Diffuse Pulmonary Uptake of Gallium-67 Induced by Pulmonary *Mycobacterium mucogenicum* and *Mycobacterium phocaicum* Infection

Acumulación pulmonar difusa de galio-67 inducida por infección pulmonar por Mycobacterium mucogenicum *y* Mycobacterium phocaicum

Dear Editor:

Nontuberculous mycobacteria (NTM) are classified by their growth rate, either slowly growing or rapidly growing. Rapidly growing mycobacteria (RGM) produce mature colonies on agar plates within 7 days.[1] They have a special ability to create a biofilm, which enhances a catheter-related bloodstream infection.[2] Furthermore, RGM induce skin and soft tissue infections, osteomyelitis, and pulmonary infections.[2] The most commonly encountered RGM are *Mycobacterium abscessus* complex, *M. chelonae*, and *M. fortuitum* complex.[3] *M. mucogenicum* group, which comprises *M. mucogenicum*, *M. aubagnense*, and *M. phocaicum*, is another set of RGM.[3] A 16S rRNA gene sequence analysis helps in discriminating between *M. mucogenicum* and *M. aubagnense*.[4] Furthermore, *M. phocaicum* and *M. mucogenicum* can be discriminated by rpoB gene and heat-shock protein (hsp)-65 gene sequence analysis.[4] In this report, we describe the case of a patient with pulmonary *M. mucogenicum* and *M. phocaicum* infection, whose gallium-67 (^{67}Ga) scintigraphy reveals diffuse pulmonary uptake without any abnormal findings on chest computed tomography (CT) scan.

We report the case of an 88-year-old non-smoking male patient who was diagnosed with hypertension. He was referred to Hikone Municipal Hospital because of malaise lasting for approximately 1 week. While he did not present with a fever or any respiratory symptoms, he complained of spontaneous pain in the right scapula. He had neither used any humidifiers nor hot tubs. His white blood cell (WBC) count was 12 610/μl and C-reactive protein level (CRP) was 17.49 mg/dL. While chest X-ray and chest CT scan revealed no remarkable changes, ^{67}Ga scintigraphy demonstrated diffuse pulmonary uptake (Fig. 1A). Although the induced sputum culture tested negative for bacteria, it gave positive results for mycobacteria. Bone marrow aspiration analysis and biopsy revealed a slightly hypocellular-to-normocellular bone marrow, and the bone marrow culture tested negative for bacteria and acid-fast bacillus. Because we initially suspected miliary tuberculosis, the antituberculosis drug isoniazid (300 mg/day) and rifampicin (450 mg/day) were administered. We conducted the bronchoscopic examination and prescribed levofloxacin (500 mg/day) 1 week after the administration of antituberculosis drugs because the patient had taken aspirin (an antiplatelet drug). Transbronchial lung biopsy did not detect any malignant tumors and granulomas. While the bronchial lavage culture tested negative for bacteria, it was positive for mycobacteria. Reportedly, the WBC count and CRP level decreased to 6710/μl and 3.09 mg/dL, respectively, 2 weeks after the antituberculosis regimen. After 3 months of the antituberculosis regimen, mycobacteria cultured from the induced sputum using a DNA–DNA hybridization method did not identify any particular species. However, *M. mucogenicum* and *M. phocaicum* were identified using 16S rRNA gene, rpoB gene, and hsp-65 gene sequence analyses. Therefore, we changed the treatment to clarithromycin (600 mg/day). At that time, ^{67}Ga scintigraphy demonstrated decreased pulmonary uptake and equivocal pulmonary uptake (Fig. 1B). In addition, the WBC count and CRP level declined to 4690/μl and 0.26 mg/dL, respectively. Three months after the administration of clarithromycin, ^{67}Ga scintigraphy revealed no changed in equivocal pulmonary uptake, and the WBC count and CRP level decreased to 5450/μl and 0.22 mg/dL, respectively.

This case is interesting from three viewpoints. First, ^{67}Ga scintigraphy helped to resolve the inflammatory condition of unknown etiology. Second, diffuse pulmonary uptake in ^{67}Ga scintigraphy was induced by pulmonary *M. mucogenicum* and *M. phocaicum* infection. Finally, we could monitor the treatment responses using serial ^{67}Ga scintigraphy.

