the International Society for the Study of Vascular Anomalies, includes venous

malformations (VMs), arteriovenous malformations (AVMs), lymphatic malformations (LMs), and combined malformations (4). This classification scheme is useful for managing patients and provides a framework for the study of these lesions (5,6). A thorough physical exam is the first step in the diagnosis of a CVM. Although it provides useful information, it is not sufficient for characterizing vascular lesions. Various imaging modalities have been used for the diagnosis and classification of CVMs. Even though traditional angiography, such as arteriography and phlebography, remain as gold standards to determine the type of CVMs, because of the invasiveness of angiography, many non-invasive diagnostic modalities have been developed which have yielded critical contributions in determining the types of CVMs (2). Magnetic resonance imaging (MRI) has been shown to have an outstanding ability not only to delineate the extent of CVM lesion involvement with many crucial adjacent structures, but also to differentiate the low- (non-AVM) and high-flow (AVM) status of CVM lesions. However, MRI has limitations, such as the difficult differential diagnosis of LMs from VMs, and the high cost, even though its accuracy remains the gold standard for CVM management after angiography (7). Color-coded duplex ultrasonography (US) is a simple, non-invasive tool that is widely used to examine superficial vascular lesions, but it is limited in the assessment of deep lesions and lesions adjacent to interfering air or bone (8). Color-coded duplex US also has a limited ability to assess the overall quantitative status of a CVM lesion, especially during embolo/sclerotherapy, even though it gives excellent information on local hemodynamic status (7). Direct puncture venography is useful for the diagnosis of VMs by confirming lymphatic fluid leaks; however, due to its relative invasiveness, direct puncture venography is used as a part of percutaneous sclerotherapy rather than as a diagnostic procedure (9). Therefore, new, non-invasive imaging modalities are needed to better characterize CVMs.

Whole body blood pool scintigraphy (WBBPS) using Tc-99m red blood cells (RBC) was first adopted as an ancillary modality to reinforce color-coded duplex US and direct puncture venography and is based on earlier experiences at the Santa Corona Hospital in Milan, Italy (R. Mattassi, personal communication). Since then, WBBPS has been shown to be one of the most practical, non-invasive tests for the diagnosis of CVMs (7). Lymphoscintigraphy (LS) is a non-invasive, useful modality for diagnosing lymphedema and for assessing post-therapeutic results (10-12). LS has largely replaced the more invasive and technically difficult technique of lymphangiography (11,13).

The purpose of this study was to determine whether combined WBBPS and LS is feasible for the characterization and differential diagnosis of CVMs in the extremities.

MATERIALS AND METHODS

Subjects

The study subjects included 134 patients (70 males and 64 females) who underwent evaluation at our hospital between December 5, 2001, and December 31, 2007, for suspected CVMs in the extremities. The subjects underwent the following studies within a 4 week interval: MRI, duplex US, WBBPS, and LS. The mean age was 19.9 years (range, 4 months to 57 years). If clinically indicated, additional studies, such as angiography (n = 60), direct puncture venography (n = 33), and biopsy (n = 17), were performed.

WBBPS and LS

For WBBPS, a dual head gamma camera (Biad®; Trionix Research Laboratory, Twinsburg, OH, USA) was used. Labeling of erythrocytes for WBBPS was performed using the modified *in vitro* RBC labeling method (14), which consisted of intravenously injecting stannous medronate 15 minutes before withdrawing 5 ml of the patient's

TABLE 1
Interpretation Criteria of WBBPS and LS According to the Type of CVM

Type	WBBPS	LS
AVM	(++)	(-)
HLM	(+)	(+)
LM	(-)	(+)
VM	(+)	(-)

(++) = positive scan result in the lesion and draining vein; (+) = positive scan result; (-) = negative scan result

blood in a syringe containing anticoagulant (ACD-A) and labeling erythrocytes with 740-1,110 MBq of Tc-99m. The radiolabeled RBCs (the lowest labeling efficiency was > 90%) were then re-injected into the patient. Whole body imaging was performed at least 10 minutes after re-injecting the radiolabeled RBCs (7).

