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Depiction of residual emboli following pulmonary embolism with thrombotic scintigraphy

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Background: In the treatment of pulmonary embolism (PE), the presence of residual emboli is known to seriously affect the recurrence and prognosis. We attempted to depict the residual emboli in the subacute stage of PE using indium-111-oxine labeled platelet scintigraphy (In-plt). ***Methods:*** In-plt was performed on 22 patients with PE who showed an improvement according to lung perfusion scintigraphy. Their accumulation was assessed along with the blood coagulation ability measured on the same day. In addition, radioisotope venography (RI-veno) was performed simultaneously with In-plt to measure the circulatory findings in the lower limb for comparison. All patients received systemic heparin during the acute stage and received warfarin at the time of testing. ***Results:*** Accumulation of In-plt was observed in 7 patients (32%), and positive signals were found in the lower limbs or pelvic cavity in all cases. Two patients were suspected of having poor lower limb circulation from their RI-veno findings, and these findings were largely consistent with the areas of In-plt accumulation. ***Discussion:*** Some emboli persist after extensive anti-coagulation therapy. The use of In-plt is effective in determining the therapeutic measures and assessing the prognosis as this method allows us to clearly depict the existence of such emboli.

Key words: platelet scintigraphy, pulmonary embolism, radioisotope-venography

BACKGROUND

ACUTE PULMONARY EMBOLISM (PE) occurs when a blood clot called embolus lodges in the pulmonary arteries. Most of the emboli are caused by deep venous thrombosis (DVT) of the lower limbs.[1] In addition, some studies showed that approximately half of DVT patients develop asymptomatic PE[2] and extra caution is required for its diagnosis. Furthermore, the death rate of patients with PE in the early stage is extremely high, and early diagnosis and early treatment are critical. Although the tool of the first choice for PE diagnosis is considered to be pulmonary scintigraphy, we often have to rely on echocardiography in clinical practice due to the poor accurate diagnosis rate of pulmonary scintigraphy according to the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study results.[3] Ultrasound contributes to the early detection of DVT.[4] In this way, the introduction of new methods frequently helps in the early diagnosis of PE and may be life-saving for patients in the acute stage.

However, in spite of extensive anti-coagulation therapy, we often experience cases of nosocomial sudden recurrence of PE after the onset.[5] The presence of residual emboli seems to be responsible for this recurrence,[5] but there are no methods established to clearly detect such residual emboli. Although CT and MRI are frequently used for detection of the residual emboli, these methods are effective only when the emboli are located relatively in the vessels in the central region, but they are not sufficient to detect emboli in the peripheral regions.[6] In addition, technical problems such as image blurring caused by respiratory-related motion and the use of insufficient contrast medium and risk of exposure to patients are serious issues when using such methods. Indium-111-oxine labeled platelet scintigraphy (In-plt) is a useful thrombotic scintigraphy to systemically localize the

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emboli or to predict their activity. In addition, this method is capable of scanning the entire body at once. Ultrasonography of the lower limbs is a useful and handy methd for the diagnosis of DVT, but require special skill.[7,8] The combined use of radioisotope venography (RI-veno) which is capable of evaluating the lower limb venous occlusion and the development of collateral circulation with In-plt may allow us to evaluate residual emboli in detail. RI-veno is able to evaluate the pulmonary circulation and collateral circulation of lower limbs with DVT at the same time. In the present study, we attempted to depict the residual emboli in the chronic stage of PE using the In-plt method.

METHODS

Patient Selection

A total of 22 in-patients who were relatively stable after treatment for acute PE were the subjects of this study. Sixteen females and 6 males with a mean age of 60 years (range: 37–83 years) participated in this study. In addition, heparin was systemically administered to all patients during the acute stages. All patients were under an anticoagulation therapy at the time of the examination. In addition, this study protocol was approved by the ethics committee at our hospital, and informed consent was obtained from each of the participants.

