

A new method for diagnosing fever of unknown origin (FUO) due to infection of muscular-skeletal system in elderly people: leukoscan Tc-99m labelled scintigraphy

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Abstract. – Twenty patients affected by fever of unknown origin (FUO), due to a likely infection of the muscular or skeletal tissues, were studied by a Total Body scan with a monoclonal antibody fragment (Leukoscan) labelled with Tc-99m. The diagnostic procedure helped reach a final diagnosis in 8 out of the 20 patients because it identified the focus of the infection of the muscles or bones in joint proximity.

Our data show that Leukoscan deserves to become a first line diagnostic procedure in the diagnostic algorithm for the evaluation of patients with FUO.

Key Words:

Fever unknown origin (FUO), Muscular or skeletal infection, Leukoscan Tc-99m labelled scintigraphy.

- a) Neutropenia
- b) Serum positivity
- c) Nosocomial
- d) Classical

• Neutropenic patients experience FUO due to localized and disseminated infections, but the etiology is usually identified in only 40-50% of cases. The more common diagnosis in these patients are bacterial infection, pneumonia, and infection of the skin or other soft tissues. Usually antibiotic therapy resolves the fever, but if the patient does not improve, antimycotic therapy can be useful. In patients with FUO, the restoration of a normal neutrophilic count, quickly improves the clinical pictures.

• Serum positive patients with fever of unknown cause persisting for 3-4 weeks, and with a clinical picture of AIDS, usually have at the basis of their febrile reaction: HIV, mycobacteria, tuberculosis, cytomegalovirus, toxoplasmosis, and lymphoma.

• Nosocomial causes for FUO should be taken into account in those patients that were not febrile at the moment of hospital admission and were admitted for diseases not likely to produce elevated temperature. In these patients the more frequent causes of elevated body temperature are drug induced fever, alithiasic cholecystopathy, and pulmonary atelectasia.

• Classic FUO is divided into 5 different categories according to etiology:

Introduction

Even though many recent advances in diagnostic procedures help in the diagnosis of febrile conditions, clinicians still come across patients whose sole symptom is cryptogenic fever. Typically a Fever of Unknown Origin (FUO) is defined as a febrile condition with daily body temperature over 38 degrees centigrade, of 1-3 days duration, and whose diagnosis remains unknown after 1 week of thorough investigation¹⁻³. Durack and Street in 1991³ proposed a classification of FUO based on the clinical symptomatology and typology of the patient. The classification is based on the following clinical signs:

- 1) Infection (33%), such as tuberculosis, negative culture endocarditis, or osteomyelitis.
- 2) Neoplasia (25%), for example lymphoma and myeloblastic syndrome.
- 3) Connective tissue diseases (13%). These include autoimmune disease, systemic lupus erythematosus, rheumatoid arthritis, and vasculitis.
- 4) Other unrelated diseases and syndromes (20%), including drug induced fever, interstitial infection or inflammation, granulomatous hepatitis, Mediterranean familiar fever, pulmonary embolism, and sarcoidosis.
- 5) Unknown cause (8%).

It appears from the causes just listed, that many episodes of FUO, especially in the elderly patient, are the result of autoimmune pathologies, soft tissue infections, vasculitis, or osteomyelitis. Also, diabetic patients with foot ulcers are especially prone to infections. Infected prosthetic devices can also lead to infection of nearby soft tissues. In these cases, especially in the diagnosis of infections of the muscular tissues and other soft tissues near the joints, scintigraphy with leukocyte markers, like Technetium-99m labelled Leukoscan, has proven useful.

Leukoscan (sulesomab) is a FabI fragment of a monoclonal antibody of murine origin, formulated to be labelled with Tc-99m. The antibody (IMMU-MN3) recognizes a common surface glycoprotein (NCA-90) of activated granulocytes. Therefore Leukoscan is indicated for the scintigraphic evaluation of patients with FUO, especially to localize infectious processes in the musculature and other soft tissues near joints^{5,6}.

