Case Report

Diagnostic Potential of 99mTc-macroaggregated Albumin Scintigraphy in the Diagnosis of Hepatopulmonary Syndrome: Insights from Two Case Studies and Critical Review of Literature

Abstract

Hepatopulmonary syndrome (HPS) is a rare pulmonary vascular complication of chronic liver disease characterized by dilatation of pulmonary capillaries leading to vascular shunting and systemic hypoxemia. Diagnosis of HPS requires documentation of intrapulmonary vasodilation (IPVD), the two most common imaging studies performed for the detection of IPVD include transthoracic contrast echocardiography (TTCE) and 99m-Tc-macroaggregated albumin scintigraphy (99mTc-MAA scan). TTCE has high sensitivity and thus, is the preferred initial investigation, while 99mTc-MAA scan is highly specific and plays an adjuvant role in diagnosis. 99mTc-MAA scan can, however, identify some cases of HPS not apparent on TTCE and can also quantify the shunt fraction. The current study describes the utility of 99mTc-MAA scan in the detection of IPVD in two suspected cases of HPS.

Keywords: *99m-Tc-macroaggregated albumin scintigraphy, hepatopulmonary syndrome, lung perfusion scintigraphy*

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Introduction

Hepatopulmonary syndrome (HPS) is a pulmonary manifestation of vascular complication of end-stage liver disease. Its prevalence varies from 4% to 47%; in chronic liver disease (CLD) patients, it is in fact the most common cause of respiratory insufficiency in patients with CLD. Its diagnosis is mainly clinical and is characterized by the triad of (i) liver disease or portal hypertension, (ii) an elevated age-adjusted alveolar-arterial oxygen gradient (AaPO2), and (iii) abnormalities of intrapulmonary vasculature.[1]

The imaging studies which can aid the diagnosis include chest X-ray, chest computed tomography (CT), coronary pulmonary angiography, transthoracic contrast echocardiography (TTCE), transoesophageal and intracardiac echocardiography, and 99m-Tc-macroaggregated albumin scintigraphy (99mTc-MAA scan).[2,3]

HPS has been associated with advanced disease and indicates a poor prognosis even with transplant, thus making the timely diagnosis of this entity important.[1] The only definitive treatment available for end-stage liver disease (ESLD) is liver transplant (LT). An expedited referral and evaluation for LT has been recommended as a standard treatment guideline for patients with ESLD and severe HPS. It is considered one of the standard exceptions in the model for end-stage liver disease (MELD) criteria for LT.[4] This study aims to comprehensively review the common clinical manifestation, diagnostic criteria, and role of nuclear medicine in the diagnosis of HPS with the description of two cases.

Case Reports

Case 1

A 54-year-old male, known case of alcohol-related CLD, presented with a history of exertional dyspnea. On evaluation, he was found to have SpO_2 of 89% and grade III clubbing. He was suspected to have HPS and thus contrast echocardiography was done, which was negative for HPS. However, due to high clinical suspicion for HPS, the patient was referred for 99mTc-MAA scan which was performed with 4.3 mCi (159 MBq) of 99m Tc-MAA. Whole body images [Figure 1] were acquired 20 min after intravenous (IV)

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injection of tracer, in anterior and posterior views. Images revealed anticipated tracer distribution in both the lungs, but significant, unexpected abnormal tracer localization is seen in the brain, bilateral kidneys, spleen, and in the liver, suggestive of intrapulmonary arteriovenous shunting. Semiquantitative values for quantification of shunt fraction in this case with HPS were:

- Whole body uptake: 61.7% (Normal-42.5%)
- Flow-adjusted brain uptake: 57% (Normal-5.7%).

