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^{99m}TC-labelled antigranulocyte monoclonal antibody FAB′ fragments versus echocardiography in the diagnosis of subacute infective endocarditis

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Abstract

Objective: We performed this pilot study to gain first clinical data of immunoscintigraphy with ^{99m}Tc-labelled anti-NCA-90 antigranulocyte antibody Fab′ fragments (^{99m}Tc-Fab′ (LeukoScan®)) in endocarditis. *Patients and methods*: ^{99m}Tc-Fab′ and echocardiography were used in 24 consecutive patients with suspected endocarditis. Nuclear medicine imaging was performed after i.v. injection of 925 MBq ^{99m}Tc-Fab′ fragments and evaluation was done by region of interest (ROI) technique and visually. *Results*: Seven patients were found to have endocarditis on the basis of the revised Duke criteria, which served as gold standard. Initial scintigraphy was true positive in five patients and false positive in one. In the five true positives, T/B ratios in projection to the heart valve plane (with $T/B \geq 1.3 \pm 0.072$) were highly suspicious for florid endocarditis. TTE and TEE were true positive in two and in six patients, whereas false positives were seen in two and in four patients. Scintigraphy was positive in four of the five patients with the false negative TTE and negative in the three false positive TEE. Vice versa, TEE was positive in the two patients with false negative scintigraphy. *Conclusions*: Immunoscintigraphy with ^{99m}Tc-Fab′ fragments in combination with TEE improves diagnostic accuracy compared with TTE/TEE in patients with subacute infective endocarditis.

Keywords: Tc-99m-antigranulocyte antibody Fab′ fragment; Endocarditis; Echocardiography

1. Introduction

Subacute infective endocarditis has recently shown an increased incidence [1]. In a surprisingly high proportion of cases, infective endocarditis is difficult to diagnose with certainty. This is due to both the inaccessibility of intracardiac vegetations and the highly variable and sometimes nonspecific nature of the clinical manifestations. Two-dimensional echocardiography combined with spectral Doppler modalities and color flow mapping is recognized as providing a good alternative to invasive studies in the assessment of a wide range of heart lesions [2]. However individual transthoracic echocardiographic (TTE) signs have only modest sensitivity (29–79%) for the detection of a valve leaflet [3], especially in cases of mitral valve leaflets. Transesophageal echocardiography (TEE) improves visualization of the valve and gives a better diagnostic window for accurate identification of ruptured cordae, valve vegetations and valve leaflets. Nevertheless, both methods are different in diagnostic accuracy, especially in patients with subtle structural changes at the cardiac valves, which is particularly true for patients

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with previous valvular sclerosis or valve replacement [4,5]. Additional diagnostic information can be provided using scintigraphy. Despite ^{67}Ga-citrate [6–10], ^{99m}Tc-pyrophosphate [7,11] and in vitro labelled ^{111}In-oxine white blood cells [12–14], only ^{99m}Tc-labelled intact murine anti-NCA95 antigranulocyte antibodies [15,16] have been able to give satisfactory results in the imaging of subacute infective endocarditis. But the major drawback of using intact murine antibodies is the development of human antimouse antibodies (HAMA) [17,18] after repeated application. The human antimouse antibody response can be addressed in two ways. The first option is the administration of radiolabelled nonspecific polyclonal human immunoglobulin G [19,20]. A disadvantage of these antibodies is their nonspecificity, since a correct differentiation between specific uptake in an infectious focus and nonspecific accumulation in an inflamed lesion often is impossible. The second option is the use of fragments of antibodies instead of intact immunoglobulin G [21]. Several multicenter studies using ^{99m}Tc-labelled antibody fragments (^{99m}Tc-Fab′ fragment) for imaging patients with bone and soft-tissue infections were able to demonstrate a high degree of sensitivity and specificity [17,18]. Because of the smaller size of only 50 kDa and deletion of the terminal-Fc-fragment a fast, safe and repeated ^{99m}Tc-Fab′ fragment imaging can be achieved [22–24], which might be necessary especially for antibiotic therapy monitoring.

2. Patients and methods

For this study, 24 patients (mean age: 67 years; range: 21–89), 14 males and ten females, referred to the nuclear medicine department with FUO and predisposing heart disease were examined for endocarditis. As gold standard subacute endocarditis was diagnosed if the patient demonstrated two or more of the revised Duke criteria [25]: (1) major criteria: positive for bacteraemia, for valvular vegetation in the cardiac echogram, and a valvular prolapse; (2) minor criteria: predisposition, rectal temperature higher than 38.3°C for at least 2 weeks or more, immunologic phenomena and/or artheriosclerosis, suggestive echocardiogram, suggestive microbiologic findings, and new or changing heart murmur. The patients who were ultimately found to have no evidence of endocarditis served as control subjects.