^{67}Ga accumulates in inflammatory and infection sites by increased vascular membrane permeability and binding transferrin, lactoferrin, and siderophores.[5] Therefore, ^{67}Ga scintigraphy guides to a physician to a fertile site for additional investigation in patients with a fever of unknown origin.[6] In our case, ^{67}Ga scintigraphy helped in resolving the inflammatory condition of unknown etiology.

The patterns of ^{67}Ga uptake in the thorax include (a) normal uptake, (b) lymph node uptake, (c) focal pulmonary parenchymal uptake, and (d) diffuse pulmonary parenchymal uptake. Of these, diffuse pulmonary parenchymal uptake of ^{67}Ga indicates *Pneumocystis jiroveci* pneumonia, miliary tuberculosis, interstitial pneumonitis, drug-induced pneumonitis, and hypersensitivity pneumonitis.[5,7–9] In addition, ^{67}Ga scintigraphy can be used to monitor the therapy response in patients with *P. jiroveci* pneumonia and miliary tuberculosis.[5,7] In this case, the presence of *M. mucogenicum* and *M. phocaicum* in the sputum and bronchial lavage and diffuse pulmonary uptake in ^{67}Ga scintigraphy lead to a differential diagnosis of NTM-induced hypersensitivity pneumonitis. However, the patient had neither used any humidifiers nor hot tubs. Furthermore, chest CT revealed no remarkable changes. Therefore, the possibility of NTM-induced hypersensitivity pneumonitis was low in this case. Nevertheless, in the future, we need to carefully investigate the disease profile of this case because not much is known about the disease profiles of patients with NTM disease and diffuse pulmonary parenchymal uptake in ^{67}Ga scintigraphy.

Reportedly, *M. mucogenicum* and *M. phocaicum* are susceptible to amikacin, clarithromycin, imipenem, trimethoprim-sulfamethoxazole, and linezolid.[2,10] In our case, the antituberculosis treatment with isoniazid, rifampicin, and levofloxacin for 3 months improved the inflammatory condition and abnormal finding of ^{67}Ga scintigraphy. After this treatment, we changed the antimicrobial regimen to clarithromycin according to the antimicrobial susceptibility described above, although we did not test the antimicrobial susceptibility. In general, the use of combination antimicrobial regimens is superior to monotherapy and tends to be associated with a lower relapse rate.[2] Here, we selected monotherapy because the subject was an elderly patient. In the future, further investigation of this disease profile is required because the efficacy of clarithromycin monotherapy for patients with pulmonary *M. mucogenicum* and *M. phocaicum* infection is not yet convincing.

Although ^{18}F-fluorodeoxyglucose positron emission tomography is a promising technique for diagnosing infection and inflammation of unknown etiologies, it has disadvantages of limited availability and high cost.[7] Therefore, ^{67}Ga scintigraphy

Abbreviations: CRP, C-reactive protein; CT, computed tomography; ^{67}Ga, gallium-67; hsp, heat-shock protein; NTM, nontuberculous mycobacteria; RGM, rapidly growing mycobacteria; WBC, white blood cell.