Lymphoscintigraphy was performed using the same dual-headed gamma camera as used for WBBPS. Anterior and posterior images of both extremities were acquired 2 hours after injecting 148 MBq (37 MBq in each of 4 injection sites) Tc-99m tin colloid filtered through a 200 m syringe filter (n = 104) or Tc-99m antimony sulfur colloid (n = 30) was injected subcutaneously into the interdigital spaces of both hands or both feet. To improve the transport of the radiopharmaceutical, a hand-grip exercise (using a rubber ball) or a walking exercise was performed for 45 min immediately following the radiopharmaceutical injection.

The scintigraphic results were interpreted by consensus of two nuclear medicine physicians, who were blinded to the results of the other diagnostic studies. The diagnostic criteria were as follows: AVM, abnormal increased blood pooling in the lesion and proximal draining veins on WBBPS with a normal LS; HLM, abnormal increased blood pooling on WBBPS and abnormal findings (presence of dermal backflow, increased uptake on the lesion, or decreased axillary/ilioinguinal lymph node uptake) on LS; LM, normal WBBPS and abnormal LS; and VM, abnormal WBBPS and normal LS (*Table 1*).

The final diagnosis of CVM was determined by physical examination, MRI, angiography, duplex US, or biopsy results. The combined results of WBBPS and LS were compared with the final diagnosis.

RESULTS

VM was the most common type of CVM, which was diagnosed in 71 patients (53.0%). The remaining 14 patients (10.5%) were diagnosed with AVMs, 29 patients (21.6%) had VLMs, and 20 patients (14.9%) had LMs. The locations of CVMs were in the lower extremities in 115 patients (85.8%) and the upper extremities in 19 patients (14.2%). *Figures 1-4* demonstrate examples of WBBBPS and LS images, representing AVMs, VLMs, LMs, and VMs, respectively.

The sensitivity of combined WBBPS and LS for characterizing CVMs was 85.7% (12/14) for AVMs, 96.6% (28/29) for VLMs, 95.0% (19/20) for LMs, and 88.7% (63/71) for VMs. The specificity of combined WBBPS and LS for characterizing CVMs was 100% (120/120) for AVMs, 91.4% (96/105) for VLMs, 99.1% (113/114) for LMs, and 98.4% (62/63) for VMs. The overall accuracy of WBBPS and LS for classification of CVMs was 91.0% (122/134). In addition, in 5 patients (3.7%) with VMs, WBBPS revealed additional clinically-unsuspected VM lesions, which were verified by additional imaging methods (*Fig. 5*).

The characterization of CVMs using combined WBBPS and LS was incorrect in 12 patients (VMs in 8, AVMs in 2, VLMs in 1, and LM in 1), which resulted from the findings of LS in 11 patients, and both LS and WBBPS in 1 patient. In 9 patients with

