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# IS THERE STILL PLACE FOR GALLIUM SCINTIGRAPHY IN FEVER OF UNKNOWN ORIGIN?

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SUMMARY – Owing to its characteristics, gallium 67 citrate still has its place in diagnostic procedures for various diseases, among them fever of unknown origin. Because of the lack of specificity of gallium 67 citrate, which is an advantage in this case, most authors agree that gallium is practically the agent of choice for initial screening of these patients. Gallium 67 citrate accumulates at the site of inflammation/infection as well as in some neoplasms. Positive gallium finding can demonstrate or exclude a focal or diffuse lesion, indicate the disease extent and activity, and identify an appropriate biopsy site if necessary.

Key words: *Gallium radioisotopes – diagnostic use; Fever of unknown origin – etiology; Radiopharmaceuticals – diagnostic use*

## Introduction

A wide range of pathologic conditions can cause prolonged fever. In the era of positron emission tomography (PET) and various new cyclotrone produced radiopharmaceuticals, there is still a question of the role of gallium (Ga) scintigraphy, especially in settings where PET is not available.

Fever of unknown origin (FUO) is defined as an illness of at least 3-week duration with fever greater than 38 °C on several occasions, and no established diagnosis after one week of studies. This definition has not changed in the last 50 years[1-3]. It should be distinguished from patients with prolonged fever, i.e. those with a coexisting disease or recent surgery.

Identifying the precise cause of FUO is not an easy task. No single test can provide the diagnosis, but scintigraphic methods play an important role. They can demonstrate or exclude a focal or diffuse lesion.

The underlying causes are numerous, often depending on the country or region of the world, with infection/inflammation accounting for approximately 20%-25% or somewhere even 40% of cases. Malignancies are the cause of FUO in 15%-25% of cases (rarely solid tumors, which are infrequent causes of FUO and tend to be diagnosed with other modalities) and collagen-vascular diseases in 15%, whereas some 10%-22% of cases remain undiagnosed[4-8].

## Material and Methods

During the 1991-2005 period, 27 patients underwent gallium scintigraphy for evaluation of FUO at our Department. There were ten women and 17 men aged 18-73 (average 48, median 49) years. The duration of fever ranged from one to 20 (average 5, median 2) months. Gallium scintigraphy was performed at 48 hours and 72 hours if necessary after the intravenous injection of 50 MBq 67-Ga-citrate. All patients underwent whole body scan and single images of 15-min duration.

## Results

Five of 27 patients had normal gallium distribution and the etiology of FUO could not be identified. Three patients had been previously ill, but developed fever several months of therapy completion and the cause of

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fever could not be detected by other methods. One of these patients had undergone urologic operation, a stoma was made, a swab obtained from the skin surface was sterile, and gallium scan was positive showing pathologic subcutaneous accumulation of the radiopharmaceutical. Another patient developed a perirenal abscess two months of completing his therapy for sepsis. One patient had undergone orthopedic reoperation and became febrile three months later. Gallium scintigraphy showed a negative local finding but diffusely increased gallium accumulation was found in both lungs, almost of the liver intensity. The patient was HIV negative, yet with a high probability of immunologic compromise, and the finding could be the cause of fever as the result of infection with some of opportunistic organism.

Three patients had gallium distribution suggesting pulmonary sarcoidosis, and one patient had increased diffuse gallium accumulation in the liver; in all of them sarcoidosis was confirmed by liver biopsy.

Gallium distribution suggesting hematoproliferative disease was recorded in eight patients; lymphomas with gastric involvement were confirmed in five of them, whereas in three patients no further information was available. One patient had gastric involvement alone, and gastritis or lymphoma could be the possible reason, however, no further information was available. Any additional information was also lacking in a patient with multifocal uptake in bones; this could be a case of multifocal osteomyelitis. Perirenal abscess was confirmed in another two patients. Pathologic gallium accumulation resembling subphrenic abscess was observed in one patient, however, without any further information. Biopsy confirmed Wegener's granulomatosis was found in two patients.

In our patient series, normal finding was recorded in five (19%) and abnormal gallium accumulation in 22 (81%) patients. Definitive diagnosis with a contributory role of gallium scintigraphy was established in 16 (59%) patients from the latter group. In six (22%) FUO patients with abnormal gallium scan we had no further information and it was considered noncontributory to the diagnosis. The percentage of noncontributory scans would be even greater (41%) if adding five (19%) patients with normal scans that did not solve the problem. The patients with normal gallium distribution could also make a group of undiagnosed cases.

An overview of our results is presented in Table 1.

## Discussion

FUO still poses a major diagnostic problem. An accurate diagnosis is essential in these patients, however, despite improved diagnostic procedures, some literature data have surprisingly shown the percentage of FUO patients in which the diagnosis cannot be achieved to be on an increase[2].

An ideal agent should be able to distinguish between infective and non-infective causes of FUO. Two thirds of the causes represent the foci of both of them, and gallium detects them all. Labeled white blood cells are

*Table 1. Overview of our results with gallium scintigraphy*

| No. of patients | Mode of distribution | Confirmed diagnosis | No response | % |
|---|---|---|---|---|
| 5 | Normal | | | 19 |
| 1 | Stoma | Inflammation | | |
| 3 | Perirenal | Perirenal abscess | | |
| 1 | Lung - diffuse | Infection | | |
| 3 | Lung - diffuse "lambda" | Sarcoidosis | | 59 |
| 1 | Liver | Sarcoidosis | | |
| 5 | Bone marrow, gastric, spleen | Lymphoma | | |
| 2 | Kidneys, lung | Wegener's | | |
| 3 | Bone marrow, | granulomatosis | | |
| | lymph nodes, hematoproliferative | | + | |
| 1 | Gastric uptake | | + | 22 |
| 1 | Multifocal bone uptake | | + | |
| 1 | Suggesting subphrenic abscess | | + | |
| 27 | | 16 | 6 | 100 |

of limited value due to the low prevalence of purulent processes. Furthermore, in lesions with predominantly monocytic and/or lymphocytic infiltration it is not expected to obtain a positive leukocyte scan. According to some authors, a negative leukocyte study in patients symptomatic for more than two weeks should be followed by gallium scintigraphy.