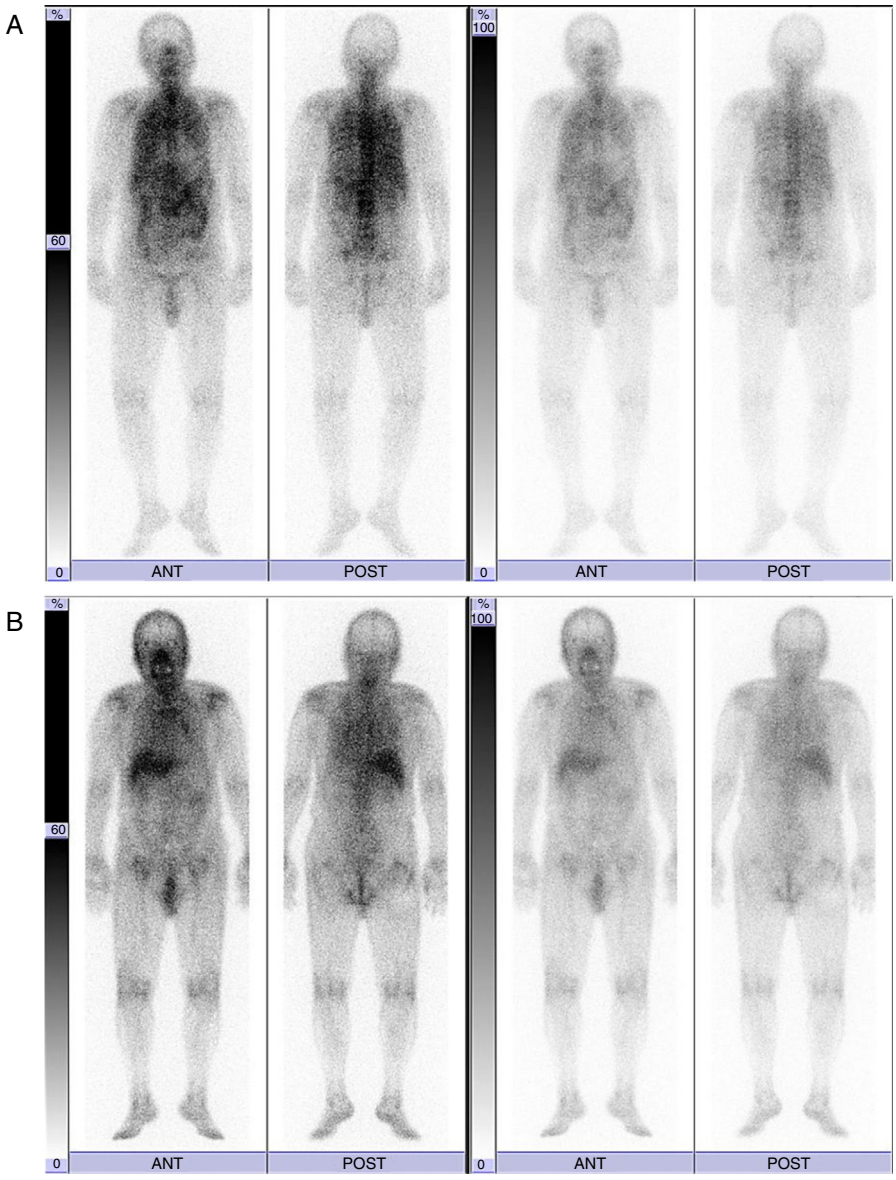

Fig. 1. ^{67}Ga scintigraphy findings before (A) and 3 months after the administration of antituberculosis drugs (B).

remains a widely used technique for radiopharmaceutical diagnostic imaging.[7] In our case, we could solve the inflammatory condition of unknown etiology and monitor the treatment responses using ^{67}Ga scintigraphy.

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Satoshi Hamada,* Natsumi Okamoto, Mitsuhiro Tsukino

Department of Respiratory Medicine, Hikone Municipal Hospital, Japan

* Corresponding author.
E-mail address: sh1124@kuhp.kyoto-u.ac.jp (S. Hamada).

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Pleural Fluid Analysis and Pleural Elastance as Predictors of Response to Pleurodesis in Patients With Malignant Pleural Effusion☆

Análisis del líquido y elastancia pleurales como predictores de respuesta a la pleurodesis en los derrames pleurales malignos

To the Editor,

The use of pleural manometry (PM) during therapeutic thoracentesis is controversial.[1,2] A small study of malignant pleural effusions (MPE) conducted 20 years ago suggested that pleural elastance (P_{EL}), the ability of the lung to return to its natural position after the extraction of pleural fluid (PF),[3] can predict the success of pleurodesis.[4] This led to the recommendation that unexpandable lung (UEL)[3] should be identified in order to guide management decisions.[5] The objective of this study was to evaluate if the success of pleurodesis in MPE can be predicted by identifying various biochemical parameters in PF and determining P_{EL}.

We performed a retrospective study of all MPEs (cytology or pleural biopsy positive for malignancy) managed with therapeutic thoracentesis with PM and subsequent pleurodesis between January 2014 and October 2016. Exclusion criteria were previous chemotherapy/radiation therapy, life expectancy <1 month, or loculated PE. Patients signed an informed consent form before therapeutic thoracentesis with PM was performed. Our study was approved by the hospital ethics committee (registry 2016/518).