Case 2

A 48-year-old male, a known case of alcohol-related CLD, presented with shortness of breath (New York Heart Association (NYHA) II/III). His resting SpO_2 was 93-94%. His alveolar-arterial oxygen gradient was 23 mmHg and partial pressure of oxygen was 80 mmHg. He underwent a bubble contrast echo which showed the appearance of bubbles in the 7th cardiac cycle, which is widely acknowledged as a significant indicator for diagnosis of HPS. These findings led to a suspicion of HPS and to confirm the same, the patient was referred for 99mTc-MAA scan that was performed with IV injection of 4.6 mCi (170 MBq) of 99mTc-MAA. Whole body images [Figure 2] were then acquired. Images revealed abnormal tracer localization in bilateral kidneys, brain, spleen, and liver, suggestive of intrapulmonary arteriovenous shunting, in addition to normal and uniform uptake in bilateral lungs. Estimated semi-quantitative shunt fraction and flow-adjusted MAA brain uptake was 6.01%.

Discussion

HPS has been considered an important complication involving pulmonary vasculature leading to systemic hypoxemia in patients with CLD and portal hypertension. Etiopathogenesis of HPS is not clearly understood, however, pulmonary vasodilation and venous shunting secondary to the presence of excess of vasodilators in circulation such as nitric oxide, hem oxygenase-derived CO, and tumor necrosis factor-alpha secondary to increased bacterial translocation and toxin release (i.e., intestinal endotoxemia), endothelial Nitric oxide synthase (NOS) activation and macrophage-activated inducible NOS have been implicated in literature. This intrapulmonary venous shunting leads to systemic hypoxemia, which is one of the defining features of HPS.[5]

The diagnosis of HPS primarily relies on clinical evaluation, and characteristic features of HPS encompass both the manifestations of the underlying liver disease and those associated with oxygenation impairment. The most common presenting feature is dyspnea, seen in almost 80% of symptomatic patients. Other features secondary to underlying CLD include fatigue, anorexia, ascites, splenomegaly, spider angioma, jaundice, palmar and plantar erythema, asterixis, anasarca, nail changes, oesophageal or gastric varices, clubbing, hypertrophic osteoarthropathy, caput medusae, gynecomastia, and testicular atrophy. Other clinical features secondary to intrapulmonary vascular dilatations include dyspnoea, platypnea, and hypoxemia.[6,7]

The diagnostic criteria for HPS were introduced by the European Respiratory Society Task Force in 2004 and include a triad of (i) CLD with or without portal hypertension, (ii) Partial pressure of oxygen <80 mmHg