2.1. Echocardiography

In all patients with suspected endocarditis, transthoracic echocardiography was performed using the two-dimensional, M-mode, Doppler and color-flow Doppler techniques in standard views. Studies were performed with Hewlett-Packard Sonos 1000 and 1500 ultrasound imaging systems with a 2.5-MHz transducer (Hewlett-Packard Co. Medical Products Group). If no vegetations were detected on transthoracic examination, transesophageal echocardiography was performed additionally using a single-plane 5.0-MHz probe with color flow Doppler capability (Hewlett-Packard 21362 A/C) on the same or the following day. The examinations were interpreted at the time they were performed by an experienced echocardiographer and documented on videotape for review by a second observer. Echocardiography was considered positive if vegetations, new valvular dysfunction with thickened valves, or perivalvular abscess could be demonstrated using either approach. Less specific signs of endocarditis, such as inconclusive valvular attachments that could either represent vegetations or sclerotic or myxomatous lesions, were considered negative.

2.2. Monoclonal antibody preparation and labelling

LeukoScan® (Sulesomab) is a ^{99m}Tc-labelled FaB′ fragment of IMMU-MN3, an immunoglobulin G1 murine monoclonal antibody produced from a hybridoma developed by fusion of murine myeloma (SP 2/0) cells with spleen lymphocytes obtained from a mouse immunized with carcinoembryonic antigen-.The antibody reacts strongly with nonspecific cross-reacting antigen 90 ($K_a = 0.5 \times 108 \pm 0.2 \times 10^8$ l/mol) present on human granulocytes [26,27]. The Fab′ fragment was provided in a ready-to-label lyophilized kit from Immunomedics, Inc. (Morris Plains, NJ). Labelling was accomplished by adding approximately 1000–1500 MBq of technetium-99m-pertechnetate in saline directly into the vial containing 0.31 mg of the monoclonal antibody Fab′ fragment and shaking sporadically during a period of 5 min. Performing the

radiolabelling exactly in this way, previous studies showed the presence of free technetium in the labelled product to be less than 1% [28]. For imaging of patients, 1100 MBq of technetium-99m sodium pertechnetate were diluted with saline and injected intravenously. Patients received an activity of 925±111 MBq for SPECT.

2.3. Imaging and interpretation

Whole-body images were obtained 4 and 24 h p.i. using a double-headed gamma camera (Prism 2000, Picker, Cleveland, Ohio) with a parallel hole, high resolution, low energy (HR) collimator using the 140-keV ^{99m}Tc peak, a 256×256 matrix and a preselected time of 25 min/image. Single photon emission computed tomography (SPECT) images of the thorax in patients with suspected endocarditis were mainly performed 17–26 h p.i. with a double-headed gamma camera (Prism 2000, Picker, Cleveland, OH; 128×128 matrix, 30 s/image, 30 images/6° angle-steps, a parallel hole high resolution, low energy collimator using the 140-keV ^{99m}Tc peak) and in rare cases with a triple-headed gamma camera (n=5) (Prism 3000, Picker, Cleveland, OH, 128×128 matrix, 30 s/image, 20 images/6° angle-steps, a parallel hole high resolution, low energy collimator using the 140-keV ^{99m}Tc peak). For SPECT reconstruction, an iterative algorithm was applied [29]. The scans were evaluated by two observers unaware of clinical data and were scored in two ways: (1) In all the patients with a circumscribed uptake in the area of the heart a ROI analysis was performed. Identically sized ROIs were drawn over the heart valve plane suspicious for endocarditis and an adjacent normal vascularized myocardial area. In patients with clinically proven endocarditis the uptake ratios (T/B= target to background ratio) together with the mean values and standard deviations were calculated. (2) A visual evaluation was performed while scans were scored as positive (tracer accumulation in the region of the valve plane or the ventricular outflow tracts visually equal to liver or bone marrow) or negative (no tracer accumulation in projection to the heart).

2.4. Statistic

Imaging sensitivity, specificity, positive predictive and negative predictive values and diagnostic accuracies were not calculated due to the small number of patients. In vitro laboratory tests were analyzed for significant differences by the paired Student's *t*-test.

3. Results

3.1. Characteristics of the endocarditis group

Of the 24 patients of this group enrolled in the study, seven proved to have subacute infective endocarditis (29%). When admitted, all seven patients had fever, an elevated Westerngreen sedimentation rate (ESR) and elevated C-reactive protein rate (CRP). All of the endocarditis patients were on antibiotics for more than 10 days prior to the scans. All of these seven patients demonstrated leukocytosis, or a left shift in the differential white blood cell count. In this group of patients with proven endocarditis, the pathogenic microorganism could be isolated in five of seven patients, whereas two patients had repeated negative cultures. Two of the seven patients had a mechanical aortic valve prosthesis and two a different cardiac condition clearly predisposing to endocarditis: one mitral valve failure, one endocarditis in the past, whereas the remaining three patients suffered from: one renal insufficiency, one hydronephrosis, and one patient had no predisposing history at all.

