The Utility of Gallium Scintigraphy in the Evaluation of Fever of Unknown Origin

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Abstract

Background: Gallium scintigraphy is frequently used in the evaluation of fever of unknown origin, although its utility has been addressed in only a few studies.

Objectives: To evaluate the utility of gallium scintigraphy in the evaluation of patients with FUO in our department.

Methods: We reviewed the charts of all patients from our department who had undergone gallium scintigraphy during the years 1995–2002 for the evaluation of FUO and who met the criteria for the definition of FUO. Demographic, clinical and laboratory data in addition to the results of gallium scintigraphy were documented. The patients were divided into two groups: those with a normal gallium study (group 1) and those with an abnormal gallium study (group 2). The second group was further divided into two groups: those whose gallium study results contributed to the diagnosis of the cause of FUO (group 2A) and those whose gallium study results did not (group 2B).

Results: A total of 102 patients met the study criteria. The male: female ratio was 54:48 and the mean age $\pm$ SD was 62.4 $\pm$ 20 years. A final diagnosis had been reached in 63 patients (62%), among whom the etiology was infectious in 54%, neoplastic in 19% and immunologic/rheumatic in 16%. Forty-one patients (40% of all the patients) (group 2) had an abnormal gallium scintigraphy, and in only 21 patients (21% of all the patients) (group 2A) did the gallium study results contribute to the diagnosis of the cause of FUO. However, in only two patients from group 2A (2% of all the patients in our study) was the contribution of gallium study considered significant or crucial to the diagnosis of the cause of FUO.

Conclusions: The utility of gallium scintigraphy in the evaluation of FUO is very limited.

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Fever of unknown origin is one of the more challenging medical problems in the medical ward. The major causes of FUO are usually infectious, neoplastic and rheumatic diseases; however, some patients are left without a clear diagnosis [1]. In order to reach a diagnosis a long series of different tests is usually performed. One of the modalities used to reveal the cause of FUO is gallium scintigraphy. The rationale for gallium scintigraphy is that this tracer accumulates in inflammatory and neoplastic cells, and since the majority of FUO cases turn out to be infectious or neoplastic etiologies this modality of evaluation should be useful [2]. However, the utility of this procedure has been addressed in only a few studies. Knockaert et al. [3] reported that gallium scintigraphy was positive in 57% of all patients with FUO and in 51% of them (29% of all the patients) the scan was considered helpful. In the same population only 14% and 7% of the computed tomograms and ultrasounds, respectively, were helpful. Therefore, they recommended using gallium scintigraphy in the evaluation of FUO as a second line if the patient's history, routine blood tests, chest X-ray and ultrasound of the abdomen were negative. On the other hand, Larson et al. [4] found gallium scintigraphy positive in 47% of patients with FUO, but in only 17% of all the patients was it helpful and many patients had false positive results. Relatively few CT and ultrasound tests were performed in that study. The authors contend that this low positive rate and the high rate of false positive results limit the use of gallium scintigraphy in the evaluation of FUO.

Over the years there has been considerable progress in the quantity and quality of the different methods used in the evaluation of FUO. Recently, new tracers were introduced for the evaluation of infectious and neoplastic diseases [5,6]. In the present study we evaluated the utility of gallium scintigraphy in the evaluation of FUO in our patients.

Patients and Methods

We reviewed the charts of all patients from our department who had undergone gallium scintigraphy according to the registry of the nuclear medicine department during the years 1995–2002. The charts of patients who underwent this procedure for the evaluation of FUO were reviewed according to the criteria for the definition of FUO: fever of > 38.3°C on several occasions for more than 3 weeks duration and no diagnosis after 1 week of in-hospital investigation [7]. Neutropenic fever was not included. The charts were reviewed by the first two authors. The parameters included age and gender of the patient, duration of fever, symptoms and signs in addition to the fever, medical background, results of the different tests including gallium scintigraphy, diagnosis of the patient if documented, types of treatment, and the course of fever.