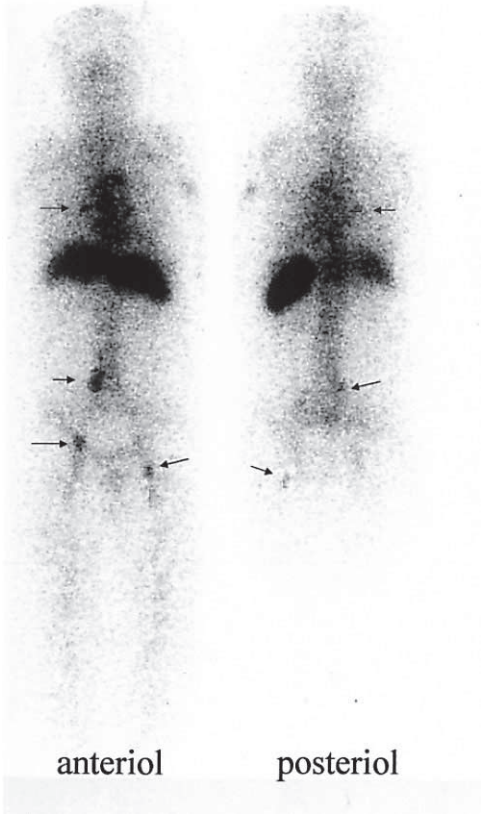

Fig. 1 In-plt image of patient No. 1. Accumulation was observed in the lower limbs, pelvic cavity and lungs.

1. Indium-111-oxine labeled platelet imaging protocol

We labeled autologous platelets aseptically according to the method described by Thakur et al.[9] A total of 50 m*l* of blood was withdrawn and collected in a blood collecting syringe containing 7 m*l* of an anticoagulant acid citrate dextrose (ACD) solution. The collected blood sample was centrifuged at 1500 rpm for 15 minutes at room temperature to isolate the platelet-rich plasma (PRP). Then, stock solution of the platelets was prepared by centrifugation at 3000 rpm for 15 minutes after the pH of PRP was adjusted to 6.5 with ACD. The platelet-poor plasma (PPP) obtained simultaneously was saved for later use. The stock solution of the platelets was mixed with 37 MBq (1 mCi) of indium-111-oxine (Nyconmed Amersham Inc., Buckinghamshire, UK), incubated for 20 minutes at the room temperature for labeling, and then, the mixture was centrifuged again at 3000 rpm for 15 minutes after adding 15 m*l* of PPP. Ten milliliters of PPP was added to the

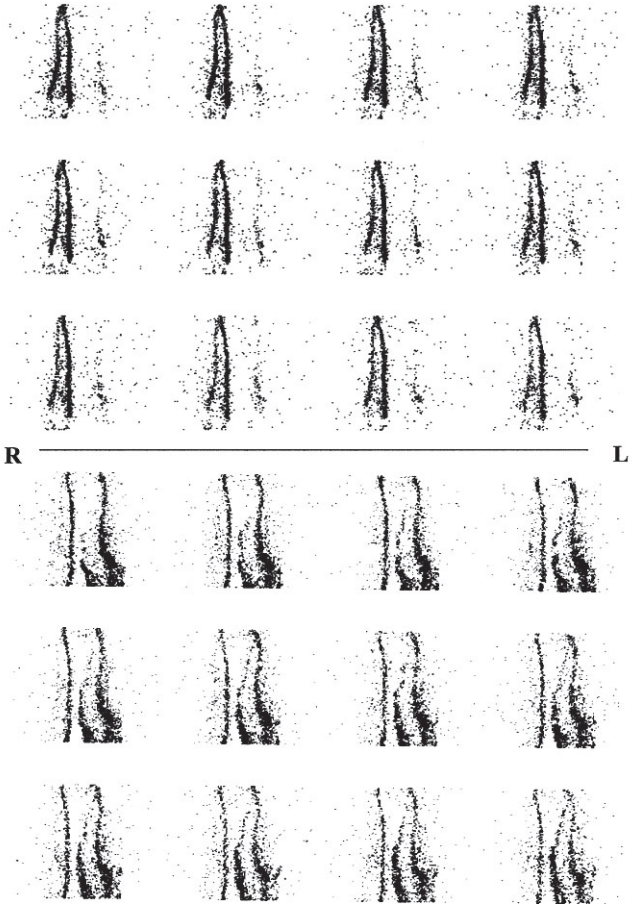

Fig. 2 RI-veno images of patient No. 1. *Upper image:* No depiction of deep veins in the left lower limb was observed while the tourniquet was wrapped around the leg above the lateral malleolus. *Lower image:* The development of the collateral circulation was observed in the left leg when the tourniquet was loosened.