3.2. Characteristics of patients without endocarditis

Seventeen of 24 (71%) patients were ultimately found to have no evidence of endocarditis. All patients in this group had heart disease predisposing to endocarditis: five patients had prosthetic valves, five had myocardial infarction, five had coronary artheriosclerosis of at least two or three coronary arteries and two patient had valvular disease. Blood cultures were positive in six patients. In this group, the final diagnosis was: urogenitary tract infection/pyelonephritis/urosepsis in four patients, pneumonia in three patients, postmyocardial infarction syndrome in three patients, spondylitis in two patients, aortic vascular graft infection in one patient, one patient with Hodgkin's disease, one patient with non-Hodgkin's disease, one patient with breast carcinoma, and

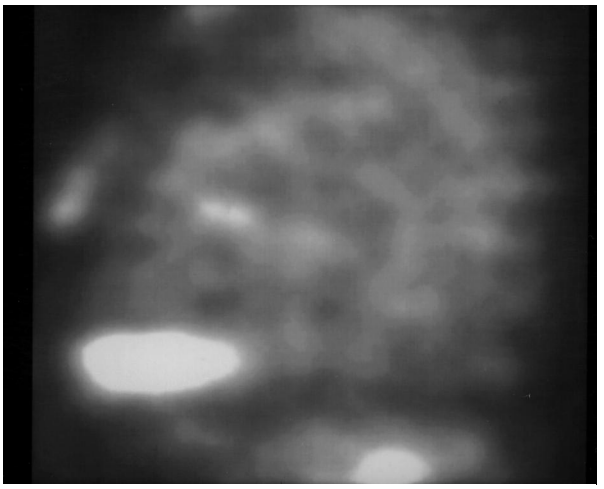

Fig. 1. A 56-year-old patient with endocarditis of the mechanical aortic prosthetic valve. ^{99m}Tc-Fab′ fragment scintigraphy (a) in the sagital slice shows the granulocytic accumulation on the valve plane.

one patient with myxoma of the right atrium associated with fever each.

3.3. Immunoscintigraphy

Immunoscintigraphy with ^{99m}Tc-Fab′ fragments showed significant tracer uptake in five of the seven studies positive for subacute endocarditis (Fig. 1). Tracer accumulation occurred in the projection to the heart valve plane, ventricular outflow tracts and adjacent endocardium. However, tracer uptake could not be assigned to a distinct cardiac valve. Semiquantitative measurements of target to background ratios in patients positive for endocarditis always showed T/B ratios $\geq 1.3 \pm 0.072$ (Fig. 2), whereas ratios below that showed true negative results.

Immunoscintigraphy was true negative in 16 of the 24 patients without endocarditis. Radioimaging was false-positive in one patient (Tables 1–3). This particular patient had pericardial effusion due to paravalvular leakage. Because of residual blood pool activity on tomographic scans, only the images obtained 24–26 h p.i. after injection could be evaluated accurately. Follow-up studies were performed in two of the five scintigraphically proven positive for endocarditis. In both patients, immunoscintigraphy became negative with clinical improvement, whereas the vegetations persisted and echocardiography remained positive.

Outside the heart immunoscintigraphy was able to detect lesions which were clinically not known:

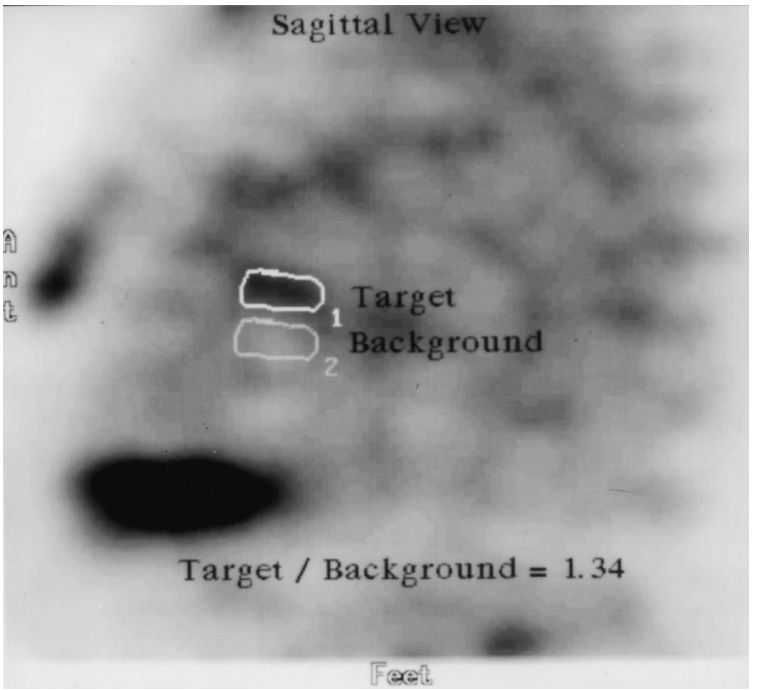

Fig. 2. The target to background ratio in the same patient with the proven mechanical aortic prosthetic valve endocarditis was T/B=1.34. Identical sized regions were laid over the suspicious heart valve and over the adjacent normal vascularized myocardial area.