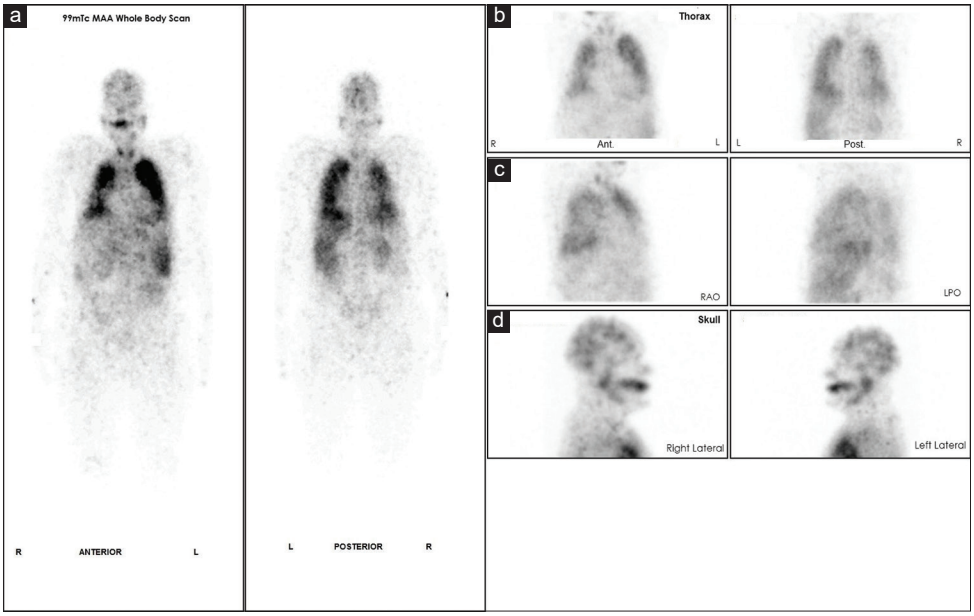

Figure 1: 99m-Tc-macroaggregated albumin lung perfusion scintigraphy planar images in 54-year-old male patient with alcohol-related end-stage liver disease, (a) Whole body, (b) Thorax, (c) Thoracic obliques, (d) Skull lateral views, showing abnormal tracer localization in brain, bilateral kidneys, spleen, and liver suggestive of significant intrapulmonary arteriovenous shunting. Quantification of shunt fraction were: Whole body uptake-61.7% and Flow adjusted brain uptake-57%. However, transthoracic contrast echocardiography was negative for hepatopulmonary syndrome in this patient

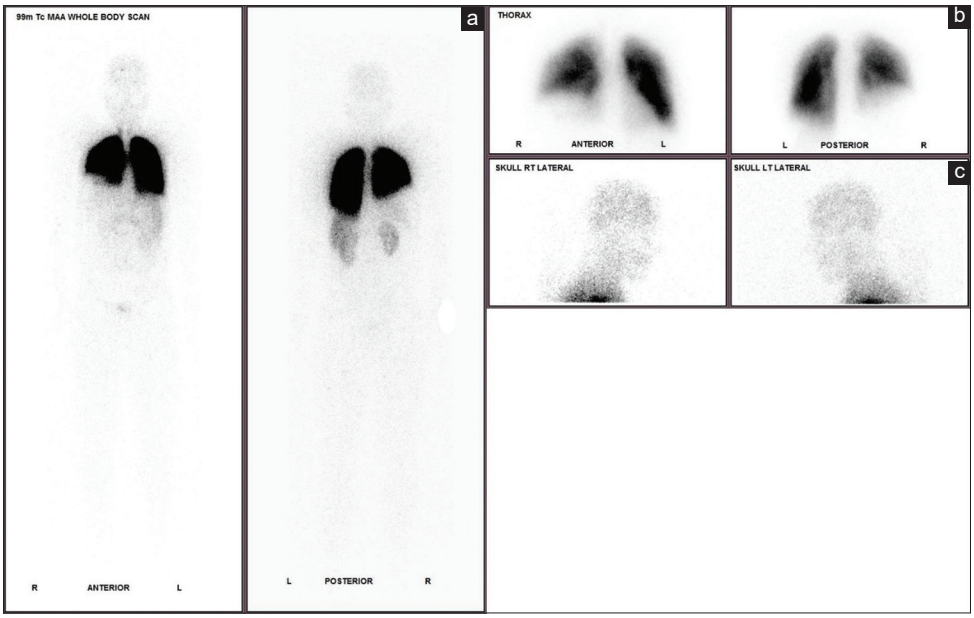

Figure 2: 99m-Tc-macroaggregated albumin lung perfusion scintigraphy images in a 48-year-old male with alcohol-related chronic liver disease. (a) Static whole body, (b) thoracic, (c) skull lateral views, showing abnormal tracer localization in bilateral kidneys, brain, spleen, and liver suggestive of intrapulmonary arteriovenous shunting. In this case estimated flow-adjusted brain uptake was 6.01%

or alveolar–arterial oxygen gradient [P (A-a) O2 gradient] ≥15 mmHg (or >20 mmHg for patients >65 years old) on ambient air, and (iii) Documented intrapulmonary vascular dilatation by contrast-enhanced echocardiography or lung perfusion scintigraphy.[1]

The prevalence of HPS varies from 4%–47% in patients of CLD, when present, it is associated with poor prognosis and decreased overall survival even with liver transplant, the prognosis being more dismal with increasing grade of hypoxemia.[1]

The grading system for HPS is based on oxygen partial pressure in the presence of alveolar–arterial oxygen gradient ≥15 mmHg and includes the following categories: (i) Mild-partial pressure of oxygen ≥80 mmHg, (ii) Moderate-partial pressure of oxygen ≥60 mmHg to <80 mmHg, (iii) Severe-partial pressure of oxygen ≥50 mmHg to <60 mmHg, and (iv) Very severe-partial pressure of oxygen <50 mmHg.[8]