The protocol for the evaluation of FUO in our department includes complete and repeated history and physical examination, daily rounds of the medical team with a senior physician, complete blood cell counts and chemistry profiles, urinanalysis, urine and blood cultures, serologic tests and chest X-ray. Further investigation includes ultrasound study of the abdomen, echocardiogram, CT of the chest, abdomen and pelvis, and finally gallium scintigraphy. Other scintigraphic studies (bone scan, thyroid scan and ventilation perfusion scan), colonoscopy, gastroscopy, bone marrow biopsy, temporal artery biopsy or other biopsies were done

FUO = fever of unknown origin

if there were clues suggesting these procedures or according to the judgment of the medical team. In addition, the consultants who had dealt with the case would be asked for their opinion.

The patients were then divided into two groups: those with normal gallium scintigraphy (group 1) and those with abnormal gallium scintigraphy (group 2). The second group was then subdivided into two groups: those in whom the abnormal finding did contribute to the final diagnosis (group 2A) and those in whom it did not (group 2B). The results were considered contributory only if the findings were related to the cause of FUO.

Gallium scintigraphy was performed as follows: planar whole-body anterior and posterior images and tomographic images were obtained 48 hours after the injection of 8–10 mCi (296–370 MBq) of gallium-67 citrate with a dual-head SPECT camera (Varicam, Elscint, Haifa, Israel) using parallel-hole medium energy collimators and triple-energy peaks of 93, 184 and 300 Kev with a 10% window. When necessary, repeat images were obtained 72 or 96 hours after the injection. On planar images 1,000 K counts were acquired per view. For the tomographic images 60 projections (45 seconds per projection) were acquired over a 360 degree circular orbit with a matrix size of 64 x 64 and zoom 1.28. Images were reconstructed with filtered back-projection, using a Metz filter with power 3 and full width half-max 14. After reconstruction trans-axial, coronal and sagital slices were obtained.

Results

Altogether, 236 patients were identified, but the charts of only 223 were located. Gallium scintigraphy not for the investigation of FUO was performed in 48 patients; 63 patients did not fulfill the criteria for the definition of FUO, and 10 patients had neutropenic fever. Thus, 102 patients were considered for evaluation. Table 1 summarizes the demographic, clinical and laboratory characteristics of these patients. Most of our patients were elderly, with a mean age of 62.4 years. A final diagnosis was reached in 63 patients (62%). Among the 39 patients without a final diagnosis, the fever resolved in 25 during their stay in the ward. Most of these patients received empiric antibiotic treatment, usually cefuroxime intravenously alone or followed by more broad-spectrum antibiotics. In 10 patients (of these 39 without a final diagnosis) the fever persisted even after empiric antibiotic treatment and extensive work-up. Four other patients died during their stay on the ward; all four were above the age of 75 and the cause of death was sepsis due to nosocomial infections that developed during their stay in the ward. None had an autopsy performed.

Table 2 summarizes the different causes of FUO in the patients with a final diagnosis. More than half the patients had an infectious etiology, 19% had a neoplastic etiology and 16% had an immunologic/rheumatic cause of FUO. Urinary tract infection, lymphoma, and temporal arteritis were the most common causes of FUO in these categories respectively.

Sixty-one patients (60% of all the patients) had a normal scintigraphy study (group 1), thus only 41 patients (40% of all the patients) in our study had an abnormal gallium scintigraphy (group 2) [Table 3]. Moreover, in nearly half the patients from group 2 (20 patients, group 2B) the finding on gallium scintigraphy did not contribute to the final diagnosis. An example is the patient with lupus who sustained a recent traumatic fracture of the left leg where

Table 1. Patients' demographic, laboratory and clinical characteristics

Age	
Mean ± SD	62.4 ± 20
Range	18–90
Male: Female	54:48
Duration of fever prior to gallium scintigraphy (days)	
Mean ± SD	33 ± 16
Range	21–82
Erythrocyte sedimentation rate	
Mean ± SD	79 ± 33
Range	12–130
White blood cells/ml	
Mean ± SD	7,545 ± 3,625
Range	1,800–16,300
No of patients with final diagnosis	63
No. of patients discharged with fever and without a diagnosis	10
No. of patients who died	4