Table 1 Patient characteristics

	gender	In-plt (location)	RI-veno	complication	recurrence
1	F	+ (pelvic cavity)	+	DVT	+
2	F	+ (pelvic cavity)	+	DVT	+
3	M	+ (pelvic cavity)	+	–	–
4	F	+ (lower extremities)	–	old myocardial infarction	–
5	F	+ (lower extremities)	–	–	–
6	F	+ (lower extremities)	–	DVT	–
7	F	+ (hilus pulmonis)	–	–	–
8	F	–	+	–	–
9	F	–	–	varicosis	–
10	F	–	–	varicosis	–
11	F	–	–	–	–
12	F	–	–	–	–
13	F	–	–	old myocardial infarction	–
14	F	–	–	–	–
15	F	–	–	atrial fibrillation	–
16	F	–	–	–	–
17	F	–	–	–	–
18	M	–	–	–	–
19	M	–	–	–	–
20	M	–	–	–	–
21	M	–	–	–	–
22	M	–	–	–	–

F/M, female/male; In-plt +/–, positive/negative accumulation; RI-veno +/–, fair/good blood passage; DVT, deep venous thrombosis; recurrence, recurrence of pulmonary embolism

labeled platelets, and the mixture was further centrifuged at 1000 rpm for 5 minutes. The supernatant PRP was injected intravenously into the patients. The mean labeling rate of the administered labeled platelets was 70 ± 6%, and the administered radioactivity dose was approximately 11.1 MBq (0.3 mCi). The time for platelet labeling was about 150 minutes.

Anteroposterior systemic images were obtained with a starcam gamma camera (General Electric, Milwaukee, WI, USA) 96 hours after the administration for assessment. Anterior and posterior whole-body views were each acquired for 15 minutes. A medium energy collimator was used to accommodate the energy spectrum of indium-111-oxine.

2. Radionuclide venography

The vessels were secured with 23 G winged needles at both dorsalis pedis veins. To depict the deep veins, a tourniquet was wrapped around the legs above the lateral malleolus, and then 370 MBq (10 mCi) of technetium-99m labeled macro-aggregated human serum albumin was administered while a tourniquet was applied. The images were taken for the legs, thighs and pelvic region, and then the development of collateral circulation in the legs was evaluated after loosening the tourniquet. Last, the pulmonary circulation was evaluated.

3. Blood coagulation test

As all patients received an anti-coagulation therapy. The platelet count, prothrombin time-international normalized ratio (PT-INR) value, fibrinogen and D-dimer level were measured at the time of the In-plt study.

Data Analysis

The accumulation in the images obtained from In-plt and RI-veno was visually evaluated by multiple examiners. The platelet count, PT-INR value, fibrinogen and D-dimer level were individually expressed as mean ± SD and evaluated with the unpaired-t test. $P < 0.05$ was considered to be significant.

RESULTS

1. Scintigraphic imaging

Accumulation was observed in 7 patients (6 females) in the In-plt study. Accumulation was located either in the pelvic cavity or lower limbs in all cases. Accumulation in the lungs was observed in one patient (Fig. 1). In half of the patients who showed accumulation in the In-plt study, the RI-veno study showed poor delineation of the deep veins in the lower thigh and development of the collateral circulation (Fig. 2). In addition, these patients clinically developed DVT as well. Furthermore, two of the patients showed recurrence of PE, and both of them demonstrated accumulation of In-plt in the pelvic cavity and lower limbs and showed poor delineation of the deep veins of the lower thigh in the RI-veno study (Table 1).

Table 2 Coagulation ability

	n	platelet ($\times 10^4/\mu l$)	PT-INR	D-dimer (mg/dl)	fibrinogen (mg/dl)
In-plt					
positive	7	20.1 ± 8.8	2.19 ± 17	3.1 ± 0.4	288 ± 36
negative	15	17.5 ± 2.0	2.26 ± 12	2.4 ± 0.6	293 ± 40
RI-veno					
fair	4	19.6 ± 5.2	2.11 ± 13	2.7 ± 0.6	303 ± 39
good	18	17.3 ± 9.4	2.21 ± 11	2.8 ± 0.3	275 ± 41
					N.S.

positive/negative, positive/negative accumulation of In-plt; fair/good, venous passage of RI-veno

2. Coagulation ability

The anti-coagulation therapy was given based on the PT-INR ratio, and all cases were controlled favorably. There were no differences in the ability of coagulation regardless of the accumulation in the In-plt and RI-veno studies.