Table 1
Description of all patients enrolled in the study[a]

Patient	Age (years)	Sex	PHD	Fever (in °C)	CRP (mg/l)	ESR (mm/h)	Leucocytes (count/mm^3)	Isolated microorganism	TTE — TEE	Localization	LeukoScan®
1	67	M	MS	39	314	68	23 300	sterile	+/+/− +/+/+	Mitralic	False −
2	78	F	AV	39.1	28.0	45	4600	*Streptococcus bovis*	−/−/− +/+/+	Aortic	Correct +
3	43	M		39.9	47	36	10 200	*Streptococcus* G	+/+/− +/+/+	Aortic	Correct +
4	36	M		38.6	103		26 000	*Bacillus fastidiosus*	−/−/− +/+/+	Mitralic	Correct +
5	21	F	AV	38.4	309	72	16 600	*Strept. constellatus*	+/−/− +/−/−	No infection	−
6	77	M	AV	37.2	54	52	6600	Sterile	−/−/− +/+/−	Aortic	False −
7	62	M		38.2	38	61	7000	*Enterococcus sakazakii*	−/−/− +/−/−	Mitralic	Correct −
8	71	F	MPV	38.8	91	55	7200	Sterile	−/−/− −/−/−	No infection	−
9	72	F	MPV	36.8	54	71	6000	*Staphylococcus epidermis*	+/−/− −/−/−	No infection	−
10	76	M	APV	38.5	33	51	14 800	*E. faecalis*	+/−/− −/−/−	No infection	False +
11	65	M	APV	40	96	62	23 000	Sterile	+/+/− +/+/−	No infection	Correct −
12	86	F	Infarct	38.5	110	85	17 800	*Staph. aureus*	+/+/− −/−/−	No infection	−
13	71	M	Infarct	38.2	95	68	13 500	Sterile	−/−/−	No infection	−
14	89	M	Infarct	38.5	332	105	11 700	Sterile	−/−/− −/−/−	No infection	−
15	75	F		38.2	143	90	10 600	Sterile	−/−/− −/−/−	No infection	−
16	81	M	APV	36.4	108	60	14 500	*Pseudomonas aeruginosa*	−/−/− −/−/−	No infection	−
17	58	M	Infarct	36.5	119	100	10 700	Sterile	−/−/− +/+/−	No infection	Correct −
18	74	F	Infarct	37.6	102	94	6700	Sterile	−/−/− +/+/−	No infection	Correct −
19	68	M	AL	39.7	144	88	12 200	*Staph. aureus*	+/−/− +/+/+	Aortic	Correct +
20	78	F	Myx	37.1	78	56	6300	Sterile	+/+/+ +/+/+	No infection	Correct −
21	71	M	CAS	37.2	60	69	6500	Sterile	−/−/− −/−/−	No infection	−
22	70	F	CAS	38.9	76		6800	Sterile	−/−/− −/−/−	No infection	−
23	59	M	CAS	38.2	81	85	8900	Sterile	−/−/−	No infection	−
24	60	F	CAS	39.2	78	54	7300	Sterile	−/−/−	No infection	−

[a] Abbreviations: ESR, erythrocyte sedimentation rate; WBC, white blood cell count (leukocytes); CRP, C-reactive protein; PHD, predisposing heart disease; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; Myx., myxoma in the atrium; +/+/+ or −/−/−, presence or absence of vegetations/new valvular dysfunction/perivalvular abscess, respectively; MS, mitral stenosis; AI, aortic insufficiency; AV, aortic vitium; MPV, mitral prosthetic valve; APV, aortic prosthetic valve; CAS, coronary artery stenosis; Infarct, myocardial infarction.

Table 2
Summary of mean value and standard deviation of the fever, CRP, ESR, and leucocyte values[a]

	Fever (in °C)	CRP (mg/l)	ESR (mm/h)	Leukocyte (count/mm^3)
Mean	38.28	112.0	68.00	11 616.00
$\bar{x}\pm$S.D.	1.01	83.7	18.63	5904.00

[a] Normal values: CRP <8.0 mg/l, ESR <15 mm/h, WBC 4.0–11.0×10^9/l.

spondylitis in two patients and aortic vascular graft infection in one patient. Independent of the grade of vertebral infection, all lesions were photopenic. Of particular interest was patient five in Table 1: in this 21-year-old female patient immunoscintigraphy was performed on day 21 after implantation of an aortic vascular graft because of traumatic aortic dissection. Due to unclear echocardiographic findings, immunoscintigraphy was performed. ^{99m}Tc-Fab′ fragments

