大韓核醫學會誌 : 第29卷 第 1 號 1995

Assessment of the Synovial Inflammation in Rheumatoid Arthritis with ^{99m}Tc-labelled Polyclonal Human IgG(HIG): Prospective Comparison with Gadolinium Enhanced MRI

Young Hoon Ryu, M.D., **Jong Doo Lee**, M.D., **Jin Suck Suh**, M.D., **Chang Yun Park**, M.D. **Pyoung Jeon**, M.D., **Jae Beom Na**, M.D. and **Soo Kon Lee**, M.D.*

Department of Diagnostic Radiology, Department of Internal Medicine, Yonsei University, Medical College, Seoul, Korea*

= 국문 초록 =

^{99m}Tc-labelled HIG 스캔을 이용한 류마티스 관절염 환자에서 활막염증의 평가 : 조영증강 자기공명영상과의 전향적인 비교

연세대학교 의과대학 진단방사선과학교실, 내과학교실*

유영훈 · 이종두 · 서진석 · 박창윤 · 전 평 · 나재범 · 이수곤*

지금까지 류마티스 관절염의 염증 정도의 평가를 위하여 많은 검사들이 사용되어져 왔다. ^{99m}Tc-labelled HIG 스캔은 동물실험과 사람에서도 염증이나 감염병소에 집적되는 것으로 알려져 있다. 본 연구의 목적은 ^{99m}Tc-labelled HIG 스캔을 이용하여 류마티스 관절염 환자에서 활동성 염증이 있는 군과 없는 군을 구별해 보고자 하였고 이러한 결과를 다른 임상인자와 조영증강 자기공명영상과 비교해 보았다.

11명의 활동성 염증이 있는 류마티스 관절염 환자와 활동성 염증이 없는 류마티스 관절염 환자 1명, 강직성 척수염 환자 2명 그리고 퇴행성 관절염 환자 1명을 대상으로 하였다. 활동성 염증(active synovitis)은 ESR의 상당한 증가와 조영증강 자기공명영상에서 조영증강을 보이는 경우로 정의하였다. ^{99m}Tc-labelled HIG를 정맥주사후 4시간후에 전신 및 국소영상을 얻었다. 섭취정도의 평가는 3명의 전문의에 의하여 3단계로 나누어 시각적으로 평가하였다. 모든 환자에 있어서 조영증강 자기공명영상을 같이 시행하였다.

활동성 염증이 있는 11명의 류마티스 관절염 환자중 10명에서 상당한 정도의 섭취증가를 보인 반면 활동성 염증이 없는 나머지 환자에서는 정상 또는 미미한 정도의 섭취증가만을 보였다. 본 연구에서 ^{99m}Tc-labelled HIG 스캔을 이용하여 류마티스 관절염에 이환된 관절들의 전반적인 국소화가 가능하였고 ^{99m}Tc-labelled HIG의 섭취정도가 다른 임상적이나 자기공명영상의 활동성 염증을 시사하는 인자들과 잘 연관되었다.

결론적으로 ^{99m}Tc-labelled HIG 스캔은 류마티스 관절염 환자에 있어서 염증 정도를 평가해 볼 수 있는 유용한 방법이 될 수 있을 것으로 생각한다.

Key Words: Radionuclide imaging, Rheumatoid arthritis, Inflammatory scintigraphy, ^{99m}Tc-labelled polyclonal human Immunoglobulin G(HIG)

INTRODUCTION

Radiolabelled polyclonal immunoglobulin G (IgG) scintigraphy has been recognized as a reliable method for the localization and evaluation of pyogenic infections in human[1-4]. Moreover, the localization and the severity of inflammatory joint disease can be detected with radiolabelled nonspecific IgG[5-7]. Proposed mechanism in the localization of infection and inflammation is nonspecific accumulation of the protein resulting from increased vascular permeability and specific trapping of IgG by inflammatory cells mediated through Fc receptors[8,9].

The evaluation of the activity of the synovial inflammation in rheumatoid arthritis is important for the management of the disease[10]. Although ^{99m}Tc-MDP whole body bone scan plays the major role in the diagnosis of arthritis, comparative studies between other radiopharmaceuticals and clinical criteria were performed to improve the inflammation specificity. ^{99m}Tc-HMPAO leukocyte, ^{99m}Tc-nanocolloid and ^{99m}Tc-pyrophosphate joint imaging were compared to clinically measured joint activity scores. However, since yet these imaging modalities could not take place in the routine procedure and none has become a reliable objective method to assess disease activity in rheumatoid arthritis[11,12]. ^{99m}Tc-labelled polyclonal human IgG(HIG) scintigraphy can be employed to detect and evaluate the disease activity, suggesting the severity of synovitis judging by nonspecific accumulation of HIG on inflammatory foci[6].

