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Technetium-99m human immunoglobulin scintigraphy in patients with adhesive capsulitis: A correlative study with bone scintigraphy

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Adhesive capsulitis (AC) is a disorder that is characterized by shoulder pain and progressive limitation of both active and passive shoulder motion. Although the underlying pathological mechanisms of the disease are not well understood, the inflammatory reactions depending on the stage have been demonstrated histologically. The purpose of the study is to investigate the inflammatory changes that can be demonstrated with Tc-99m HIG in AC, and to determine the presence of correlations between scintigraphic findings and the clinical assessment. Twenty-one patients (12 females and 9 males) with a mean age of 50.57 ± 8.49 were included in the study. AC was diagnosed according to recognized criteria. The planar X-ray images of the affected shoulders of all patients were normal. The patients were evaluated with the Constant Scoring System, and the functional and pain assessment parts of the American Shoulder and Elbow Surgeons' Form (ASES). Three phase bone scans and Tc-99m HIG scintigraphy were performed at least two days apart. Bone scan and Tc-99m HIG scintigraphy were evaluated visually and HIG uptake was evaluated in comparison with the contralateral normal shoulder. Bone scan demonstrated hypervascularity in 9 of the 21 patients (43%), whereas increased osteoblastic activity was detected in 19 (90%) in the affected shoulder. Tc-99m HIG uptake was positive in 12 (57%), and negative in 9 (43%) patients. All patients with increased Tc-99m HIG accumulation in the affected shoulder, also had increased osteoblastic activity on Tc-99m bone scintigraphy. A significant correlation was found between HIG uptake and constant, functional and pain scores. The difference between these scores was also statistically significant in patients with HIG positive and negative uptake. This study indicates that there is a good correlation between Tc-99m HIG scan findings and clinical scores. Tc-99m HIG accumulation in the affected shoulder may be related to continuing inflammatory reaction to AC. Tc-99m HIG scan may be a noninvasive, complementary method for demonstrating continuing inflammatory changes and may help in staging the disease.

Key words: adhesive capsulitis, technetium-99m human immunoglobulin, technetium-99m MDP, inflammation

INTRODUCTION

Adhesive capsulitis (AC), also known as frozen shoulder, is characterized by significant restriction of both active and passive shoulder motion.[1] The etiology is unknown. AC has typically been classified into two forms, primary and secondary. The primary form is idiopathic. Many predisposing factors can lead to secondary AC, including diabetes mellitus, immobilization, pulmonary disease and stroke.[2] There is disagreement as to whether the underlying pathologic process is an inflammatory condition or a fibrosing condition.[3,4] It has been stated in the relevant literature that pathologic changes in AC are synovial inflammation with subsequent reactive capsular fibrosis,

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dependent on the stage of the disease.[5,6] Staging of AC is crucial in determining the appropriate treatment and can dramatically affect the outcome of treatment. Demonstration of a continuing inflammatory process is one of the parameters for staging AC.[6]

Technetium-99m-labeled human immunoglobulin (Tc-99m HIG), is a radiopharmaceutical which accumulates at the sites of infection and inflammation.[7–10] It has been widely used to detect various infectious and inflammatory diseases including musculoskeletal disorders and to determine the inflammatory activity in some rheumatologic diseases such as rheumatoid arthritis, psoriatic arthropathy and osteoarthritis.[11,12] In this prospective study we aimed to investigate the inflammatory changes that can be demonstrated with Tc-99m HIG and to determine the presence of correlations between scintigraphic findings and the clinical assessment.

MATERIALS AND METHODS

This study was performed after approval by Dokuz Eylül University Hospital Ethics Committee. Written informed consent was obtained from all patients in accordance with Helsinki Declaration II.

Twenty-one patients (12 females and 9 males) with a clinical diagnosis of AC were included in this study. Their ages ranged from 34 to 70 years (average 50.57 ± 8.49 yrs). AC was diagnosed according to recognized criteria.[1] These criteria were as follows: 1) a history of restricted shoulder motion without major injury or reconstructive surgery, 2) marked loss of active and passive shoulder motion, 3) normal findings on plain radiographs of the shoulder. The patients with polyarticular inflammatory diseases based on clinical examination and history or with acromioclavicular joint arthritis or with bilateral shoulder lesions were excluded from the study.