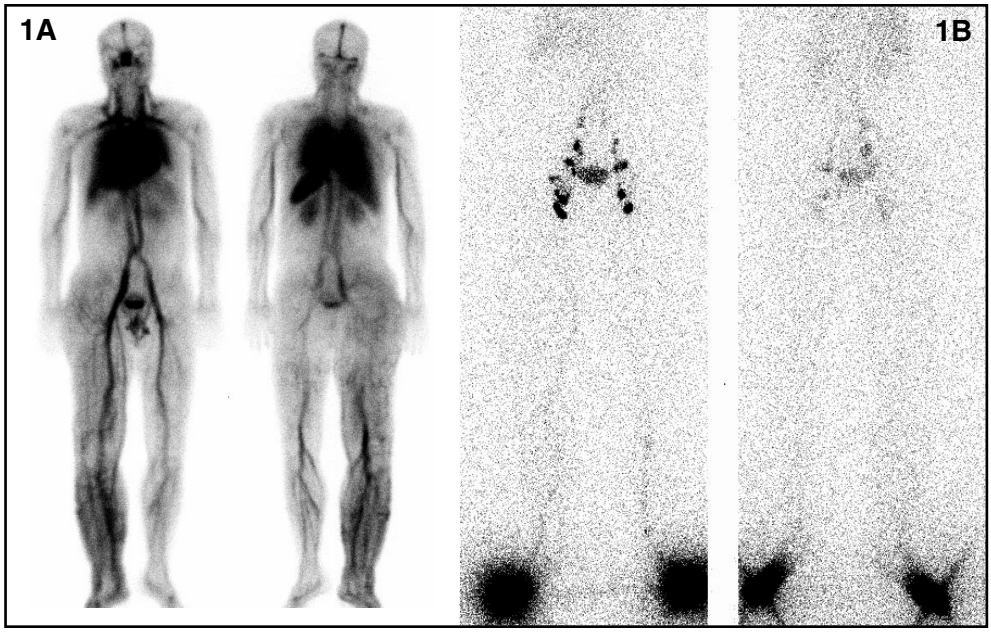

Fig. 1. WBBPS (A) and LS (B) of a 45-year old male patient. There are abnormal blood pooling lesions in the right lower extremity and increased blood pooling in the right femoral and ilioinguinal draining veins on WBBPS. LS shows no abnormal findings. These findings indicate an AVM.

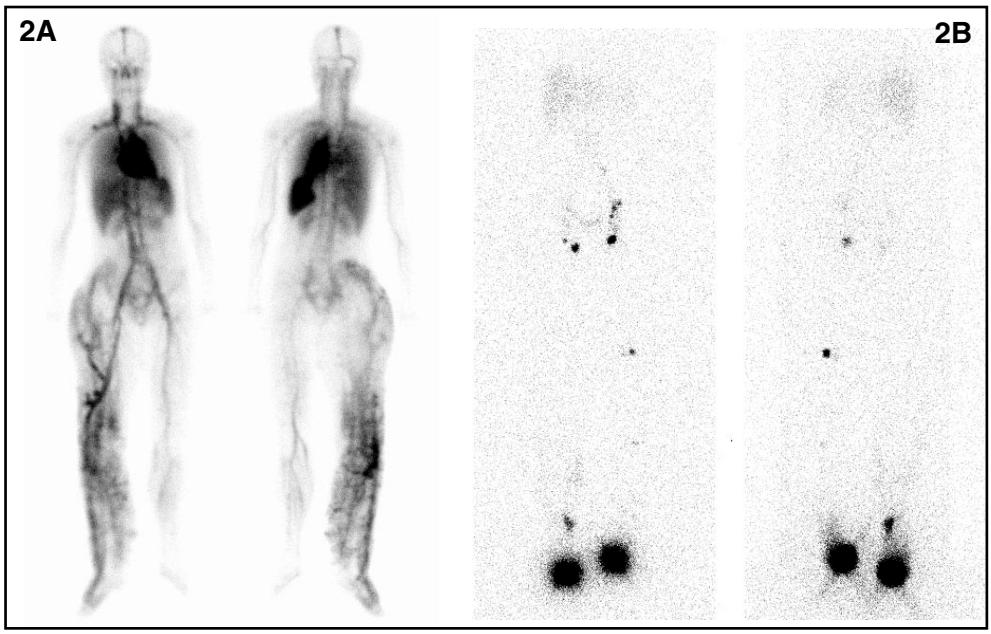

Fig. 2. WBBPS (A) and LS (B) of a 27-year old female patient. There are abnormal blood pooling lesions in the right lower extremity without increased blood pooling in the right ilioinguinal draining veins on WBBPS. LS shows localized radio-retention in the right ankle area and decreased right ilioinguinal lymph node uptake. These findings indicate a VLM.