The purpose of this study was to distinguish arthritis with active inflammation from those without active inflammation and to correlate the degree of radiotracer uptake in patients with rheumatoid arthritis with clinical and MR indices of the joint inflammation by using ^{99m}Tc-labelled HIG scan.

PATIENTS AND METHODS

15 patients, 12 patients fulfilling the criteria of American Rheumatism Association for definite or classic rheumatoid arthritis, 2 with ankylosing spondylitis and 1 with degenerative osteoarthritis were included in this study. Informed consents were obtained from all patients. Scintigraphic, radiologic and clinical evaluation were done to all patients.

Modified polyclonal human IgG(Technescan HIG, Mallinkrodt Diagnostica, Petten, Holland) was labelled with ^{99m}Tc-pertechnate according to the instruction of the manufacturer. Static images were obtained 4 hours after intravenous injection of 20mCi(740 MBq) of ^{99m}Tc-labelled HIG, using large field of view dual head gamma camera, equipped with a low energy high resolution parallel hole collimator. Anterior and posterior whole-body images as well as spot views of the focal sites of increased radiotracer uptake were obtained in a 256×256matrix.

In all patients, 20mCi of ^{99m}Tc-methylene diphosphate(MDP) was injected intravenously within a week after HIG scan for whole body bone scan(WBBS). Anterior and posterior whole body images and static images were obtained 4 hours after intravenous administration of ^{99m}Tc-MDP to compare with HIG scan.

Clinical severity of the joint inflammation was assessed by the degree of elevation of erythrocyte sedimentation rate(ESR). Magnetic resonance(MR) images were obtained from the joints in which markedly increased activities was noted on HIG scan. Each joints undertaken gadolinium enhanced MRI were wrist(n=11), knee(n=2) and hip joint(n=2). MR imaging was performed with a 1.5T signa unit(General Electrics Medical systems, Milwaukee, Wis). MR studies included

spin echo T1 weighted images(500/16[repetition time in msec/echo time in msec]) with 5 mm thickness, 256×192 matrix size and multiple echo T2 weighted images(2000/20, 70) with dynamic gadolinium enhancement studies using multiplanar gradient recalled echo imaging (MPGR)(68/12, flip angle 60°) after intravenous administration of 0.2mmol/kg gadopentate meglumine(Magnevist; Schering, Berlin, Germany). Measurement of both ESR and MR imaging were performed within a week following HIG scan.

The scintigraphic images were interpreted by 3 radiologists in a blinded fashion. Interobserver discrepancies were resolved by means of a consensus decision, if at least 2 of 3 interpretation were in agreement. The scintigraphic images were evaluated according to the following criteria; normal, if no focus of abnormal ^{99m}Tc-labelled HIG localization was identified; mild, if localized increased radioactivity within the joint area was greater than that of soft tissue and