Pleural pressure was measured with a digital manometer (Compass; Mirador Biomedical),[6] using a previously described technique.[7] Thoracentesis was completed when no more fluid could be extracted, pleural pressure reached −20 cmH_2O, or if chest pain developed.[8] P_{EL} was calculated based on the formula: [opening pressure–closing pressure (cmH_2O)]/volume of fluid extracted (in liters). A diagnosis of UEL was reached if incomplete pulmonary reexpansion was observed on the post-thoracocentesis chest X-ray.

Pleurodesis with a slow injection of suspension of 4 g talc in 50 cc 0.9% saline solution was administered after evacuating the PE via a chest tube (16F) and checking lung reexpansion on X-ray, irrespective of the amount of fluid drained on a daily basis.[9] The tube was closed for 2–3 h, and then connected to mild progressive aspiration. The chest tube was removed after 24 h, regardless of the volume of fluid obtained, and without radiological monitoring.[10] Pleurodesis was considered to have been successful if no reaccumulation or only partial accumulation of PE not requiring further thoracentesis occurred until the time of death.[11] It was considered to have failed if the effusion recurred or new procedures were needed for the relief of symptoms. The decision to perform pleurodesis was not based on the PF analyses or P_{EL} results.

Fasting PF and blood specimens were obtained simultaneously. Biochemical parameters determined in PF were those included in the routine protocol of our hospital. Data are listed as mean ± standard deviation, or median and 25th–75th percentiles, depending on whether the distribution of the samples was normal or not. Pearson's Chi-squared test was used for the comparison between groups if the variables were qualitative, and the non-parametric Mann–Whitney test was used if they were quantitative. ROC curves and the area under the curve were calculated to assess the discrimination capacity of the markers in the prognosis of pleurodesis (success/failure).

In total, 148 PMs were performed, of which 110 were cases of MPE. Pleurodesis was performed in 36 patients [20 women and 16 men (mean age: 65.2 ± 12.9 years; range, 18–89)]. Seventy-four patients were excluded due to previous chemotherapy/radiation therapy (31), short life expectancy (28), loculated PE (8), and no signed informed consent (7). UEL was diagnosed in 8 patients (22.2%).

Pleurodesis was successful in 26 patients (72.2%), and failed in 10 (27.8%) (Table 1). Significant differences between the groups were only found for neuron-specific enolase in PF (NSE_{PF}) (P=.046) and for P_{EL} (P=.000). The diagnostic yield of these 2 variables for predicting pleurodesis failure is shown in the same table [areas under the ROC curves for NSE_{PF} and P_{EL} of 0.717 (0.526–0.908) and 0.935 (0.842–1.027), respectively].

This study confirms that P_{EL} is a useful parameter for predicting the response to pleurodesis in MPE, and that values ≥18 cmH_2O/l suggest that the procedure will fail, due to poor apposition of the two pleural membranes[12] and the inability of the lung to return to its natural position as the PF is extracted. Pleurodesis can also fail in patients with an expandable lung and P_{EL} below this cut-off point (2/28; 7.1%). This seems to indicate that other factors may cause pleurodesis failure, such as insufficient inflammatory response to cause fibrosis and produce pleural symphysis, or time elapsed between diagnosis and starting drainage.[13]

The only biochemical parameter that showed some discriminant value for predicting the failure of pleurodesis was NSE_{PF}, which was not significantly different from that of P_{EL} (P=.07564), probably because of the small size of the series and the width of the confidence intervals. Thus, the lower limit of the positive likelihood ratio of NSE_{PF} (1.5) has little effect on the probability of diagnosing pleurodesis failure. The reason why NSE_{PF} is high in these patients is still unknown. Perhaps, as in rheumatoid arthritis, a situation of hypoxia is generated that activates anaerobic glycolysis and causes this marker to rise.[14,15] The main limitations of the study are its retrospective nature, the small number of cases in the study, and the fact that all patients were recruited in a single center.

Our study suggests that NSE_{PF} and P_{EL} measurements can predict response to pleurodesis in MPE. In patients with raised P_{EL} (≥18 cmH_2O/l), the probability of pleurodesis failure is very high and, therefore, other therapeutic alternatives that may offer a chance of success should be considered for the prompt control of the patient's symptoms.

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