The role of technetium-99m sulfur colloid bone marrow scintigraphy in diagnosis of diffuse pulmonary extramedullary hematopoesis secondary to myelofibrosis: experience of a tertiary hospital

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Abstract

**Objective:** To define the role of combined Tc-99m sulfur colloid bone marrow (SC BM) scintigraphy, single-photon emission computed tomography (SPECT/CT), and chest CT in diagnosing diffuse pulmonary extramedullary hematopoiesis (PEMH) in patients with myelofibrosis (MF).

**Methods:** We retrospectively reviewed Tc-99m SC BM scintigraphy scans performed at our institution for the diagnosis of diffuse PEMH, as well as accompanying chest CT and SPECT/CT imaging findings. Relevant clinical information, including respiratory manifestations, pulmonary hypertension (PH), and subjective response to whole-lung radiation therapy, was also summarized.

**Results:** Twenty-two MF patients with 27 Tc-99m SC BM scintigraphy scans were diagnosed with diffuse PEMH. In 21 (95%) patients with accompanying chest CT and SPECT/CT scans, the most common CT findings were ground-glass opacity, interstitial infiltration, and pleural effusion. Of 20 patients (91%) who underwent 2-dimensional echocardiography studies, 12 (55%) were diagnosed with PH. All 12 patients exhibited the aforementioned nonspecific CT imaging findings with 8 (66%) of them presenting with respiratory symptoms, including dyspnea, shortness of breath, and cough. In the remaining 8 patients without PH, half had similar respiratory symptoms. Fourteen patients (64%) of this cohort received whole-lung radiation therapy, of whom 7 (50%) experienced symptom relief after therapy.

**Conclusions:** Nonspecific respiratory symptoms should raise concern for PH and diffuse PEMH in patients with advanced-stage MF. Combined Tc-99m SC BM scintigraphy and SPECT/CT is a promising noninvasive imaging tool to diagnose this rare clinical entity.
Introduction

Myelofibrosis (MF) is a chronic myeloproliferative bone marrow disease. It is characterized as a clonal disorder involving hematopoietic stem cells, which causes ineffective erythropoiesis and dysplastic megakaryocyte hyperplasia (1). There are two forms of MF: 1) primary MF, and 2) those secondary to polycythemia vera or essential thrombocytemia. In the clinical course of MF, as the bone marrow compartment becomes hyperfibrotic, extramedullary hematopoiesis (EMH) ensues. EMH is the formation and development of blood cells outside of the bone marrow, which is normal in fetal gestation but abnormal after birth. The most common sites of EMH are the liver and spleen, often resulting in hepatosplenomegaly. However, various other organs and tissues may also be involved, including the mediastinum, paravertebral regions, abdomen, pleural space, and lung, with associated site-specific symptoms and imaging manifestations (2).

In the thorax, EMH commonly occurs within the paravertebral regions and presents as a fatty, dense mass lesion on chest CT (3). Pulmonary EMH (PEMH) has also been sporadically described in the pleural space, pulmonary parenchyma, and even within the pulmonary artery (4,5). The diffuse pattern of PEMH is uncommon and typically diagnosed at autopsy because of its nonspecific clinical
manifestations (6-8). Clinically, diffuse PEMH usually presents with nonspecific respiratory symptoms and atypical CT imaging features (9-11). Sporadic case reports and small cohort studies suggest diffuse PEMH is casually associated with pulmonary hypertension (PH).

Technetium (Tc)-99m sulfur colloid bone marrow (SC BM) scintigraphy, a noninvasive nuclear medicine imaging modality, has been widely used for evaluation of bone marrow activity and diagnosis of EMH. This study reviews the findings of Tc-99m SC BM scintigraphy—in combination with chest computed tomography (CT) and single-photon emission computed tomography (SPECT)/CT—in MF patients diagnosed with diffuse PEMH at a major tertiary care hospital.

Methods

We retrospectively reviewed Tc-99m SC BM scintigraphy in MF patients performed at our institution from April 2009 to November 2016. Imaging findings from chest CT and accompanying SPECT/CT scans were also reviewed. Clinical charts were reviewed to obtain documented hemoglobin levels, clinical respiratory manifestations, 2-dimensional (2D) transthoracic echocardiography (ECHO) evidence of PH, and patients’ subjective responses to whole-lung
radiation therapy. This study was approved by our institutional review board and the requirement to obtain informed consent was waived.