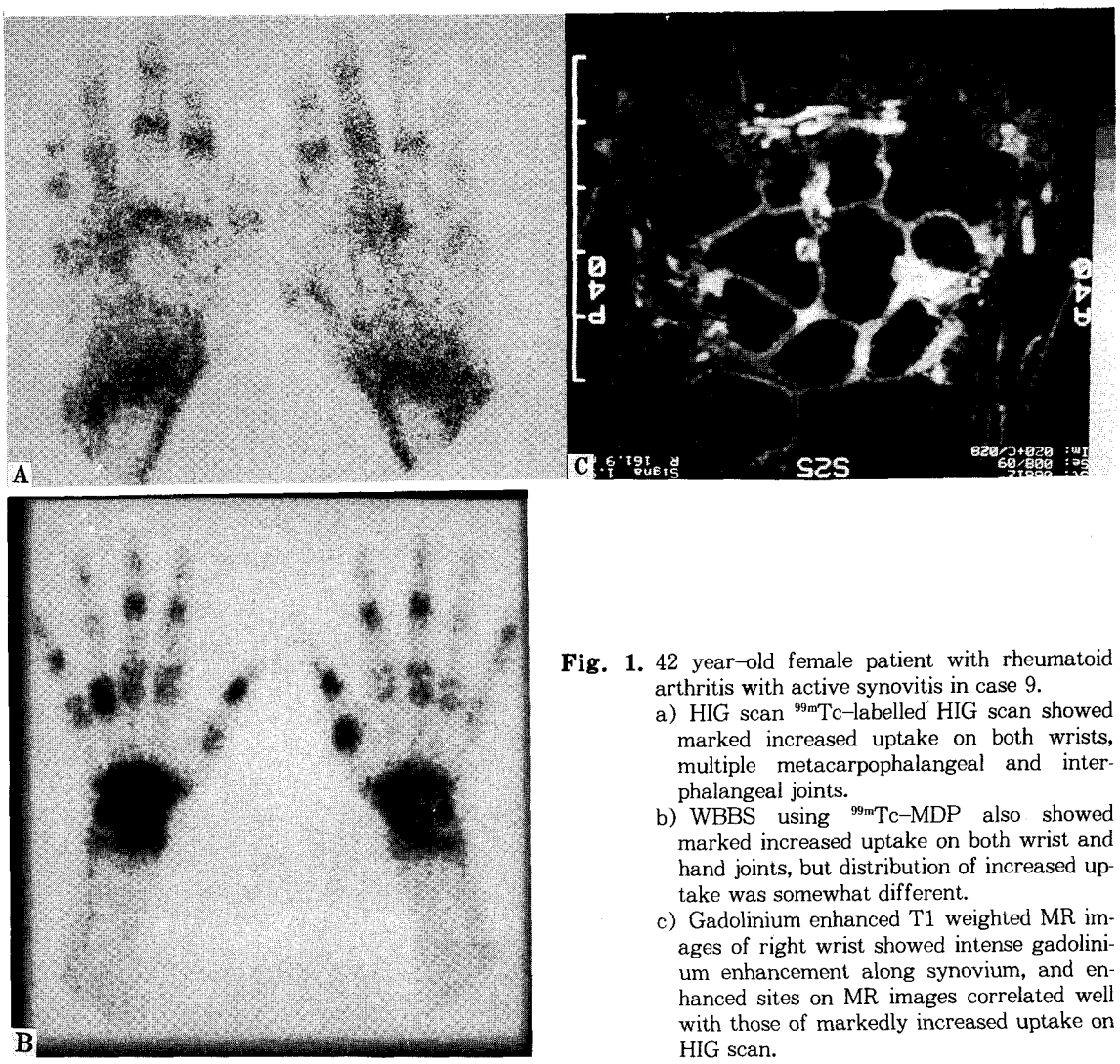

Fig. 1. 42 year-old female patient with rheumatoid arthritis with active synovitis in case 9.
a) HIG scan ^{99m}Tc-labelled HIG scan showed marked increased uptake on both wrists, multiple metacarpophalangeal and interphalangeal joints.
b) WBBS using ^{99m}Tc-MDP also showed marked increased uptake on both wrist and hand joints, but distribution of increased uptake was somewhat different.
c) Gadolinium enhanced T1 weighted MR images of right wrist showed intense gadolinium enhancement along synovium, and enhanced sites on MR images correlated well with those of markedly increased uptake on HIG scan.

lesser than that of blood vessels; marked if localized increased radioactivity was greater than that of blood vessels. The grade of uptake was then compared with the clinical and radiologic severity of synovial inflammation. Active synovitis was defined when elevation of ESR and gadolinium enhancement of synovium on MRI were exhibited. Since active synovitis were not demonstrated in 2 patients with ankylosing spondylitis, 1 with degenerative osteoarthritis and 1 with rheumatoid arthritis, we used them as control patients.

RESULTS

Scintigraphy of the joints of patients with rheumatoid arthritis demonstrated a definite localization of ^{99m}Tc-labelled HIG at the articular sites with clinically active arthritic process. Joints with high uptake were clearly discernible on the whole body images. Markedly increased radiotracer uptake within the joints was seen in 10 of 11 rheumatoid arthritic patients with active synovitis, whereas normal or mild increased uptake was noted in joints with rheumatoid arthritic patient(n=1) or nonrheumatoid patients(n = 3) without active synovitis, respectively. In patients with active synovitis, an elevation of ESR and gadolinium enhancement along synovium on T1 weighted images were noted, and both early and late enhancements of both pannus and joint effusion on dynamic gadolinium-enhanced studies were noted. The degree of uptake of ^{99m}Tc-HIG correlated well with the degree of inflammation(Fig. 1, 2)(Table 1).