The imaging test is generally required for documentation of intrapulmonary vasodilation (IPVD) and helps to rule out other causes of symptomatology. The imaging studies used for the demonstration of intrapulmonary vascular dilatations include TTCE, transesophageal and intracardiac echocardiography, 99mTc-MAA scan, and contrast pulmonary angiography.[2,3] Apart from the imaging studies, 100% oxygen method has been shown to demonstrate the shunting and shunt fraction, however, results are prone to errors and not commonly used.[5,8]

The two most common and well-accepted approaches used for assessing intrapulmonary vascular dilatation include TTCE and 99mTc-MAA scan.[5]

Trans thoracic contrast echocardiography aka "bubble study"

This involves the production of microbubbles of size >10 μm in size by agitating normal saline vigorously. Which is then administered intravenously in a peripheral vein while performing four-chamber transthoracic echocardiography. These microbubbles normally get trapped in the pulmonary circulation as the size of pulmonary capillaries is normally less than 10 μm. In HPS, there is dilation of pulmonary vascular bed and/or intrapulmonary arteriovenous shunting, the microbubbles thus cross pulmonary vasculature and reach the left cardiac chambers. In HPS, microbubbles are characteristically seen in the left atrium between the fourth and sixth cardiac cycle after the repletion of the right atrial, while the appearance of microbubbles in left chambers before the third cycle is indicative of intracardiac shunting, thus rendering the study inconclusive for HPS. TTCE is considered the most sensitive technique for the identification of IPVD, however, the literature is limited with some studies showing contradictory results. The disadvantages of this technique include its complexity and high operator dependence.[1,3,5,9]

99mTc-macroaggregated albuminscintigraphy

It is performed by injecting macroaggregated albumin particles labeled with 99mTc. The average size of particles is approximately 10–100 μm with a mean of 30 μm. These particles when injected in the peripheral vein get lodged in the pulmonary capillaries having a mean diameter <10 μm and will not be seen in systemic capillaries [Figure 1]. However, in the case of HPS, pulmonary capillaries are dilated up to a diameter that varies from 15 to 100

μm and in severe cases to 500 μm. Thus, 99m Tc MAA particles traverse dilated pulmonary capillaries and enter the systemic circulation. These particles then get lodged into the first capillary bed they encounter, leading to visualization of other organs such as the brain, kidneys, thyroid, and liver. The extrapulmonary shunt fraction can also be calculated from the whole body images by drawing the region of interest around the brain the lungs and whole body.[3,6,9,10] 99mTc-MAA scintigraphy is considered to be less sensitive but more specific than TTCE and can miss some cases detected on TTCE.[11] However, sensitivity for clinically significant hypoxia-inducing IPVD is almost similar to TTCE.[9] Some recent studies have also found better sensitivity for 99mTc-MAA scintigraphy.[10,12]

Assuming 13% of the cardiac output goes to the brain. Brain uptake can be calculated as:[6,13]

$$\text{Brain uptake}: \frac{\left(\begin{array}{c}\text{Geometric Mean of}\\ \text{brain counts} / 0.13\end{array}\right)}{\left(\begin{array}{c}\text{Geometric Mean of}\\ \text{brain counts} / 0.13 +\\ \text{Geometric Mean of lungs counts}\end{array}\right)}$$

The optimal cutoff values of brain uptake and whole-body uptake for detecting IPVD is 5.7 with sensitivity, specificity, and accuracy of 23%, 89%, and 59%, respectively.[6,14]

In contrast, the whole-body MAA uptake was calculated using the geometric mean of counts in the whole body and the lungs as follows:[6,13]

$$\text{Whole - body uptake}: \frac{\text{Geometric Mean of lungs counts}}{\text{Geometric Mean of whole - body counts}}$$

The optimal cutoff values for whole-body uptake for detecting IPVD have been reported to be 42.5%, having a sensitivity, specificity, and accuracy of 100%, 52%, and 74%, respectively.[14] CT when done as a part of 99mTc-MAA SPECT/CT, can also help to exclude primary pulmonary causes of hypoxemia.