All patients were evaluated according to the Constant Scoring System.[13] The Constant Scoring System evaluates pain in the shoulder, activities in daily living, range of motion and strength of muscles. In this scoring system, the maximum possible score is 100. The higher the score, the better the shoulder function. The pain score and functional score of American Shoulder and Elbow Surgeons' Form (ASES) were also used.[13] The functional score in the ASES form evaluates 15 different activities and every activity performance is rated from 0 to 4 on the scale (0 = unable to 4 = normal). Pain assessment according to the ASES form is in 5 degrees (0 = complete disability, 5 = none).

Although it has been postulated that antibiotics, nonsteroidal anti-inflammatory drugs and corticosteroids do not affect the accumulation of Tc-99m HIG in inflammatory and infectious areas, nonsteroidal anti-inflammatory drugs were discontinued at least 2 days before the imaging study. There was no patient taking corticosteroids and antibiotics.

A three-phase bone scintigraphy was performed in all patients. Twenty-five millicuries (925 MBq) of Tc-99m MDP (Amerscan™ Medronate II Agent) was injected as a bolus through a venous line on the dorsum of the feet and

Table 1 The characteristics, clinical scores and scintigraphic findings of patients

Patient No.	Age	Sex	Symptom duration (months)	Tc-99m HIG	Tc-99m MDP			Constant score	Functional score	Pain score
					BP	Early	Late			
1	49	F	10	–	–	–	–	60	40	3
2	49	M	3	+	–	–	+	26	15	1
3	47	F	6	+	–	–	+	33	19	2
4	46	F	2	+	–	–	+	43	21	1
5	49	F	12	–	–	–	+	41	21	2
6	52	F	4	+	+	+	+	34	24	1
7	51	F	3	–	+	+	+	43	30	2
8	40	F	12	+	–	–	+	49	31	2
9	64	F	3	+	–	–	+	28	5	1
10	51	M	2	–	+	+	+	42	30	3
11	50	F	3	–	+	+	+	24	12	1
12	51	F	4	+	+	+	+	27	22	1
13	51	F	9	+	+	+	+	30	11	1
14	56	M	3	–	–	–	+	46	30	3
15	42	M	12	–	–	–	+	62	47	3
16	56	M	2	+	–	–	+	41	29	2
17	70	F	2	+	+	+	+	43	24	3
18	49	M	3	+	+	+	+	38	38	1
19	40	M	6	–	–	–	+	42	36	1
20	65	M	24	–	–	–	–	48	27	3
21	34	M	18	+	+	+	+	30	21	1

Table 2 The difference of clinical scores between Tc-99m HIG negative and positive patients

	HIG (–)	HIG (+)	p
Constant score	45.33 ± 11.91	35.16 ± 7.4	0.04
Functional score	30.33 ± 10.23	21.66 ± 8.8	0.05
Pain score	2.33 ± 0.8	1.41 ± 0.6	0.01

anterior dynamic flow images of the shoulders, anterior and posterior blood pool (3 min), 4 hour planar images (5 min) and pinhole images of both shoulders (200,000 counts/ each shoulder) were obtained in the anatomical position.

Tc-99m HIG scintigraphy (DRN 4369 Technescan® HIG Mallincrodt Medical B.V. Petten, Holland) was performed within 2–5 days afier bone scintigraphy. The radiopharmaceutical (555 MBq) was injected into an antecubital vein in the arm without the lesion. Anterior and posterior planar images of shoulders were obtained at 10 minutes, 4 (10 min) and 24 hours (15 min) after the venous injection. Pinhole imaging of both shoulders (200,000 counts/each shoulder) were obtained at the 4th hour. All of the planar images were obtained in the anatomical position.

A low energy general purpose collimator and a 64×64 matrix were used for dynamic and a low energy high resolution collimator and 256×256 matrix were used for planar images.

A Siemens Multispect II gamma camera was used for dynamic and planar, and a GE XCT gamma camera was used for pinhole imaging. A 20% window set at a 140 keV energy peak was used.

The images were evaluated visually by two nuclear medicine physicians who were blinded to the patients' clinic and anatomic images. The HIG scan images after 4 hours were scored by consensus. Visual evaluation of the Tc-99m HIG uptake was done for the contralateral shoulder: symmetrical uptake in both shoulders was accepted as HIG negative, and increased activity in the normal shoulder was evaluated as HIG positive.