The localization of the involved joints and the degree of radiotracer uptake were different in WBBS, compared to ^{99m}Tc-HIG scan. In patient with degenerative osteoarthritis, WBBS revealed

Table 1. Comparison between findings of ESR, MRI and HIG Scan

HIG \ MR	Gd Enhance (+)	Gd Enhance (−)	ESR(mm/hr)
Marked	10		47–134
Mild	1	2	21–38
Normal		2	14–16

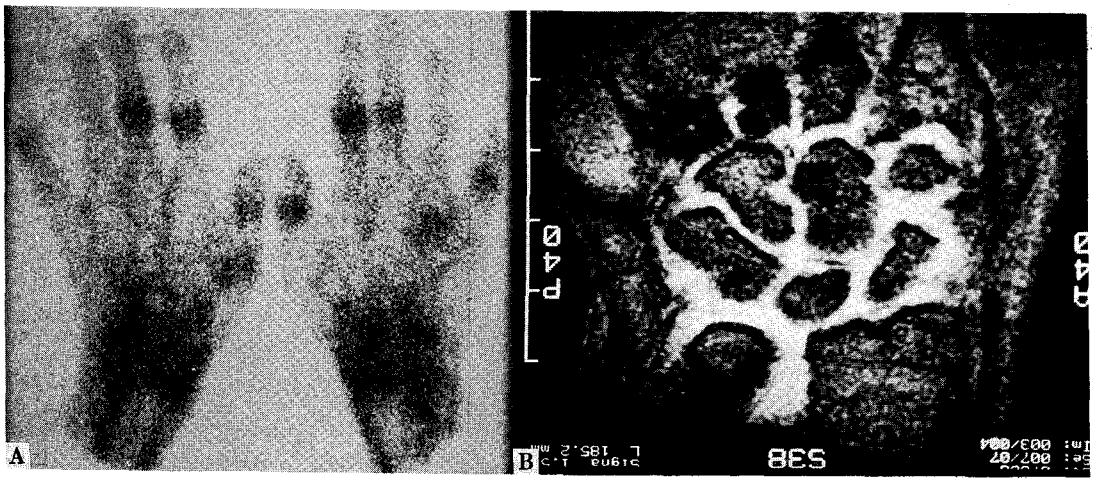

Fig. 2. 49 year-old male patient with rheumatoid arthritis with active synovitis in case 2.
a) ^{99m}Tc-labelled HIG scan showed markedly increased uptake on both wrist and hand joints.
b) Gadolinium enhanced T1-weighted MR image of left wrist showed enhancement along the synovium and those finding suggested active synovitis and enhanced sites were well correlated with markedly increased sites on HIG scan.

increased radiotracer uptake on both sides of knee joints whereas ^{99m}Tc-HIG scan showed no evidence of abnormally increased uptake of ^{99m}Tc -HIG. On MR images of both knee joints, multiple osteophytes and loose bodies within the joints were demonstrated, but gadolinium enhancement was not demonstrated(Fig. 3).

Clinical characteristics of the investigated patients, the results of the ^{99m}Tc-labeled HIG scintigraphy, ^{99m}Tc-MDP whole body bone scan and

