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GALLIUM-67 SCINTIGRAPHY IN MACROPHAGIC MYOFASCIITIS

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Objective. **To evaluate gallium-67 (^{67}Ga) uptake and the value of ^{67}Ga scintigraphy for diagnosis of macrophagic myofasciitis (MMF), a recently identified inflammatory myopathy.**

Methods. **Twelve consecutive patients with MMF confirmed by muscle biopsy, 10 with polymyositis, 10 with sarcoidosis, 8 with fibromyalgia, and 10 with lymphoma without muscle symptoms (serving as normal controls for muscle) were included. Patients received 1.8 MBq ^{67}Ga per kg body weight by intravenous injection, and scintigraphy was performed with a 2-head gamma camera. The various views were acquired for the 3 main photopeaks of ^{67}Ga 48 hours after infusion, and were analyzed in 2 blinded experiments by nuclear physicians. A semiquantitative scale was used to compare the uptake of ^{67}Ga in the vascular soft tissue background with that in the muscles or joints of MMF patients, and with that in the normal controls.**

Results. **The MMF patients (4 men and 8 women, mean ± SD age 47.8 ± 8.7 years) had chronic myalgia (n = 11; predominantly in the lower limbs), asthenia (n = 10), arthralgia (n = 7), mild muscle weakness (n = 5), and high serum creatine kinase levels (n = 6). All MMF patients had significantly higher levels of ^{67}Ga uptake in the muscle and para-articular areas than that recorded for the soft tissue background and for the controls. Muscle uptake was bilateral, symmetric, and homogeneous, and predominantly localized in the legs. No linear enhancement corresponding to fascias or synovial involvement was observed. In patients with polymyositis, symmetric, but heterogeneous, ^{67}Ga uptake was observed in muscle, but not in the fascia. In patients with sarcoidosis, ^{67}Ga uptake was nodular and heterogeneous in muscle, was not detected in the fascia, and was suggestive of synovial involvement in the joints. The uptake of ^{67}Ga in fibromyalgic patients was similar to that in normal controls and to that in the soft tissue background.**

Conclusion. **MMF is a new condition involving characteristic changes that can be detected by deltoid muscle biopsy. It usually manifests as a weakly specific, chronic arthromyalgic syndrome that predominates in the lower limbs. ^{67}Ga scintigraphy is a noninvasive method that may make it easier to differentiate MMF from fibromyalgia and sarcoidosis.**

A new type of inflammatory myopathy, macrophagic myofasciitis (MMF), is being reported with increasing frequency in French myopathology centers (1,2). Since 1993, this condition has been diagnosed in 70 patients in France and in 5 patients in other countries (United States, United Kingdom, Spain, and Portugal). Affected patients generally report symptoms of diffuse myalgia, arthralgia, marked asthenia, and, less frequently, muscle weakness and fever (3). Some patients also present with signs of central nervous system involvement (4). Arthromyalgia and fatigue improve under steroid therapy in most patients. Laboratory investigations have, in some cases, shown slightly elevated levels of creatine kinase (CK), a high erythrocyte sedimentation rate, and evidence of myopathy on electromyogram (EMG). Deltoid muscle biopsies have shown a unique pathologic pattern that is characterized by 1) focal infiltration of the epimysium, perimysium, and perifascicular endomysium by sheets of large, nonepithelioid macrophages, which show fine granular staining for periodic acid–Schiff (PAS) and appear as small, osmio-

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philic, spiky structures on electron microscopy, 2) occasional CD8+ T cells, intermingled with macrophages or surrounding microvessels, and 3) inconspicuous muscle fiber damage. The images that have been obtained differ from those obtained for idiopathic inflammatory myopathies, sarcoid myopathy, and fasciitis-panniculitis syndromes (5). MMF is likely to have an environmental cause, which is infectious or toxic in nature (3). It has been suggested that MMF may be an unusual type of Whipple's disease (6) or a rare complication of vaccinations (7).

Citrate gallium-67 (^{67}Ga) is an iron protein that binds specifically to the transferrin receptor expressed at the surface of activated macrophages and some types of lymphoid cells (8–12). ^{67}Ga scintigraphy is widely used in the diagnosis and followup of infections, lymphomas, and granulomatous diseases such as sarcoidosis (13–17). To assess systemic inflammatory muscle involvement associated with MMF, we performed ^{67}Ga scintigraphy prospectively in 12 consecutive patients with MMF confirmed by muscle biopsy, and compared the findings with those in control subjects.

PATIENTS AND METHODS

Patients. Twelve consecutive MMF patients evaluated at the Pitié-Salpêtrière and Henri-Mondor hospitals underwent ^{67}Ga scintigraphy at the initial stages of their disease (i.e., after muscle biopsy and before treatment). The patients were admitted from December 1997 to March 1999 and were all adult (4 men and 8 women). Their mean (±SD) age was 47.7 ± 8.7 years (range 25–70 years).