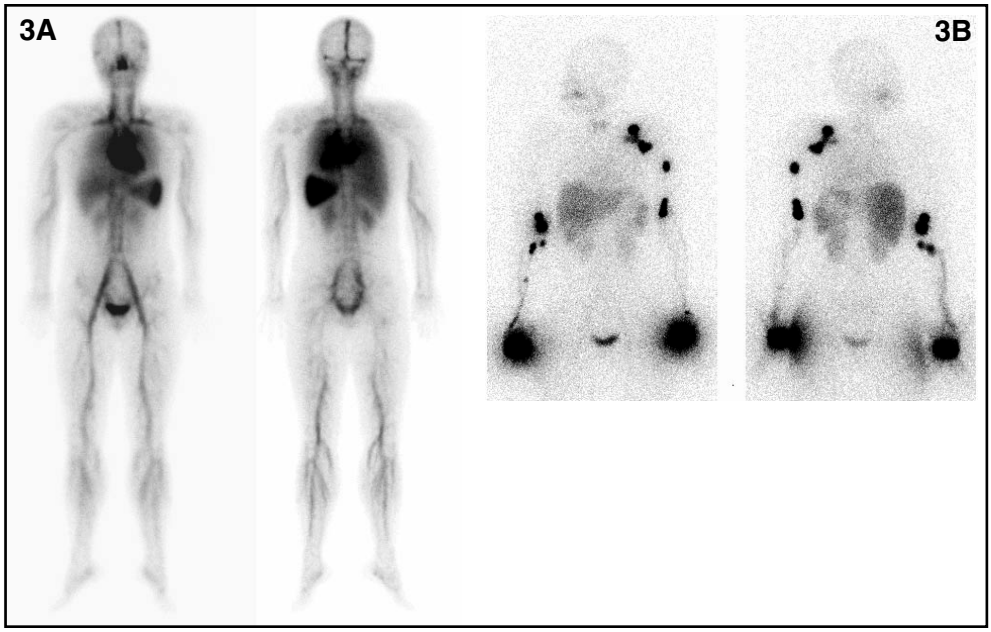

Fig. 3. WBBPS (A) and LS (B) of a 15-year old female patient. There is radioactive retention in the lymphatic vessels and nodes of the right forearm and non-visualization of the right axillary lymph nodes on LS. WBBPS shows no significant abnormal findings. These findings indicate a LM.

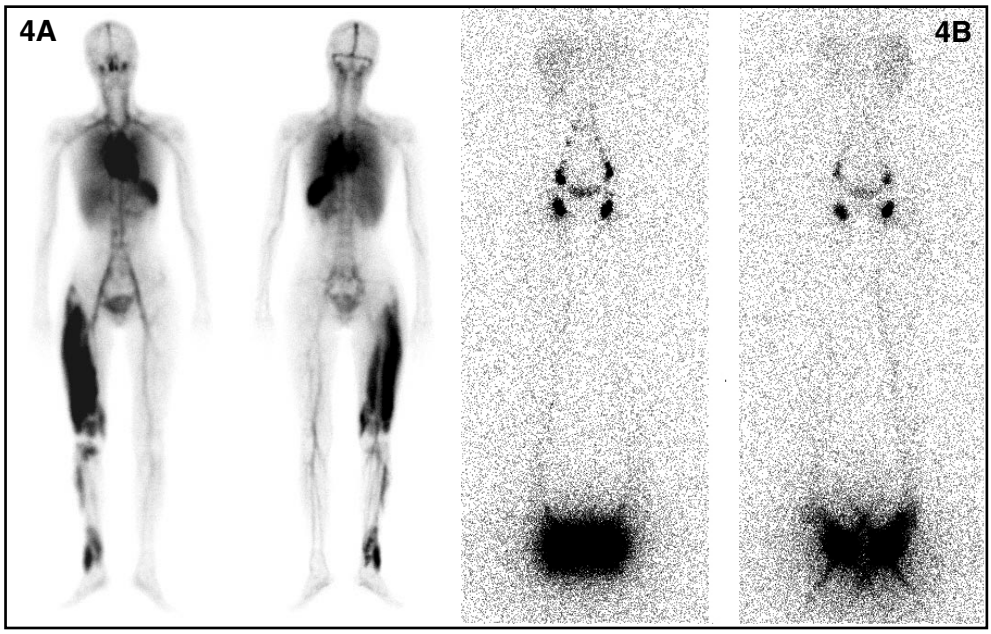

Fig. 4. WBBPS (A) and LS (B) of a 14-year old female patient. Heterogenously increased blood pooling in the right thigh and lower leg were noted on the WBBPS. Lymphoscintigraphy was within normal limits. These findings indicate a VM.