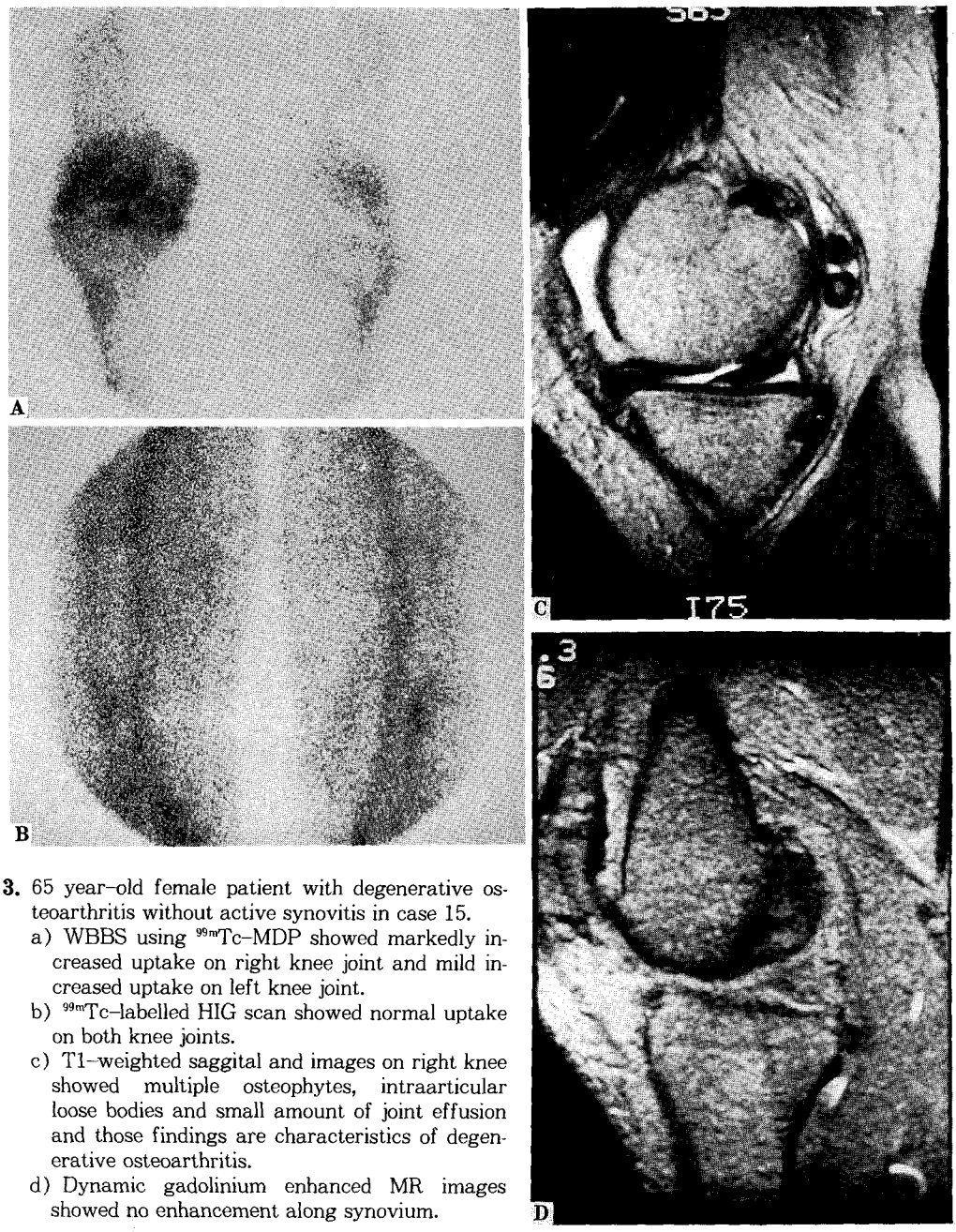

Fig. 3. 65 year-old female patient with degenerative osteoarthritis without active synovitis in case 15.
a) WBBS using ^{99m}Tc-MDP showed markedly increased uptake on right knee joint and mild increased uptake on left knee joint.
b) ^{99m}Tc-labelled HIG scan showed normal uptake on both knee joints.
c) T1-weighted saggital and images on right knee showed multiple osteophytes, intraarticular loose bodies and small amount of joint effusion and those findings are characteristics of degenerative osteoarthritis.
d) Dynamic gadolinium enhanced MR images showed no enhancement along synovium.

Table 2. Summary of Patient Data

No/Sex/Age	Clinical Dx	HIG	MRI	ESR	WBBS
1/F/57	RA	II	+	88	++
2/M/49	RA	II	+	105	++
3/M/60	RA	II	+	67	++
4/F/40	RA	II	+	100	++
5/F/16	RA	II	+	56	++
6/M/41	RA	II	+	53	+
7/F/62	RA	II	+	47	++
8/F/17	RA	II	+	80	++
9/F/42	RA	II	+	134	++
10/F/40	RA	II	+	115	++
11/F/52	RA	I	+	38	++
12/M/50	RA	I	–	23	+
13/M/28	AS	I	–	21	+
14/M/23	AS	0	–	16	+
15/F/65	DOA	0	–	14	++

Abbereviation : RA : rheumatoid arthritis, AS : ankylosing spondylitis,
DOA : degenerative osteoarthritis.
HIG : II–marked, I –mild increased, 0–normal uptake within the joints
MRI : (+)–gadolinium enhancement positive
(–)–gadolinium enhancement negative
WBBS : ++–stong positive
+–weakly positive.