Table 2. Causes of FUO according to category

Causes of FUO	No
Infectious (n=34)	
UTI	6
Endocarditis	4
Pulmonary	3
Brucella	3
Epididymitis	3
Tuberculosis	2
Sinusitis	2
Infected bed sores	2
Epstein-Barr virus	2
Cytomegalovirus	2
Osteomyelitis	1
Pelvic inflammatory disease	1
Otitis	1
Mediastinitis	1
Shoulder abscess	1
Neoplastic (n=12)	
Lymphoma	7
Adenocarcinoma of colon	2
Bronchogenic carcinoma	2
Malignant fibrous histiocytoma	1
Immunologic/rheumatic diseases (n=10)	
Temporal arteritis	4
Systemic lupus erythematosus	2
Sweet's syndrome	1
Churg-Strauss syndrome	1
Chronic erythema nodosum	1
Sarcoidosis	1
Others (n=7)	
Drug fever	3
Inflammatory bowel disease	2
Pulmonary emboli	1
Radiation pneumonitis	1

Table 3. Gallium scintigraphy results according to category and contribution to diagnosis

		Abnormal gallium scintigraphy		
Causes of FUO	Normal gallium	Total	Contribute	Did not contribute
Infectious (n=34)	23	11	7	4
Neoplastic (n=12)	0	12	9	3
Immunologic/rheumatic (n=10)	4	6	3	3
Others (n=7)	4	3	2	1
Unknown causes (n=39)	30	9	0	9

Numbers given are the number of patients

there was increased uptake. In only two patients from group 2A (out of a total of 21 patients) was there a significant contribution to the diagnosis. One patient who had Hodgkin's lymphoma and was in remission suffered from mild left lateral thigh pain in addition to the fever. X-ray of the left thigh was negative, as was the other usual work-up of FUO, including chest and abdominal CT. Gallium scintigraphy showed a focus of increased uptake at the proximal left femur. Bone biopsy from this area yielded Hodgkin's lymphoma involving the bone; fever resolved after chemotherapy. The second patient with a fever of 3 weeks duration had a suspected urinary tract infection. CT of the abdomen showed a cystic lesion most probably of the right ovary, and ultrasound revealed a poorly defined lesion above the uterus. Gallium scintigraphy demonstrated increased uptake at the right lower abdomen. A gynecologist suspected pelvic inflammatory disease and eventually surgery revealed tubo-ovarian abscess.

In the remaining 19 patients of group 2A there was some contribution of the study but it was not significant, and in most of the cases the findings were compatible with those yielded by CT, ultrasound, physical examination and/or other evaluating modalities that were performed prior to gallium scintigraphy. An example is the patient with cervical and mediastinal lymphadenopathy and elevated lactate dehydrogenase level in whom lymphoma was highly suspected. Gallium scintigraphy showed increased uptake at the enlarged lymph nodes and eventually the diagnosis was confirmed by biopsy.

Discussion

Our study shows that the utility of gallium scintigraphy in the evaluation of fever of unknown origin is very limited. In only 2% of the studies for the evaluation of FUO did this modality contribute significantly towards reaching a diagnosis. Sixty percent of all our patients and 77% of those without a final diagnosis had a normal study. These figures are higher than those reported by Knockaert et al. [3] and closer to the figures given by Larson et al. [4].

More than two-thirds of the patients with infectious etiology had a normal gallium scintigraphy. Abnormal studies were seen in patients with a more localized source of infection like osteomyelitis, bed sores, mediastinitis and shoulder abscess. In the study by Knockaret et al. [3], the percentage of contributory gallium scintigraphy among infectious etiologies was more than 50%. The distribution of different etiologies, with increased prevalence of urinary tract infection and decreased prevalence of more localized infections like abscesses, most probably contributed to the low positivity of gallium scintigraphy among our patients. The percentage of UTIs in our series is relatively high. All of these patients had partially treated infections or resistant bacteria. Only a few series include UTI as a cause of FUO [1], however UTI is a frequent and important cause of FUO among children [8]. All of our patients with endocarditis had either a normal or a non-contributory study. According to the literature, the results obtained with gallium scintigraphy in patients with endocarditis are not convincing [9]. Most of the reports of contributory positive findings are case reports. In only one patient of those with an infectious etiology was the contribution of gallium scintigraphy significant. This patient had a para-uteral mass seen by CT and ultrasound, but this was more characteristic of an abscess according to the gallium scintigraphy. In the other patients the results of the scans were compatible, especially to the CT findings, but not crucial for the diagnosis. The specificity and sensitivity of CT in the evaluation of localized infection is very high [10]. Accordingly, among patients with a suspected infectious etiology and features suggestive of a non-localized source, the gallium scintigraphy will probably be normal.