Table 3
Statistical evaluation of T/B ratios in all patients with proven endocarditis[a]

Patient No. (see above)	Age (years)	TTE — TEE	Localization	T/B ratio LeukoScan®
2	78	−/−/− +/+/+	Aortic	1.34
3	43	+/+/− +/+/+	Aortic	1.41
4	36	−/−/− +/+/+	Mitralic	1.36
7	62	−/−/− +/−/−	Mitralic	1.29
19	68	+/−/− +/+/+	Aortic	1.48
Mean				1.376
$\bar{x}\pm$S.D.				0.072

[a] Abbreviations: T/B, target to background; TTE — TEE, transthoracic/transesophageal echocardiography; PV, predictive value.

correctly detected the extension of the graft's infection as well as a mycotic aneurysm (Fig. 3) of the popliteal artery.

Regarding the diagnostic accuracy of ^{99m}Tc-Fab′ fragments and in vitro laboratory tests, no significant differences were found for the white blood cell count, the Westerngreen erythrocyte sedimentation rate and the C reactive protein in patients with endocarditis ($P=0.37–0.44$).

3.4. Echocardiography

Transthoracic echocardiography was suggestive of active endocarditis in two of seven patients with proved endocarditis. The transesophageal (Fig. 4) approach revealed signs of endocarditis in six of seven patients. Transesophageal echocardiography proved to be superior compared with transthoracic echocardiography especially in patients with vegetations $\leq$1.5 cm and mechanical valve prosthesis.

Transesophageal echocardiography was false positive in four of the 17 control patients. The four patients thought to have valve vegetation ultimately proved to have thickening of mechanical aortic valve insertion, floating but not infected flail leaflet, pericardial effusion, and myxoma of the right atrium (Fig. 5).

3.5. Comparison between immunoscintigraphy and echocardiography

Immunoscintigraphy with ^{99m}Tc-Fab′ fragments was true negative in all four patients in the control group with suspected echocardiographic findings,

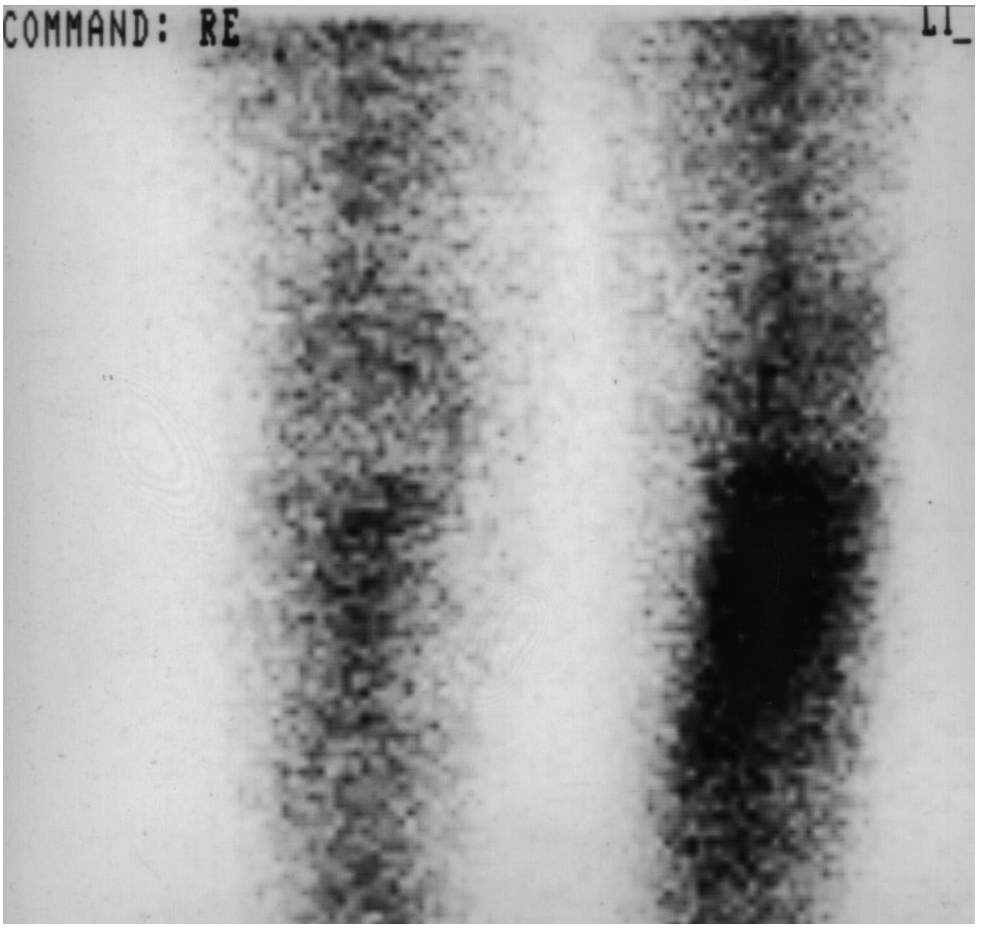

Fig. 3. In one patient outside the thorax ^{99m}Tc-Fab′ fragment imaging localized an increased uptake in projection to the right tibia, which histologically corresponded to a mycotic aneurysm of the popliteal artery. This finding was not known so far.