In addition, the values possibly affecting thrombogenesis, such as the platelet count and fibrinogen level, were within the normal ranges in all cases, and there were no differences regardless of the accumulation in the In-plt and RI-veno studies.

DISCUSSION

In the present study, we attempted to visualize residual emboli in patients with acute PE using a nuclear medical method. Consequently, we successfully demonstrated the silhouette of the emboli with In-plt while the patients were under the anti-coagulation therapy. In addition, two patients who showed the accumulation of In-plt had recurrent PE, and many patients had poor delineation of the deep veins of the leg in the RI-veno study.

The In-plt study has been established as a diagnostic modality for localization of emboli, and the emboli have been reportedly detected in relatively large cavities such as the cardiac chambers[10] as well as in fine vessels such as the coronary arteries.[11] Although the emboli can be assessed with CT scanning or ultrasound examination,[12] their activity can not be assessed to these methods. The In-plt study is effective for the functional evaluation of the emboli as this method can image fresh and active emboli that are attached with platelets and fibrin.[9] The sensitivity of In-plt for the detection of DVT was 40–100% and corresponded to that of venography by according to reports.[13] $^{99}Tc^m$-HMPAO labeled platelets scintigraphy and $^{99}Tc^m$-apcitide scintigraphy were introduced as a thrombus.[14,15] Though their method is handy in comparison with In-plt, they require studying in a large number of patients.[15] In-plt has the advantage of being able to identify detection of thrombus. The imaging of In-plt might be difficult to distinguish it from blood pool activity.[13] The RI-veno study has been established as a method to evaluate the venous circulation,[6] and we believe that the combination of these nuclear medicine examinations can depict the residual venous emboli accurately.

Some cases of acute PE may have a dramatic course, and their prognosis and pathology are reported in many articles. Among them, the cases manifesting hemodynamic abnormalities such as shock and hypotension are considered to have a poor prognosis.[16] Moreover, the recurrence of PE from residual DVT is also considered to indicate a poor prognosis. However, the reports investigating recurrent PE cases due to DVT are few. Even when the condition of pulmonary emboli improves, the evaluation of residual venous emboli is believed to be clinically critical.

In the present study, we successfully depicted the residual emboli in the entire body including the pelvic cavity in addition to the lower limb veins using the In-plt study. We conducted the study when the patients were in a relatively stable condition after the onset of PE. As an anti-coagulation therapy, warfarin was administered to the patients at PT-INR ratio of approximately 2–3 based on previous reports.[17] The accumulation of In-plt can be decreased or lost in the patients who receive the anti-coagulation therapy, and it can be used to evaluate the efficacy of the anti-coagulation therapy.[9] In the present study, although we used a favorable anti-coagulant therapy as a control, we also considered using more powerful anti-coagulant therapy to obtain high accumulation of In-plt, but the use of more powerful anti-coagulant therapy may lead to the complication of hemorrhage.[17] Therefore, according to the evidence,[16–20] we treated the patients who showed accumulation of In-plt by administration of an additional dose of heparin or by placing a venous filter on an individual basis.

In addition, in the present study, we used RI-veno to visualize the venous circulation. Although evaluation in the RI-veno study is limited to the legs,[17] this approach is useful in terms of assessing the effect of emboli on the circulation. In our cases, we also noticed that the patients with accumulation of In-plt in their lower limbs showed poor circulation in the RI-veno study. Furthermore, the RI-veno study can assess the pulmonary circulation after evaluating the lower limb circulation. We believe that the combined examination of the pulmonary circulation and lower limb circulation with one method is extremely useful for the treatment of PE which has an unstable pathology requiring quick diagnosis since it allows diagnosis in an early stage and can strategize the early therapeutic measures. Although it is difficult to predict the relationship between the RI-veno results and the recurrence of PE as there were not enough cases to investigate in this study, we observed that the patients who showed accumulation of In-plt in the lower limb had poor circulation in the RI-veno study, indicating that this method is worthwhile to implement in the future to estimate the residual venous emboli after PE.

CONCLUSION

In the present study, we attempted to depict the residual venous emboli after acute PE by combining two nuclear medicine examinations of thrombotic scintigraphy and RI venography. Consequently, the residual emboli were depicted while the anti-coagulant therapy was administered, thus providing essential information in planning the future therapeutic strategy.

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