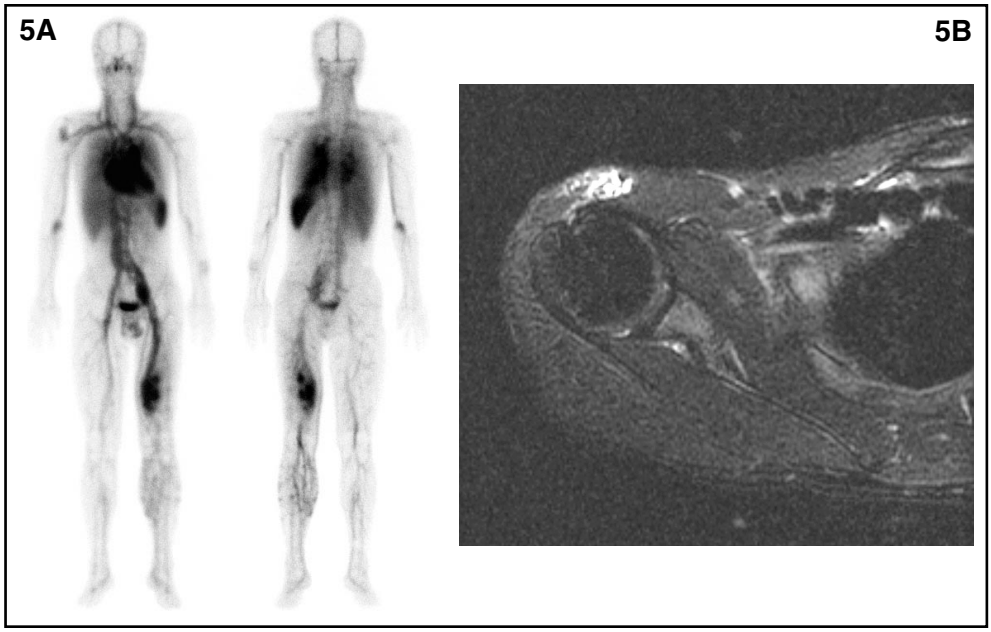

Fig. 5. (A) WBBPS of a 27-year old male patient with a suspected CVM in the left thigh shows additional abnormal blood pooling in the right shoulder and arm along with left thigh and pelvic area blood pooling lesions. (B) MR T2-weighted transverse image performed after WBBPS confirmed an additional low flow-type VM in the right shoulder.

VMs or AVMs, LS showed decreased lymph node uptake without dermal backflow or radio-uptake in the lesions. In 2 patients with VLMs or LMs, LS showed no abnormal findings since the lesions were superficially located. Both WBBPS and LS were normal in a 1-year-old patient with a VM. Due to the young age, the *in vivo* RBC labeling method was used instead of the *in vitro* method, and a walking exercise for LS could not be performed.

DISCUSSION

The identification of the predominant form of CVMs (i.e., VMs or AVMs) is essential for the proper management of each of these different hemodynamic abnormalities and reflects characteristics of the particular embryogenesis (7). WBBPS has proven to be one of the most practical non-invasive tests in the diagnosis of CVMs. When combined with other non-invasive tests, WBBPS has the ability to confirm CVM lesions by positively identifying abnormal blood pools throughout the body. In our previous study, WBBPS identified VM lesions with a sensitivity of 93.8% and a positive predictive value of 98.4%, and corresponding AVM lesions values of 92.3% and 92.3%, respectively (7). However, WBBPS had a limited role in the diagnosis of LMs. LS was introduced by Sherman and Ter-Pogossian in 1953 (15), and it now has been advocated as a non-invasive, useful modality for diagnosing lymphedema and for assessing post-therapeutic results (10,16). LS has largely replaced the more invasive and technically difficult technique of lymphangiography (13). The clinical application of LS includes the differential diagnosis of extremity edema, assessment of results of therapeutic interventions, prediction of outcome of lymphedema therapy, and assessment of the risk of developing lymphedema (11).

Our results suggest that combination WBBPS and LS can characterize the forms of

CVMs with high accuracy (91.0%). The sensitivity and specificity of combination WBBPS and LS was high, irrespective of the type of CVM. In 3.7% of the patients, WBBPS revealed additional clinically-unsuspected VM lesions, which supports the advantage of whole body imaging. Therefore, combined WBBPS and LS should be regarded as routine diagnostic modalities for evaluating CVM.