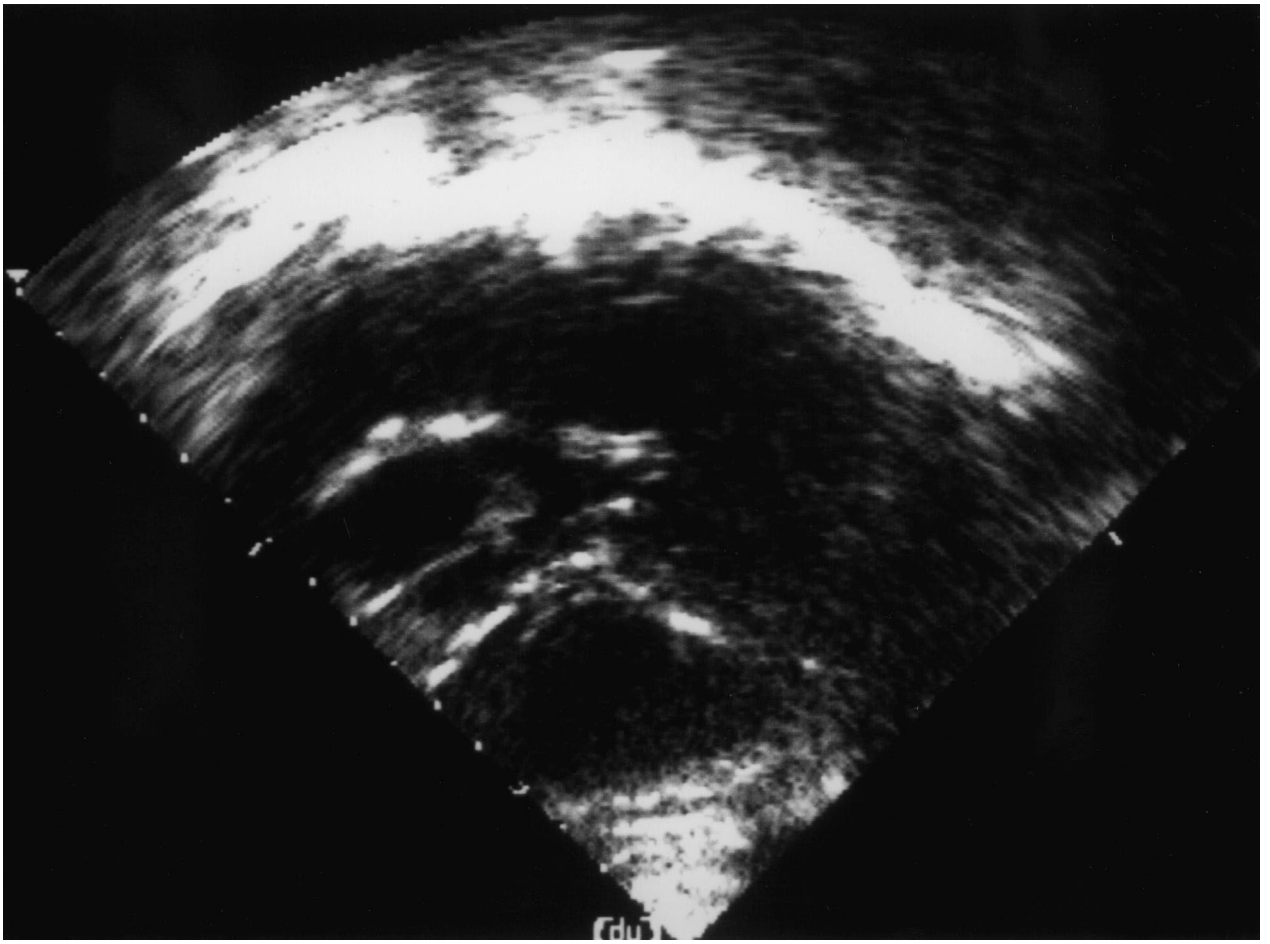

Fig. 4. The transesophageal echocardiography reveals the mechanical aortic prosthetic valve endocarditis illustrated with ^{99m}Tc-Fab′ fragment imaging in Fig. 1.

and, vice versa echocardiography was true positive in the two patients with false negative scans. There was no patient with proven endocarditis without either positive scintigraphy or echocardiography. Therefore, the combination of both methods increased the number for detecting subacute infective endocarditis drastically.