All patients with neoplastic diseases as a cause of FUO (12 patients) had abnormal gallium scintigraphy, and in 9 of them (75%) the uptake had contributed to the final diagnosis including one patient with a crucial contribution. This patient had a flare of Hodgkin's lymphoma involving the bone. Gallium scintigraphy has a high sensitivity and specificity for the diagnosis of lymphoma of the bone [11]. However, in the other eight patients the final diagnosis was high on the list of the differential diagnoses with gallium scintigraphy based especially on the CT findings. In general, CT is considered more sensitive than gallium scintigraphy for the diagnosis of lymphoma of the abdomen, and vice versa for the chest [12]. The newly used tracer of fluorine-18 fluorodeoxyglucose positron emission tomography is considered even more sensitive for the detection of active lymphoma tumor than gallium scintigraphy or CT [13]. Therefore, in patients with a suspected neoplastic etiology of FUO but with findings not clearly defined, gallium scintigraphy could be helpful.

All our patients with temporal arteritis (four patients) had normal gallium scintigraphy. In a recent study it was shown that gallium is specifically incorporated into the temporal area in patients with temporal arteritis [14]. Our results could be attributed to the fact that our studies did not focus on the temporal area, since none of them was highly suspicious for temporal arteritis. Among the rest of the patients with immunologic/rheumatic diseases (n=6), all had an abnormal study and in half of them the study contributed to the diagnosis but was not crucial.

Gallium scintigraphy is considered more sensitive than chest radiographs for the early detection of radiation pneumonitis [15]. The study in our patients was considered contributory and the diagnosis was suspected prior to that by CT.

UTI = urinary tract infection

Treatment with empiric antibiotics is common practice in patients with FUO, especially when many patients end with infectious etiology. In many of the 25/39 patients without a final diagnosis the fever abated on the ward where patients were given empiric antibiotics. This recovery could be directly related to the treatment or it might have been coincidental. This is purely speculative regarding the cause of FUO in these patients. Some of them could have had a small focus of infection that could not be detected and responded to antibiotics.

Conclusions

The value of gallium scintigraphy in the evaluation of FUO is very limited. In patients with infectious etiology and in those without a final diagnosis the scan is usually normal. However, in those with rheumatic and neoplastic etiologies the scan is usually positive but will rarely add information not obtained by previously performed studies and anatomic imaging. A higher yield could be attained if gallium scintigraphy is ordered selectively, especially for those in whom abscess or neoplastic etiology is likely to be the cause of FUO.

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Capsule

Is physical exercise effective rehabilitation for all cancer patients?

Physical exercise as an intervention in cancer patients has attracted increasing interest. Oldervoll examined the published randomized controlled trials on physical exercise during and after cancer treatment, focusing primarily on recruitment of patients, patient compliance, content of the intervention programs and outcome measures. The authors performed systematic searches of PubMed, PsychInfo, Cancerlit and the Cochrane Library, using the MESH terms exercise, neoplasms, cancer, rehabilitation, and intervention, and identified 12 randomized trials with sample sizes ranging from 21 to 155 patients. Only four studies reported the number of patients assessed for eligibility and the reasons for exclusion; 15% to 30% of patients assessed for eligibility were randomized into the intervention programs. Drop-out rates in the trials ranged from 0% to 34%. Most studies included female breast cancer patients (nine studies, 62% of total number of patients). Interventions included aerobic exercise training (10 studies) and resistance exercise (two studies). The studies used a wide range of instruments to assess health-related quality of life (HRQOL) and the physical exercise capacity. The studies indicated promising effects on both physiologic and psychological outcomes. Randomized clinical studies are few, small in scope, and mainly focus on breast cancer patients. Complete knowledge about the type of physical exercise most beneficial for patients at different stages of the disease progression is still lacking. Future work should identify fewer and more specific endpoints.

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