Materials and Methods

Our study population consisted of 20 patients with a mean age of 75 ± 7 S.D. years. The group consisted of 12 females and 8 males, referred for evaluation of FUO to Nuclear Medicine Department at the Institute of Internal and Geriatric Medicine of the Hospital Cannizzaro of Catania. Aim of this study was to estimate the prevalence of infectious processes of the muscular-skele-

tal system in elderly patients with FUO using Total-Body scintigraphy with technetium-99m radiolabelled Leukoscan. Among the patients studied, 4 were indwelling in the hospital and 16 were examined on a one-day imaging regimen. All patients fasted since 8 p.m. of previous day. Each patient first underwent Total Body bone scintigraphy with HDP-Tc-99m (20 mCi). Those with positive findings (8 cases) on the bone scintigraphy, 48 hours later underwent a Total-Body scan with Tc-99m labelled Leukoscan (20 mCi). Scintigraphy with Leukoscan started 2 hours after the venous injection of the labelled marker.

Results

In 8 patients out of 20 (40%) scintigraphy demonstrated a high accumulation of the tracer (positive result) indicating a probable infection (see Figures 1-8). Our results are the following:

- High accumulation of tracer in the knee was noted in 5 patients; 2 of which had a prosthesis, 1 was affected by rheumatoid arthritis, 1 by chronic meniscopathy, and 1 had undergone an arthroscopic reconstruction of the crossed ligament.
- One patient with hip prosthesis exhibited high accumulation of the tracer in the hip with the prosthetic device.
- Increased tracer uptake at the neck of the foot was noted in one patient with diabetic foot.
- The shoulder of a patient with chronic scapulohumeral peri-arthritis also showed positive scintigraphic results.

None of the patients showed any adverse effects during the scintigraphic studies.

Discussion

This study shows that in patients with FUO and a positive bone scintigraphy, Leukoscan helped reach a final diagnosis in 8 out of 20 (40%) patients examined, by identifying the point of the infection involving the muscular or bone tissues in proximity of the joint. With the exception of the patient with diabetic foot, all

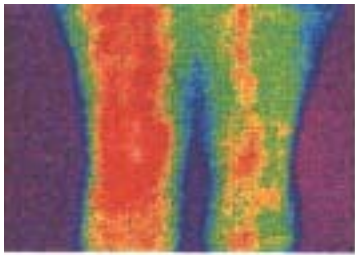


Figure 1. Focus of infection in the right knee in operated patient for break of the crossed ligaments. (Leukoscan - Tc99m).

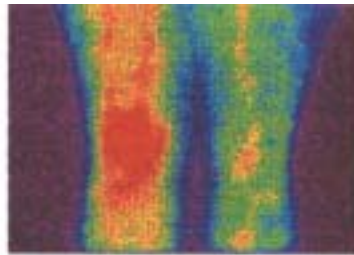


Figure 2. Focus of infection in the right knee in patient with rheumatoid arthritis. (Leukoscan - Tc99m).

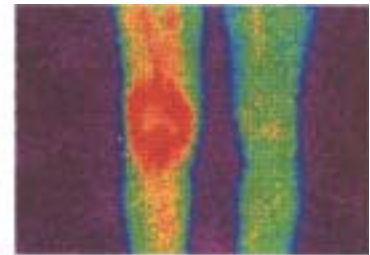


Figure 3. Focus of infection in the right knee in patient with chronic meniscitis. (Leukoscan - Tc99m).

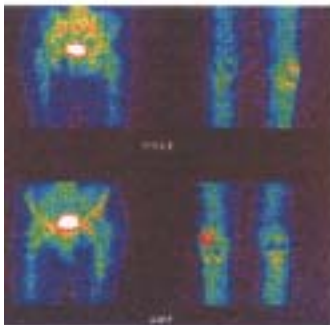


Figure 4. Focus of infection in the right knee in patient with bilateral prosthesis of the knees and hips. (Leukoscan - Tc99m).