3.6. Follow-up studies

Follow-up studies were performed in 2 of 7 patients with proved endocarditis. In both patients ^{99m}Tc-Fab′ fragments scintigraphy became negative parallel to clinical improvement. Echocardiographically vegetations persisted to be positive at the time point of imaging. Late follow-up studies were not obtained in these patients due to nuclear medicine and clinical results.

No adverse reactions due to the antibody injection were observed.

4. Discussion

This study presents a novel indication of a ^{99m}Tc-labelled monoclonal antigranulocyte Fab′ fragment for non-invasive localization of florid granulocytic lesions involving endocarditis. Especially in patients with valve prostheses ($n=7/24$ in this study), there is a well known increase in prosthetic valve endocarditis among patients with endocarditis [30–33]. In clinical practice, the majority of patients with infective endocarditis are still diagnosed using clinical,

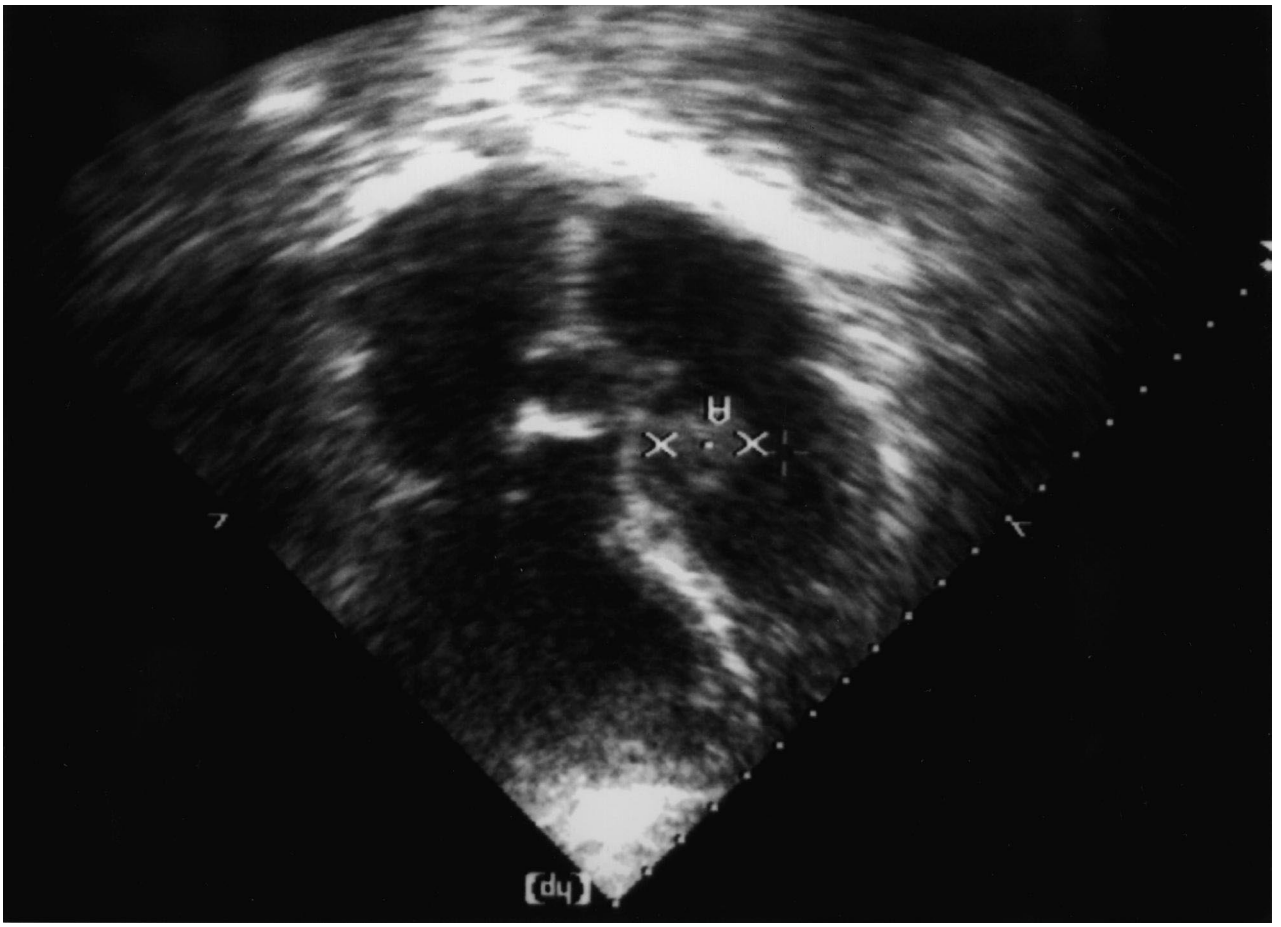

Fig. 5. The transthoracic echocardiography shows a structure in projection to the valve plane highly suspicious for an infected vegetation. Immunoscintigraphy with ^{99m}Tc-Fab′ fragment instead correctly showed no uptake. The final diagnosis was a myxoma of the right atrium.