MRI are summarized in Table 2.

DISCUSSION

Previous scintigraphic studies with ^{111}In-labelled human nonspecific polyclonal IgG demonstrated that it accumulated at the sites of inflammation in both rats and human subjects with focal pyogenic infection[1-4,8]. It was demonstrated that scintigraphy with ^{99m}Tc-IgG could also localize area of pyogenic infection in mice and sterile inflammation in the collagen-induced model of arthritis in rats[6]. Recently scintigraphy with ^{99m}Tc-labelled HIG produced good images of synovial inflammation in patients with rheumatoid arthritis[7].

It is thought that rheumatoid arthritis is autoimmune origin[3,4,10]. In approximately 80% of the patients with rheumatoid arthritis, an autoantibody produced by synovial tissues and B lymphocytes targeting the Fc portion of IgG were present. The exact mechanism of HIG accumulation at the site of inflammation still has not clearly understood. However, the increased vascular permeability at the involved sites and the exudation of plasmaprotein through a leaking capillary bed at the site of inflammation are thought to play a significant role. It is also suggested that an intact Fc portion is favorable for the concentration of IgG at the site of inflammation[8,9]. Possible role of rheumatoid factor in the rheumatoid arthritis and HIG accumulation had been discussed[13]. Probably the HIG accumulation occurs in relation with yet unknown immunologic mechanism and/or the physicochemical characteristics of HIG molecule play the dominant role.

Until recently, in the evaluation of disease activity in rheumatoid arthritis, the goal of objectivity in quantitation has largely remained elusive. Joint scintigraphy has a potential to provide an objective noninvasive way of measuring synovial involvement in arthritis[14].

The results of our study indicated that scintigraphy with ^{99m}Tc-labelled HIG in patients with rheumatoid arthritis could localize and measure the activity of the synovial inflammation in clinically and radiologically involved joints. The elevation of ESR and gadolinium enhancement along the synovium and pannus and joint effusion on T1 weighted images of MRI could reflect the activity of synovial inflammation, clinically and radiologically. In rheumatoid patients with active synovitis, localized, mild to markedly increased uptake of ^{99m}Tc-labelled HIG within the involved joints were demonstrated. However, in rheumatoid and non-rheumatoid patients without active synovitis exhibited either normal or mild increased uptake of ^{99m}Tc-labelled HIG within

the involved joints.

When compared to ^{99m}Tc-MDP WBBS, the distribution and degree of the radiotracer uptake were different. Although ^{99m}Tc-MDP WBBS is indispensable for rapid localization of the site of the lesions and visualization of the osseous structures, little information can be obtained about soft tissue involvement and the actual extent and nature of the lesion because it lacks specificity to discriminate between reactive increased bone turn-over and actual inflammation[15,16].

Although gadolinium enhanced MRI can also reflect activity of synovial inflammation, ^{99m}Tc-labelled HIG scintigraphy has the advantage of imaging of the whole involved joints at glance and cost effectiveness.

In conclusion, although the number of patients we studied was small, our study suggested that ^{99m}Tc-labelled HIG scintigraphy was a useful method in the evaluation and screening of the joints with active synovial inflammation in rheumatoid arthritis.

SUMMARY

Many clinical and laboratory tests have been employed to evaluate disease activity in rheumatioid arthritis. ^{99m}Tc-labelled polyclonal IgG(HIG) has been demonstrated to accumulate in focal sites of infection or inflammation in both animals and human subjects. The purpose of this study was to distinguish arthritis with active inflammation from those without active inflammation and to correlate relative intensities of ^{99m}Tc-labelled HIG uptake of the rheumatoid arthritis with clinical and MR indices of the joint inflammation.

This study included twelve patients with active rheumatoid arthritis, two with ankylosing spondylitis and one with degenerative osteoarthritis without active inflammation. A Whole-body and spot images were obtained 4 hours after intravenous injection of 20mCi of ^{99m}Tc-labelled HIG. Scintigrams were assessed visually by 3 experienced radiologists, and graded as normal or mildly and markedly increased uptake within the joints, and the degree of uptake was compared with clinical and radiologic severity of synovial inflammation. MRI studies were done on the involved joints consisted of wrist(n=11), knee(n=2) and hip joint(n=2). Active synovitis was defined when marked elevation of ESR and gadolinium enhancement of synovium on MRI were demonstrated.