**Tc-99m SC BM scintigraphic imaging protocol**: Tc-99m SC BM scintigraphy was performed at 2 nuclear medicine imaging laboratories at our institution. At site 1, an average dose of 370 MBq ±10% was administrated intravenously. Thirty minutes later, whole-body anterior and posterior planar images were simultaneously acquired with a dual-head camera. At site 2, an average of 555 MBq ± 10% was administrated intravenously. Whole-body anterior and posterior planar images were acquired simultaneously with a dual-head camera with a 30-60 minute delay. At both sites, a low-energy, high resolution collimator at 140 KeV with 20% window was applied for planar imaging. If there was suspicious uptake in the lung fields, static anterior and posterior planar images of the chest were performed with the liver and spleen shielded, with the option for SPECT/CT of the chest

**Diagnostic criteria**: A diagnosis of diffuse PEMH was made if the following criteria were met: EMH in the liver and spleen on Tc-99m SC BM scintigraphy planar images; diffusely increased tracer uptake in both lung fields, which is visually greater in intensity than blood pool; and no other abnormal focal
increased tracer uptake greater than blood pool seen in the thorax on combined SPECT-CT or chest CT images to indicate focal EMH involvement (Figure 1).

Based on above criteria, we identified 22 MF patients (out of 49 patients) with 27 Tc-99m SC BM scintigraphy scans. Two independent observers certified by the American Board of Radiology and American Board of Nuclear Medicine (M.Y. and M.C.R.) reviewed the Tc-99m SC BM scintigraphy images, chest CT images, and SPECT/CT images. Any differences in opinion were resolved by consensus.

Since no fine-needle aspiration or open lung biopsy was performed in this group of patients, confirmation of a diagnosis of diffuse PEMH was alternatively based on imaging findings of Tc-99m SC BM scintigraphy and clinical response to radiation therapy.

Results

The 22 patients diagnosed with diffuse PEMH, had an average age of 67 ± 2.8 years and a male-to-female ratio of 17:5. All 22 patients had advanced-stage MF for more than 3 years. The average hemoglobin level in this cohort of patients was 9.3 g/dL. Nine (41%) patients completed splenectomy.
CT Findings: Twenty-one (95%) patients had a diagnostic chest CT, and 3 of them (14%) had additional combined SPECT/CT performed. On the combined SPECT/CT and chest CT images, the most common chest findings were one or more areas of GGO (13 patients, 62%), interstitial infiltration (4 patients, 19%), pleural effusion (4 patients, 19%), and incomplete patchy atelectasis (2 patients, 9%). No patients showed evidence of focal EMH in the pleural space, paravertebral region, or any other region in the thorax.

Pulmonary hypertension: Twenty patients underwent transthoracic 2D Doppler ECHO studies. Twelve patients (55%) showed evidence of PH with systolic pressure greater than 25 mm Hg. Additional ancillary ECHO findings also consisted of various degrees of right ventricle dilation and/or tricuspid valve regurgitation. All 12 patients had chest CT images available, of which 9 (75%) exhibited GGO, 2 exhibited small pleural effusions, and 1 exhibited diffuse pulmonary infiltration (Figures 2 and 3). There were 8 patients (67%) without ECHO evidence of PH. Among them, 4 (50%) exhibited GGO on chest CT, 2 demonstrated infiltrative changes, 1 had no pulmonary abnormalities, and 1 had no accompanying chest CT scan. In 2 patients without ECHO studies, there was both pleural effusion and pulmonary infiltration on chest CT. The relationship between PH and CT findings is summarized in Table 1.
**Respiratory manifestations:** In 12 patients with ECHO evidence of PH, 8 (66%) presented with dyspnea, shortness of breath, and cough, while in 8 patients without ECHO evidence of PH, only 4 (50%) presented with a similar clinical manifestation. In 2 patients without 2D transthoracic ECHO, 1 patient (50%) had a cough. The distribution between PH and respiratory manifestations is summarized in Table 2.

**Whole-lung radiation therapy:** A total of 14 patients in this cohort (64%) underwent whole-lung, high-energy photon radiation beam therapy with the AP-PA technique up to a maximal dose of 100 cGy in a single fraction. Seven patients (50%) experienced subjective relief/improvement of respiratory discomfort following radiation therapy (Figure 3).