bacteriological and endocardiographic findings, but major diagnostic problems usually have to be expected [1], and overdiagnosis and underdiagnosis of infective endocarditis are common. Endocarditis generally can be subdivided into culture positive and culture negative cases. Among all patients suffering of endocarditis, culture positive cases were reported to be predominant in 83% of all cases (33). Culture negative cases instead were reported in 7–24% of all cases and were especially found in patients under long-term antibiotic therapy and the apparent cause of negative culture was the administration of antibiotics [34]. Vital granulocytes on the surface of vegetations can be expected in culture positive more often than in culture negative cases. Potential targets for using immunoscintigraphy with ^{99m}Tc Fab′ fragments in infective endocarditis are inflammatory infiltrates in the valvular and perivalvular endocardium and adjacent myocardium, as well as myocardial and perivascular abscesses. The inflammation tends to involve the valvular annulus and the adjacent myocardium, especially in endocarditis of native aortic valves [35,36] and mechanical prostheses [37–41]. The kinetics of radiolabeled antibodies for in vivo labelling of granulocytes are different from those of in vitro-labelled granulocytes and may foster cardiac uptake. This may partially account for the markedly improved sensitivity in past studies using ^{99m}Tc-intact antibodies (BW 250/183) [16] compared with the in vitro approach [42].

Cardiac ultrasound still plays the key role in the diagnosis and follow-up of subacute infective endocarditis [5]. Echocardiographic recognition of a vegetation does not necessarily mean that the lesion is

active. The reliability of echocardiography depends upon the quality of available equipment and the experience of the staff [43]. Especially the transesophageal approach detects vegetations with confirmed infective endocarditis, with a resolution down to 2–3 mm of size [1,44]. The spatial resolution of transesophageal echocardiography is far better than that of ^{99m}Tc-Fab′ fragment SPECT immunoscintigraphy and transthoracic echocardiography. The sensitivity of transesophageal echography is known to be superior to transthoracic echocardiography [5]. In our study the number of true positives of transthoracic echography was within the usual range with 2/7, but comparatively better for transesophageal echocardiography, at 6/7 [5]. This in part might be due to the high proportion of false positive findings (n=4) for transesophageal echocardiography which were predominantly seen in patients with mechanical prosthesis, previously diseased valves or myxoma of the atrium in the present series. A correct exclusion of an inflammatory process at the valve level in these 4 patients could be performed with ^{99m}Tc Fab′ fragments.

However, scintigraphic activity accumulation on the other side does not seem to be confined to vegetations, but rather localizes granulocytic inflammatory disease involving valvular leaflets, connective tissue of the valvular annulus and adjacent endocardium. For this reason radioimmunoimaging using ^{99m}Tc-Fab′ fragments provides information of the extent of the granulocytic infiltration of endocardium and the floridity of infection. This seems to be the reason why diagnostic limitations were seen with immunoimaging with ^{99m}Tc Fab′ fragments in two patients with culture negative results, since both classified as false negative cases. In these particular cases, a correct diagnosis of infected endocarditis was possible with transesophageal echocardiography in both patients and with transthoracic echocardiography in only one patient.

Owing to limited spatial resolution and partial-volume effects, however, a correct determination of the valve involved in the inflammatory process by SPECT immunoscintigraphy with ^{99m}Tc-Fab′ fragments alone was not possible.

In two patients with repeated radioimaging, tracer accumulation resolved parallel to clinical improvement under long-term antibiotic therapy. In these two patients echocardiography remained positive in demonstrating a vegetation on the valve level. This suggests that immunoscintigraphy with ^{99m}Tc-Fab′ fragments is able to monitor the floridity of granulocytic infiltration in infected endocardium. On the other hand, echocardiography is known not to be able to differentiate between active and inactive vegetations.

We know that the small number of patients is the major drawback of this pilot study and that the small number of the patients does not allow any definite conclusions as of yet. But the results of the present data show that echocardiography and immunoscintigraphy can be complementary; that is, especially in all patients with false positive echocardiography, immunoscintigraphy with ^{99m}Tc Fab′ fragments was correctly negative and vice versa. Therefore, the sensitivity for diagnosing infective endocarditis using the combination of both methods increases dramatically.

5. Conclusion

The combination of echocardiography and immunoscintigraphy using ^{99m}Tc Fab′ fragments aids in the diagnosis of infective endocarditis. The results of ^{99m}Tc-Fab′ fragments are comparable to published data of intact IgG (BW 250/183) [15,16] in the same patient population. HAMA formation is not to be expected after repeated use.

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