Ga-67 citrate is the only commercially available gamma emitter which images acute, chronic, granulomatous and autoimmune inflammation as well as various malignant diseases. The lower specificity of gallium 67 citrate can be used as an advantage because the aim of the scan is to localize any pathology, inflammatory or any other, thus making it the radiopharmaceutical of choice, and very useful as a diagnostic screening test[4-9]. The normal distribution of gallium 67 citrate includes the reticuloendothelial system, breasts, gut and genitalia. The appearance of the normal gallium image can vary considerably from individual to individual, and the scan is dependent on time elapsed between the radiopharmaceutical injection and the study[4,5,10]. Therefore the procedure is standardized, and is performed at 48 h and 72 h after injection. The exception is the suspicion of a lesion located in the abdomen. In this case the first image should be obtained at 6 h of gallium administration, second 24 h later, and third 48 h later. This is the only way to be sure that the finding in the abdomen is not the radiopharmaceutical in the gastrointestinal tract.

The accumulation of gallium is multifactorial. It binds to iron-binding proteins such as transferrin, lactoferrin, haptoglobin, ferritin and bacterial siderophores, and is related to increased capillary permeability and increased extravascular fluid. Due to the iron-transporting mechanism, there is direct bacterial accumulation; that is why neutropenic patients may still accumulate gallium within an abscess. It should be noted that because of its mechanisms of uptake, gallium accumulation reflects binding to live cells and not to necrotic or scar tissue[4,7,8].

During the last 14 years, 27 patients with the diagnosis of FUO underwent gallium scintigraphy at our Department. There were five (19%) normal findings categorized as the group of undiagnosed cases, which is consistent with literature data (10%-22%)[4,5]. According to subsequent information, abnormal accumulation of gallium had a contributory role in reaching the diagnosis in 59% of patients. In the rest of patients without subsequent information, it was classified as noncontributory. With the exception of normal findings, gallium scintigraphy can in the majority of cases help in reaching the diagnosis, localizing the potential cause, determining the extent and activity of the disease, and identifying an appropriate biopsy site if necessary. The method is noninvasive and has the advantage of the possible whole-body scanning.

Yet, *22%* of our cases remained undiagnosed. The likelihood of an infective cause decreases with the duration of fever. Among malignancies, lymphomas and leukemias prevail. In FUO lasting for more than 12 months, granulomatous causes are more common[4,10,11].

Other radiopharmaceuticals used to image infection/inflammation are labeled (99mTc-, 111-In, 123-I, etc.) antigranulocyte antibodies, human IgG, anti-E-selection monoclonal antibodies, anti-E-selection F (ab')2 fragments, liposomes, interleukin-1, -2, -8, and platelet factor 4. None of the agents can discriminate between infection and inflammation. Rather promising is 99m-Tc-labeled ciprofloxacin (Infecton), which does not accumulate in sterile inflammation[8].

Magnetic resonance (MR) imaging and spiral computed tomography are able to locate relatively small focal abnormalities. However, these methods rely on morphological changes and therefore are less accurate in early stages. They are unable to discriminate active processes from scar tissue. On the contrary, nuclear medicine methods are based on physiochemical processes in tissues, so they can visualize the lesions in their early phase, when morphological changes are not yet apparent[7].

It should be admitted that a number of abnormal gallium scans do not contribute to the diagnosis; the same also holds for other imaging modalities (ultrasonography, CT, MR, or even PET ), but it is not as pronounced as in nuclear medicine[7,8].

## Conclusion

Gallium is less expensive than other agents, leukocyte labeling is not available at many institutions, and the gallium drawback in terms of limited specificity and lack of desirable sensitivity turn to be an advantage having in mind all the possible causes of FUO. Therefore, gallium 67 citrate will continue to be a very important agent in the radionuclide evaluation of FUO in the near future, especially in settings without PET. It should be a second step in the diagnostic procedure, and if possible used before drug administration.

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Sažetak

IMA LI SCINTIGRAFIJA GALIJEM JOŠ UVIJEK SVOJE MJESTO U DIJAGNOSTICI VRUĆICE NEPOZNATOG UZROKA?

K. Kovačić

Zahvaljujući svojim značajkama, 67-Ga-citrat još uvijek ima svoje mjesto u dijagnostici različitih bolesti, među njima i u vrućici nepoznatog uzroka. Zbog njegove nedovoljne specifičnosti, koja se u tom slučaju pretvara u prednost, većina autora se slaže da je galij zapravo radiofarmaceutik izbora u početnom probiru tih bolesnika. Galij se nakuplja na mjestu upale/infekcije, ali i u tumorima. Pozitivan nalaz potvrđuje ili isključuje žarišno ili difuzno oštećenje, ukazuje na proširenost i aktivnost bolesti, te određuje mjesto biopsije ako je potrebna.



Ključne riječi: *Radioizotopi galija – dijagnostička primjena; Vrućica nepoznatog uzroka – etiologija; Radiofarmaceutici – dijagnostička primjena*