Markedly increased radiotracer uptake was seen in 10 of 11 rheumatoid arthritic patients with active synovitis whereas normal or mildly increased uptakes were noted in others, including rheumatoid arthritic patient(n=1) and non-rheumatoid patients(n=3) without active synovitis. This study showed that the localization of involved joints in rheumatoid arthritis could be detected with ^{99m}Tc-labelled HIG and that the degree of uptake correlated well with the degree and activity of inflammation.

In conclusion, ^{99m}Tc-labelled HIG scan is a useful method in the evaluation of active inflammation in rheumatoid arthritis.

REFERENCES

1) Rubin RH, Fischman AJ, Needleman M, et al.: *Radiolabelled, nonspecific, polyclonal human immunoglobulin in the detection of focal inflammation by scintigraphy: Comparison with Gallium-67 citrate and Technetium-99m-labelled albumin. J Nucl Med 30:385-389, 1989*

2) Rubin RH, Fischman AJ, Callahan RJ, et al.: *In-111-labeled nonspecific immunoglobulin scanning in the detection of focal infection. N Engl J Med 321:935-940, 1989*

3) Abrams MJ, Juweid M, Schwartz DA, et al.: *Technetium-99m-labelled polyclonal IgG rad-*

iolabelled via hydrazino nicotinamide derivative for imaging focal sites of infection in rats. J Nucl Med 31:2022-2028, 1990

4) Calame W, Feitsma HIJ, Ensing GJ, et al.: *Detection of a local staphylococcal infection in mice with Technetium-99m-labelled polyclonal human immunoglobulin. J Nucl Med 32:468-474, 1991*
5) Arndt JW, Blok D, Griffioen G, et al.: *A prospective comparison of ^{99m}Tc-labelled polyclonal human immunoglobulin and ^{111}In granulocytes for localization of inflammatory bowel disease. Acta Radiol 33:140-144, 1992*
6) Van der Lubbe PAHM, Arndt JW, Calame W, et al.: *Measurement of synovial inflammation in rheumatoid arthritis with technetium-99m-labelled human polyclonal immunoglobulin G. Eur J Nucl Med 18:119-123, 1991*
7) Breedveld FC, Van Kroonenburgh JPG, Camps JAJ, et al.: *Imaging of inflammatory arthritis with technetium-99m-labelled IgG. J Nucl Med 30: 2017-2021, 1989*
8) Morrel EM, Tompkins RG, Fischman AJ, et al.: *Autoradiographic method for quantitation of radiolabelled proteins in tissues using indium-111. J Nucl Med 30:1538-1545, 1989*
9) Fischman AJ, Rubin RH, White JA, et al.: *Localization of Fc fragment and Fab fragment of nonspecific polyclonal IgG at focal sites of inflammation. J Nucl Med 31:1199-1205, 1990*
10) Isselbacher KJ, Braunward E, Wilson JD, et al.: *Harrison's principles of internal medicine, New York, McGaw-Hill book company, pp1638-1644, 1993*
11) Datz FL Editorial: *Radionuclide imaging of joint inflammation in the '90s. J Nucl Med 31:684-687, 1990*
12) De Bois MHW, Arndt JW, Tak PP, et al.: *^{99m}Tc-labelled polyclonal human immunoglobulin G scintigraphy before and after intra-articular knee injection of triamcinolone hexacetonide in patients with rheumatoid arthritis. Nucl Med Comm 14:883-887, 1993*
13) Berna L, Torres G, Diez C, et al.: *Technetium-99m human polyclonal immunoglobulin G studies and conventional bone scans to detect active joint inflammation in chronic rheumatoid arthritis. Eur J Nucl Med 19:173-176, 1992*
14) Green FA: *Joint scintiscans: Present status. J Rheumatol 6:370-373, 1979*
15) Oyen WJG, Claessens RAMJ, Van Horn JR, et al.: *Scintigraphic detection of bone and joint infection with indium-111-labelled nonspecific polyclonal human immunoglobulin G. J Nucl Med 31: 403-412, 1990*
16) Seabold JE, Ferlic RJ, Marsh JL, Nepola JV.: *Periarticular bone sites associated with traumatic injury: False-positice findings with In-111-labelled white blood cell and Tc-99m MDP scintigraphy. Radiology 186:845-849, 1993*