The characterization of CVM using combined WBBPS and LS was incorrect in 12 patients. There are several known findings suggestive of LMs, such as non-visualization of lymphatic vessels on the involved side, no or barely detectable lymph nodes, dermal backflow, cross-over filling of retroperitoneal nodes secondary to proximal obstruction, and collateral lymphatic circulation (17). In 9 patients with VMs or AVMs, LS showed decreased lymph node uptake without dermal backflow or radio-uptake in the lesions, suggesting decreased lymph node uptake without dermal backflow or radio-uptake in the lesions is a secondary change in lymphatic flow according to other CVMs, rather than a direct sign of LMs. Our results suggest the presence of dermal backflow or radio-uptake in the lesions may be the best diagnostic criteria for LMs (16). LS showed no abnormal findings in 2 patients with VLMs or LMs. Small size and superficial location may contribute to the false negative results of LS. Both the WBBPS and LS were normal in a 1-year-old patient with a VM. Low labeling efficiency by the *in vivo* RBC labeling method and a lack of walking exercise may have resulted in false negative findings on WBBSP and LS.

Our study was limited given that only patients undergoing MRI, duplex US, WBBPS, and LS were included based on clinicians' decisions and the retrospective design; this may have resulted in selection bias.

In conclusion, combined WBBPS and LS are useful in characterizing CVMs of extremities with high diagnostic accuracy. Therefore, combined WBBPS and LS are suitable routine diagnostic modalities for evaluation and therapeutic planning of CVMs. A prospective study would be of value to substantiate our findings.

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REFERENCES

1. Mulliken, JB: Cutaneous vascular anomalies. Semin. Vasc. Surg. 6 (1993), 204-218.
2. Rutherford, RB: Congenital vascular malformations: diagnostic evaluation. Semin. Vasc. Surg. 6 (1993), 225-232.
3. Lee, BB: Critical issues in management of congenital vascular malformation. Ann. Vasc. Surg. 18 (2004), 380-392.
4. Mulliken, JB, J Glowacki: Hemangiomas and vascular malformations in infants and children: A classification based on endothelial characteristics. Plast. Reconstr. Surg. 69 (1982), 412-422.
5. Enjolras, O, JB Mulliken: Vascular tumors and vascular malformations (new issues). Adv. Dermatol. 13 (1997), 375- 423.
6. Garzon, MC, JT Huang, O Enjolras, et al: Vascular malformations: Part I. J. Am. Acad. Dermatol. 56 (2007), 353-370.
7. Lee, BB, R Mattassi, BT Kim, et al: Contemporary diagnosis and management of venous and arterio-venous shunting malformation by whole body blood pool scintigraphy. Int. Angiol. 23 (2004), 355-367.
8. Hyodoh, H, M Hori, H Akiba, et al: Peripheral vascular malformations: imaging, treatment approaches, and therapeutic issues. Radiographics 25 Suppl 1 (2005), S159- 171.
9. Lee, BB, DI Kim, S Huh, et al: New experiences with absolute ethanol sclerotherapy in the management of a complex form of congenital venous malformation. J. Vasc. Surg. 33 (2001), 764-772.
10. Hwang, JH, JY Choi, JY Lee, et al: Lymphscintigraphy predicts response to complex physical therapy in patients with early stage extremity lymphedema. Lymphology 40 (2007), 172-176.
11. Szuba, A, WS Shin, HW Strauss, et al: The third circulation: radionuclide lymphoscintigraphy in the evaluation of lymphedema. J. Nucl. Med. 44 (2003), 43-57.

12. Weiss, M, RG Baumeister, K Hahn: Dynamic lymph flow imaging in patients with oedema of the lower limb for evaluation of the functional outcome after autologous lymph vessel transplantation: an 8-year follow-up study. Eur. J. Nucl. Med. Mol. Imaging 30 (2003), 202-206.
13. Weissleder, H, R Weissleder: Lymphedema: evaluation of qualitative and quantitative lymphoscintigraphy in 238 patients. Radiology 167 (1988), 729-735.
14. Bauer, R, I Haluszczynski, H Langhammer, et al: In vivo/in vitro labeling of red blood cells with 99mTc. Eur. J. Nucl. Med. 8 (1983), 218-222.
15. Sherman, AI, M Ter-Pogossian: Lymph-node concentration of radioactive colloidal gold following interstitial injection. Cancer 6 (1953), 1238-1240.
16. Hwang, JH, JY Kwon, KW Lee, et al: Changes in lymphatic function after complex physical therapy for lymphedema. Lymphology 32 (1999), 15-21.
17. Ter, SE, A Alavi, CK Kim, et al: Lymphoscintigraphy. A reliable test for the diagnosis of lymphedema. Clin. Nucl. Med. 18 (1993), 646-654.

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