The correlations between clinical scores and scintigraphic findings were analyzed with Spearman's rank correlation. The difference between clinical scores for Tc-99m HIG positive and negative groups was tested with Mann-Whitney U, and $p < 0.05$ was accepted as significant in all statistical analyses.

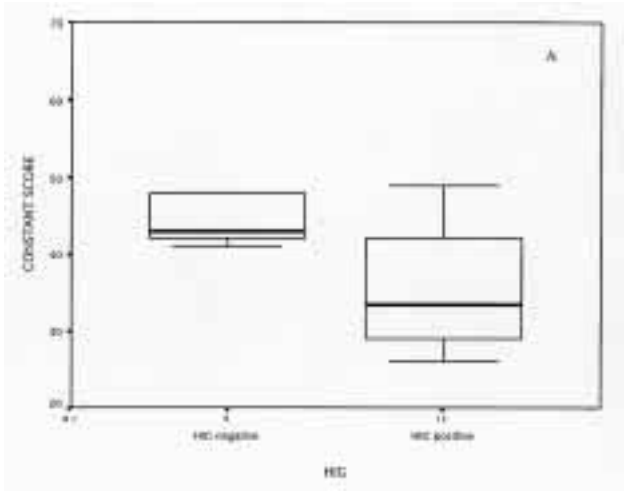
RESULTS

The characteristics, clinical scores and scintigraphic findings in the patients are shown in Table 1. The mean monthly duration of AC symptoms in the patients was 6.80 ± 5.97.

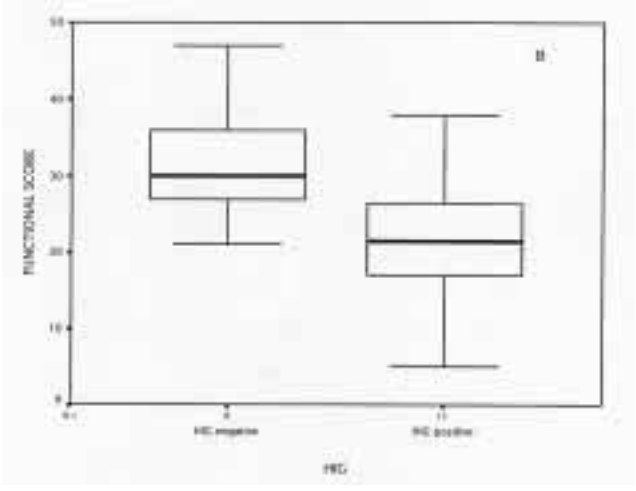
Tc-99m MDP bone scintigraphy showed increased blood flow and hypervascularity in 9 of the 21 (43%) patients, whereas increased osteoblastic activity was detected in 19 (90%) patients with an affected shoulder. Tc-99m HIG uptake was positive in 12 (57%), and negative in 9 (43%) patients. All of the patients demonstrating increased Tc-99m HIG accumulation in their affected shoulder also showed increased osteoblastic activity on bone scintigraphy, but there was no significant correlation between Tc-99m HIG accumulation and all phases of bone scintigraphy.

We found significant correlation between Tc-99m HIG scan findings and constant scores (r: –0.45, p: 0.03), functional scores (r: –0.43, p: 0.05) and pain scores (r: –0.52, p: 0.01). There was no significant correlation between the findings of Tc-99m MDP bone scan and clinical scores.

The constant, functional and pain scores of the Tc-99m HIG positive patients were statistically different from



A



B

Fig. 1 Box plots for constant score (A) and functional score (B) in HIG positive and HIG negative patients. Horizontal lines show the median.