Interval development/progression of diffuse PEMH was identified in 4 of 22 patients (18%) with follow-up Tc-99m SC BM scintigraphy studies. One of these patients had decreased tracer uptake in the lung after radiation therapy and showed recurrence of bilateral diffuse PEMH on a follow-up scan (Figure 4).

At the end of the study period, 18 patients (83%) had died 3 to 36 months after diagnosis of diffuse PEMH, including 7 patients (39%) who received whole-lung radiation therapy during their clinical course.
Discussion

EMH refers to hematopoiesis taking place outside of the bone marrow compartment. It is a common complication in multiple hematologic diseases, including MF, sickle cell anemia, and thalassemia. It mainly occurs in the liver and spleen, which typically manifests as hepatosplenomegaly. However, EMH may also occur in various other organs or structures, which are categorized as non-hepatosplenic EMH (2), of which prior splenectomy may be an etiologic factor. The spleen plays an important role in the removal of displaced hematopoietic stem cells. If the spleen is resected, hematopoietic stem cells may deposit at other sites (2). In our cohort, 9 patients (41%) had prior splenectomy, which might support this theory. The clinical indications for scintigraphy imaging to evaluate EMH are 1) to determine the extent of EMH in the liver or spleen; 2) to evaluate for splenectomy; and 3) to differentiate between EMH and other processes for any suspicious mass-like lesions outside of the liver and spleen (12).

Tc-99m SC BM scintigraphy is a well-accepted, noninvasive nuclear medicine imaging modality to evaluate bone marrow activity by targeting the reticuloendothelial system (RES) which consists of macrophages located mainly in the liver, spleen and bone marrow. After intravenous injection, radiolabeled
colloids are phagocytosed by macrophages throughout the RES. Because RES and erythropoietic tissues coexist in the bone marrow, the in vivo Tc-99m SC distribution is an indicator of erythropoietic activity (13,14). SPECT/CT images from 3 patients in our study provided additional value by confirming the absence of focal increased uptake in the pleural space and paraspinal regions (Figure 2), thereby confirming the diagnosis of diffuse PEMH.

Our study also shows that common CT features of diffuse PEMH include nonspecific diffuse GGO, pulmonary nodules, and/or interstitial thickening, which supports findings of prior studies (2,6,15). A GGO is a nonspecific finding and may be present in heart failure, infection, chronic interstitial disease, and acute alveolar disease. However, in the clinical setting of MF, a GGO should raise suspicion for diffuse PEMH, thromboembolism, or chemotherapy-induced lung toxicity (16).

The most frequent clinical complaint in PEMH is dyspnea (17,18), which might be caused by confounding chronic anemia, hypoxemia, hepatosplenomegaly, and/or PH. Other less common etiologies for PEMH may also exist, including liver and bone marrow transplant, hepatic veno-occlusive
disease, liver cirrhosis, and/or liver metastasis \((16, 19)\). None of these less common etiologies for PEMH were identified in our cohort of patients.

The association between PH and MF has been described in case reports and a small number of cohort studies \((20-23)\). PH is defined as elevated systolic pulmonary pressure greater than 30 mm Hg. The exact etiology of PH in MF is unclear and might be multifactorial \((24)\). There are two major forms of PH described in patients with a myeloproliferative disorder: PH secondary to chronic thromboembolism and precapillary PH with the most frequent clinical manifestations as dyspnea, chest pain, and syncope \((25)\). The noninvasive 2D Doppler ECHO should be recommended to evaluate PH, RV dilation, and cardiac valvular disease in MF patients with the aforementioned clinical manifestations.

Under microscopy, there is accumulation of monocytes, megakaryocytes, and erythroblasts, with associated obliteration of lymphatic flow in specimens of PEMH \((26)\). These microscopic findings are typical for myeloid metaplasia, which is sometimes used as an interchangeable term to describe the pathologic process of PEMH.

Hematopoietic tissues are extremely radiosensitive. Hence, the consensus treatment of diffuse PEMH is whole-lung, high-energy, low-dose radiation therapy
(100 cGy at AP and PA projection) (27,28), which is usually curative without concern for radiation-induced myelotoxicity. In our cohort, half of treated cases (7/14) reported relief/improvement of clinical symptoms following radiotherapy.