Although 99mTc-MAA scintigraphy is generally well tolerated by all patients, it is advisable to use a less number of particles, specifically less than 100,000, in elderly patients, those with severe pulmonary artery hypertension and right-to-left shunts. In addition, utilization of 99mTc-MAA scintigraphy is accompanied by certain limitations, primarily stemming from its labeling procedure, labeling efficiency, and particle size assessment. It is essential to incorporate quality control measures during the labeling procedure to ensure optimal labeling efficiency and accurate assessment of particle size, which can be accomplished using a hemocytometer.[15]

The management strategies available for HPS are very limited with liver transplant being the only definitive therapy available for ESLD but are mainly reserved for severe cases. The only medical therapy known to improve gas exchange and decrease hypoxemia is long-term supplemental oxygen therapy (LTOT). Rarely, treating the underlying acute liver disease has been reported to improve HPS (e.g., granulomatous hepatitis treated with steroids). LTOT is mainly indicated for patients with mild-to-moderate HPS with resting or exercising SpO2 ≤89% or PaO_2 ≤55 mmHg and severe cases.[8]

Transplant: The current guidelines strongly recommend a prompt referral and evaluation for liver transplantation (LT) in patients with severe HPS. The decision to proceed with transplantation is guided by the severity of liver disease, as determined by the MELD points score and the United Network for Organ Sharing criteria.[4,16] In context to HPS and arterial blood gas analysis, patients exhibiting evidence of intrapulmonary shunting with PaO2 (partial pressure of oxygen) below 60 mmHg (at room air) is assigned as a standard MELD exception score of 22. It is crucial to note that if the PaO2 remains below 60 mmHg for an extended period, there is an associated increase in mortality by 10% every three months.[17] Consequently, the accurate and timely diagnosis of HPS assumes paramount importance. Furthermore, it is important to highlight that the aforementioned exception scores can be further increased, if the PaO2 drops below 50 mmHg.

Liver transplantation can potentially provide significant survival benefits to patients with HPS. As long-term survival, rates in patients with HPS who undergo liver transplantation are comparable to those without HPS with near-complete resolution of pulmonary changes following liver transplant.[1]

Until now, limited data are available, to suggest that 99mTc-MAA scan is more specific for the identification of IPVD than TTCE for preoperative staging of HPS. Although 99mTc-MAA scan can also quantify the shunt fraction, which is not possible with TTCE.[1]

The sensitivity of TTCE has been reported to be higher than 99mTc-MAA scan. Moreover, TTCE has demonstrated the ability to detect clinically insignificant IPVD, even in the absence of hypoxemia. However, in a recent case series, a higher rate of HPS identification has been reported exclusively with 99mTc-MAA scan.[10,12] Furthermore, the 99mTc-MAA scan has exhibited a stronger correlation with the severity of HPS when compared to TTCE.[9,14,18]

The above illustrated cases very well describe the role of 99mTc-MAA scan in the diagnosis of HPS as a stand-alone modality, as well as an adjuvant to TTCE.

Conclusion

HPS is a rare vascular manifestation of CLD, which presents as dilation of pulmonary capillaries resulting in shunting of blood and hypoxemia. This invariably is associated with poor prognosis especially, if treatment is delayed, making early

identification of HPS important. The imaging studies most commonly used for the assessment of IPVD include TTCE and 99mTc-MAA scans. Although TTCE, owing to its high sensitivity is considered the preferred initial investigation, 99mTc-MAA scintigraphy should be considered an important adjuvant to TTCE, because it has the potential to identify certain cases of HPS that are not apparent on TTCE and can also help to quantify the shunt fraction. The current study shows the utility of 99mTc-MAA scintigraphy in the identification of HPS as a stand-alone modality, however, large studies are required to consolidate these findings.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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