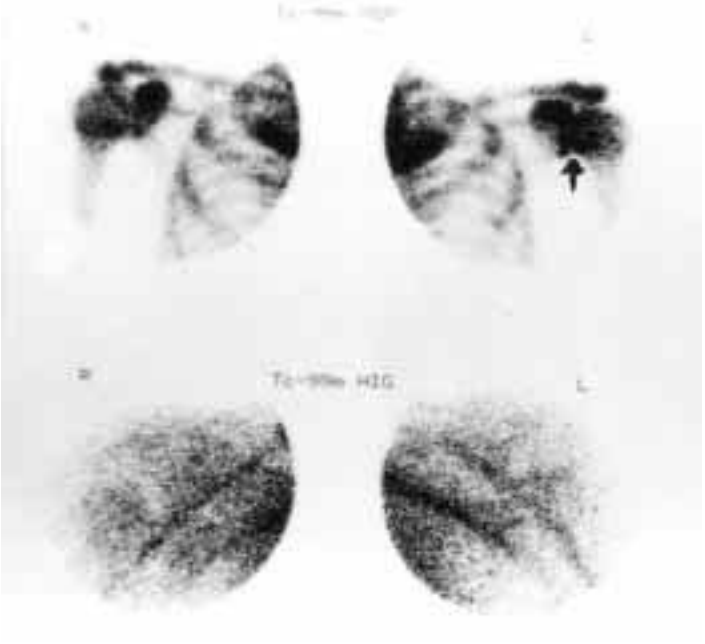


Fig. 2 4th hour pinhole images of Tc-99m MDP bone scintigraphy (*upper left:* right shoulder, *upper right:* left shoulder) and Tc-99m HIG scintigraphy (*lower left:* right shoulder, *lower right:* left shoulder). A mild increased activity on late phase of the bone scan was observed on the left corocoid and the adjacent humeral head (*arrow*). Tc-99m HIG scintigraphy demonstrated symmetrical radiopharmaceutical accumulation in both shoulders.

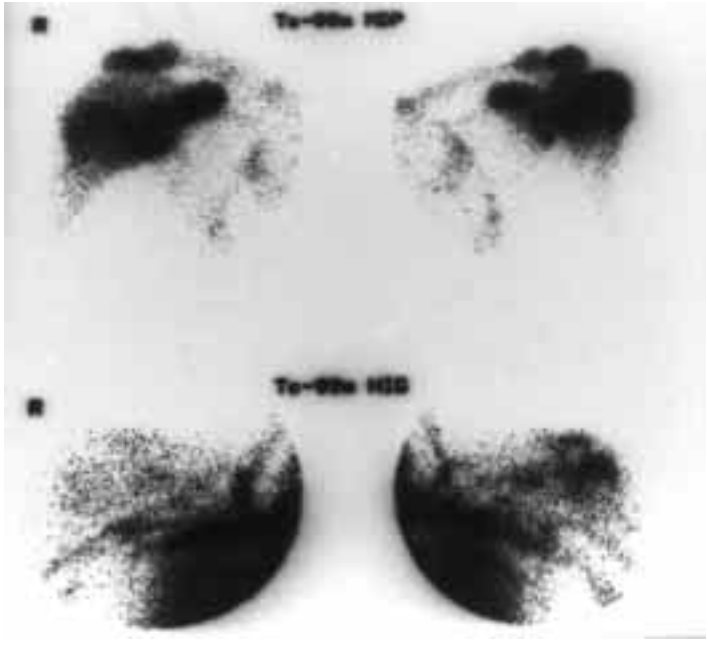


Fig. 3 4th hour pinhole images of Tc-99m MDP bone scintigraphy (*upper left:* right shoulder, *upper right:* left shoulder) and Tc-99m HIG scintigraphy (*lower left:* right shoulder, *lower right:* left shoulder). A marked osteoblastic activity was observed on acromion and humeral head of the affected left shoulder on bone scan. Tc-99m HIG scintigraphy demonstrated marked radiopharmaceutical accumulation on left shoulder.

those of Tc-99m HIG negative patients. Table 2 shows the mean clinical scores in Tc-99m HIG positive and negative groups. All the clinical scores were better in HIG negative patients than in HIG positive patients. Figure 1 shows box plots graphics for the constant score and functional score.

Figure 2 shows a 42-year-old male patient with AC (patient No. 15). Mild hyperemia and mild increased activity on the late phase bone scan were observed in the left corocoid and the adjacent humeral head. Tc-99m HIG scintigraphy showed symmetrical radiopharmaceutical accumulation in both shoulders.

Figure 3 shows a 34-year-old male patient with AC (patient No. 21). Noticeable hyperemia and osteoblastic activity were observed in the acromion and humeral head of the affected left shoulder on bone scan. Tc-99m HIG scintigraphy showed marked radiopharmaceutical accumulation in the left shoulder.