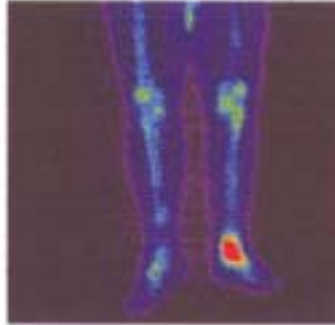


Figure 5. Focus of infection in patient with diabetic foot syndrome (anterior projection). (Leukoscan - Tc99m).

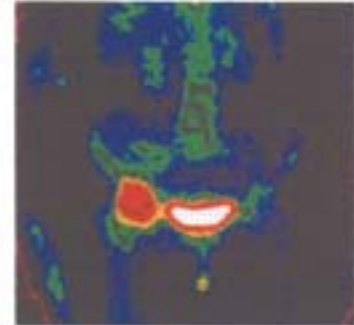


Figure 6. Infected prosthesis of the right hip (anterior projection). (Leukoscan - Tc99m).

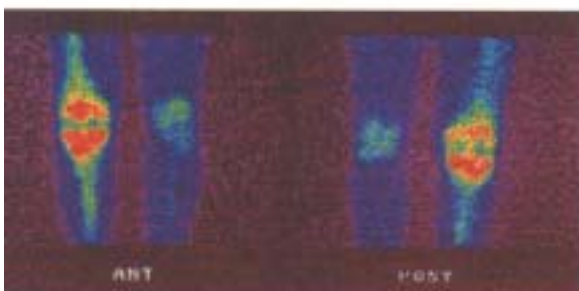


Figure 7. Infected prosthesis of the right knee. (Leukoscan - Tc99m).



Figure 8. Focus of infection in patient with chronic periarthritis of the right shoulder (anterior projection). (Leukoscan - Tc99m).

the patients presented with fever and a minimal or insufficient specific symptomatology. Indeed the only complaint of these patients was limited to modest ache or functional limitations also present in the corresponding opposite joint. The insidious nature of deep-seated infections, in particular those developing near an articular prosthesis, poses a dilemma for the orthopedic specialist facing the difficult task of reaching a quick and precise diagnosis. A similar dilemma is present in patients suffering from diabetic ulcers. In this case, an underlying osteomyelitis usually needs to be ruled out. Anamnesis, physical examination and hematological findings are always important to reach a presumptive diagnosis in cases of FUO. But only through scintigraphic confirmation shown by high accumulation of infection specific radiomarkers, like Leukoscan, can conclusive results be achieved. In this group of patients, the best therapeutic approach of the diseases joint consisted in the re-implantation of a new prosthesis or osteotomy.

The results of our study showed a significant positive shift in the final diagnosis of patients with FUO, that in our case reached 40% of the population studied as a direct result of scintigraphy with Leukoscan-Tc99m. This scintigraphic study is extremely easy to perform and seems to be secure with a total absence of side effects. In our experience it was often decisive in resolving a diagnostic dilemma.

In conclusion, scintigraphy with Tc-99m radiolabelled Leukoscan represents a quick and useful method for the search for infectious foci that are often the cause of the so-called FUO. Previous clinical practice employed other diagnostic methods, such as scintigraphy with gallium-67, autologous leukocytes labelled with 111-Indium^{8,11}, or human immunoglobulin (HigG) labelled with Technetium-99m^{12,13}. Leukoscan provides high quality images, with greater speed and accuracy at a modest cost. The ease of preparing the labelled product, the absence of toxic side effects and without manipulation of human blood, make scintigraphy with Leukoscan the technique of choice. Our opinion is that Leukoscan deserves to become one of first-line of exams in the diagnostic algorithm for the evaluation of patients with FUO.

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