Our study has several limitations. First, no lung biopsies were performed in this cohort of patients to provide pathologic confirmation of PEMH out of concern for a potential sampling error and risk of pulmonary hemorrhage, particularly in the setting of PH. However, based on our institutional experience, imaging with Tc-99m SC BM scintigraphy, SPECT/CT, and/or chest CT provides accurate noninvasive diagnosis of diffuse PEMH, and consequently favorable outcomes in the management of MF patients. Therefore, noninvasive imaging based diagnosis of PEMH is likely preferable to percutaneous fine-needle aspiration or open lung biopsy in this setting.

Second, the binary diagnosis of diffuse PEMH in this retrospective study depends on visual inspection of uptake intensity in the bilateral lung fields; a quantitative cutoff ratio of lung to blood pool is likely not necessary to confidently make this diagnosis on imaging. Additionally, it is not possible to perform a quantitative analysis on snapshot planar images on our retrospective review.
Future studies utilizing a quantitative cutoff ratio of lung to blood pool to diagnose PEMH could be of benefit.

Finally, among 14 patients who were treated with whole-lung radiation therapy, only 1 had follow-up Tc-99m SC BM scintigraphy demonstrating resolution of diffuse PEMH in both lung fields (Figure 4). Follow-up Tc-99m SC BM scintigraphy could potentially provide a non-invasive alternative to biopsy to confirm response to therapy, although such a practice cannot be supported given the single patient with both histopathologic and imaging follow-up.

Conclusion

Diffuse PEMH is a rare clinical entity, commonly seen in advanced-stage MF patients presenting with nonspecific respiratory presentations. We recommend Tc-99m SC BM scintigraphy with SPECT/CT as the noninvasive imaging modality of choice in the diagnosis of diffuse PEMH. In patients diagnosed with diffuse PEMH, prompt palliative whole-lung, low-dose radiation therapy should be initiated to alleviate respiratory symptoms and improve quality of life.
Figure 1. Tc-99m sulfur colloid bone marrow (SC BM) scintigraphy whole-body planar images of two secondary myelofibrosis (MF) patients (A & B). In the patient without diffuse PEMH (A), the intensity of tracer uptake in bilateral lung fields was
visually equivalent to that of the blood pool (arrows in A). In the patient with diffuse PEMH (B), there was diffusely increased tracer uptake in the bilateral lung fields, greater than that of the blood pool (arrows in B). Both patients exhibited EMH in the liver and spleen, as well as decreased bone marrow uptake in the central compartment of the skeleton.
Figure 2. Bilateral lung fields in a 72-year-old man with end-stage MF demonstrated diffuse, mildly increased radiotracer uptake on planar images compared to tracer uptake in the blood pool (arrows in A). Low-dose chest CT showed bilateral lung diffuse ground-glass opacities at the level of the lower lobes. A fused image at the same level showed diffusely increased radiotracer uptake, corresponding with findings on planar images on SPECT/CT of the chest (B & C). The patient died 5 months later, after receiving whole-lung radiation therapy.
Figure 3. Anterior (A) and posterior (B) thoracic static scintigraphy images with partially shielded liver in a 59-year-old woman with MF post splenectomy.
Diffusely increased tracer uptake was visualized in both lungs compared to the blood pool (arrows in A & B). On the representative chest CT image, there was diffuse smooth interstitial thickening (white arrows in C).
Figure 4. A 54-year-old female MF patient with diffuse PEMH. Pre-radiation therapy image showed diffusely increased radiotracer uptake in bilateral lung fields, greater than the blood pool (arrows in A). The patient underwent a splenectomy and whole-lung radiation therapy, with additional radiation to her
liver. Near-complete resolution of pulmonary tracer uptake visually equivalent to the blood pool was seen 2 months later (arrows in B), with accompanying substantial relief of respiratory discomfort. Eleven months later, increased tracer uptake of bilateral lung fields reappeared (arrows in C), greater than the blood pool, suggesting recurrent diffuse PEMH.
Table 1. Pulmonary hypertension versus CT findings

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Abbreviations: CT, computed tomography; PH, pulmonary hypertension.
Table 2. Pulmonary hypertension versus respiratory symptoms

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Abbreviations: PH, pulmonary hypertension; RS, respiratory symptoms.
Reference