DISCUSSION

Previous studies indicate that both inflammatory and fibrotic conditions take part in the pathophysiology of

AC.[5,6] Through arthroscopic study, Neviaser defined four stages in AC.[14] In stage I (0 to 3 months), there is mild synovial inflammation that is detectable especially in and around the axillary fold of the joint. In stage II (3 to 9 months), there is acute synovitis with adhesion of the dependent folds of the synovial lining. In stage III (9 to 15 months), there is maturation of the adhesions with little inflammation. In stage IV (15 to 24 months), the adhesions are fully mature. It is therefore very important to show a continuing inflammatory process in the staging of AC.

Tc-99m HIG is a nonspesific radiopharmaceutical that localizes infectious and noninfectious inflammation in the body. It is widely used in detecting musculoskeletal inflammation such as rheumatoid arthritis,[11] psoriatic arthritis[12] and abscess localization.[7] Although increased blood flow and vascular permeability causing localization at edematous interstitial spaces are known mechanisms for Tc-99m HIG localization at inflammatory sites, we could not find a significant correlation between the blood pool phase of bone scintigraphy and HIG accumulation in our study. We believe that there are some other mechanisms which take part in Tc-99m HIG localization at inflammatory sites other than increased vascularity.

Clunie et al. reported distinctive patterns on Tc-99m MDP bone scan in patients with painful shoulder lesions.[15] These data are promising in establishing the role of Tc-99m MDP bone scan in differential diagnosis of painful shoulder lesions. But the uptake mechanisms of Tc-99m MDP and its role in clinical staging of AC are unclear. In this study, we investigated the correlation of Tc-99m MDP findings with clinical scores and Tc-99m HIG uptake. There was no correlation between clinical scores and Tc-99m MDP findings. These findings suggest that increased osteoblastic activity that is demonstrated with Tc-99m MDP bone scan in AC is due to nonspecific bone reactions of the underlying pathologic conditions of the disease rather than inflammation. Other possible mechanisms of increased Tc-99m MDP accumulation in the affected shoulder may be due to disuse osteopenia that can be seen in patients with AC.[16]

We have found few published data on Tc-99m HIG imaging in AC. Clunie et al. studied Tc-99m HIG scintigraphy in 4 patients with AC.[17] Their median duration of symptoms was 12 months and the patients were under treatment. They could not find differences between Tc-99m HIG images of symptomatic and asymptomatic shoulders. They thought that it was related to long symptom duration and success of therapy. They also indicated that the mechanisms responsible for accumulation of Tc-99m HIG were likely to be different from mechanisms that can be postulated for increased Tc-99m MDP uptake in AC. In this study we found marked Tc-99m HIG uptake in patients with low constant and functional scores and increased shoulder pain. Although the uptake mechanisms of Tc-99m HIG in inflammatory and infections sites are not clear, there is no doubt that the biochemical or functional inflammatory changes in the tissue may affect its uptake. Increased Tc-99m HIG uptake in patients with low scores in the clinical scoring system may be related to continuing inflammatory reactions that deteriorate clinical scores and cause pain. In a particular patient shown in Figure 3, although the duration of symptoms was 18 months, the patient's pain score was 1 and he had restriction of motion. According to the duration of symptom the patient was expected to be in stage 4, both the clinical scores and marked increased Tc-99m HIG uptake suggested continuing inflammatory reactions in this patient. Considering our findings we suppose that Tc-99m HIG, as an inflammatory imaging agent, can demonstrate inflammatory changes, which is compatible with reported histologically proven hypertrophic and hypervascular synovitis in AC.

To the best of our knowledge, this is the first study that investigates the correlation of Tc-99m HIG and Tc-99m MDP findings with the clinical scores in patients with AC. One limitation of this study is the lack of arthroscopic and histological findings in the patients as a gold standard for inflammation. Because arthroscopy and arthroscopic biopsies are invasive techniques, we did not use these methods for ethical reasons. In the future, a study that correlates Tc-99m HIG imaging with histological findings can be organized in volunteers.

We concluded that there is close correlation between Tc-99m HIG scan findings and clinical scores. As Tc-99m HIG is known as a nonspecific agent for demonstrating inflammation, this correlation may be due to continuing inflammatory reaction in AC. Tc-99m HIG scintigraphy may be a noninvasive, complementary method for investigating continuing inflammatory reactions and will help clinicians to make decision while staging patients with AC. Bone scintigraphy has limited usefulness in demonstrating possible inflammatory reaction in AC and has no correlation with clinical scores. Further studies with a large number of patients are needed.

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