During the same time period, 4 control groups were included and underwent ^{67}Ga scintigraphy. Control subjects included 10 patients with lymphoma without muscle involvement and articular ^{67}Ga uptake (6 women and 4 men, mean ± SD age 53.1 ± 11.1 years; 8 with diffuse, large B cell lymphomas and 2 with follicular center lymphomas, according to the REAL [Revised European-American classification of lymphoid neoplasms] classification [18]; used as normal controls for muscle). One group of 10 patients had polymyositis that was confirmed by biopsy (5 women and 5 men, mean ± SD age 49 ± 8.7 years), and another group comprised 10 patients with sarcoidosis and thoracic involvement (6 women and 4 men, mean ± SD age 34.5 ± 7.1 years). The last group included 8 consecutive patients with a definite diagnosis of fibromyalgia syndrome, according to the American College of Rheumatology (ACR) 1990 criteria (19) (7 women and 1 man, mean ± SD age 37.1 ± 11.1 years). This group was included to determine whether MMF could be distinguished from fibromyalgia syndrome by ^{67}Ga scintigraphy before muscle biopsy.

Muscle biopsy. Deltoid muscle biopsy samples were divided into 3 portions for freezing, paraffin embedding, and epoxy embedding, and were processed using standard techniques. Myopathologic changes were evaluated by 3 expert myopathologists from the GERMMAD (Groupe d'Etudes et de Recherche sur les Maladies Musculaires Acquises et Dysimmunitaires), which was the first group to describe MMF (1,2). Immunocytochemical studies were performed using the alkaline phosphatase–anti–alkaline phosphatase technique with monoclonal antibodies specific for lymphocytes (CD3, CD4, CD8, CD20, CD45), macrophages (CD68), Langerhans' cells (CD1a), transferrin receptor (TfR/CD71), class I and class II major histocompatibility complexes (MHC; HLA–ABC and HLA–DR), S100 protein, desmin, and smooth muscle actin, all of which were purchased from Dako (Trappes, France).

Gallium scan. All patients gave their informed consent for participation in the study. Scintigraphy was performed at the Nuclear Medicine Unit at Avicenne Hospital (Bobigny, France). ^{67}Ga scanning was performed using a 2-head gamma camera (Adac, Vertex-plus; Milpipas, CA) equipped with rectangular, medium-energy collimators and thick crystal (16 mm). The patients received 1.8 MBq ^{67}Ga per kg body weight by intravenous injection. The various images were acquired for the 3 main photopeaks of ^{67}Ga 48 hours later. ^{67}Ga uptake was analyzed using the dedicated Sun Sparc station of the Adac gamma camera. We performed a global scintigraphic analysis and then more specific analyses for each limb (muscles and joints).

Scintigraphy results were analyzed by 2 experienced nuclear physicians who were blinded to the diagnosis. A semiquantitative scale was used to compare the uptake of ^{67}Ga in the vascular soft tissue background with that in the muscles or joints of patients, and with that in the controls. The semiquantitative scale used was as follows: 0 = no significant difference in uptake between the vascular soft tissue background, the muscles, or the joints, 1+ = slight delineation between the muscle or joint uptake of ^{67}Ga, 2+ = clear delineation between the muscle or joint uptake of ^{67}Ga, 3+ = strong uptake of ^{67}Ga in the muscles or joints. We initially carried out a global analysis and then focused on each limb (muscle and joint fixation).

RESULTS

Characteristics of patients. The patients with MMF were originally referred with presumptive diagnoses of polymyositis (n = 6), fibromyalgia (n = 3), polymyalgia rheumatica (n = 1), muscular dystrophy (n = 1), or mitochondrial cytopathy (n = 1). Their clinical characteristics are listed in Table 1.

All of the MMF patients had muscular symptoms that had developed at 3–36 months before biopsy. Chronic myalgia, mild to moderate in intensity, was the most common manifestation, occurring in 11 patients, and associated with marked asthenia in 10 patients. Myalgia predominantly affected the lower limbs, particularly the calves. Tender points typical of fibromyalgia were not observed. Two patients reported mild lumbar pain. Seven patients (58%) had arthralgia, affecting both the large joints and the finger joints. Five patients had

Table 1. Characteristics of the patients*

Patient/ age/sex	Clinical manifestations	CK levels	ESR	EMG findings	Muscle biopsy findings
1/70/F	Myalgia, arthralgia	Normal	110	Normal	MMF
2/29/F	Myalgia, arthralgia, fatigue	× 5	4	Myopathic	MMF
3/25/M	Myalgia, fever, fatigue	× 3	8	Normal	MMF
4/52/F	Myalgia, arthralgia, mild muscle weakness	Normal	65	Neuropathic	MMF
5/53/F	Myalgia, arthralgia, fever, fatigue	Normal	22	Normal	MMF
6/52/F	Myalgia, fatigue, muscle weakness	× 2	13	Myopathic	MMF
7/54/M	Myalgia, fatigue, mild muscle weakness, dyspnea	× 3	8	Myopathic	MMF
8/46/F	Myalgia, fatigue, mild muscle weakness	Normal	4	Myopathic	MMF
9/42/F	Myalgia, arthralgia, fatigue, tenderness	Normal	10	Normal	MMF
10/51/F	Arthralgia, fatigue, mild muscle weakness	× 1.5	7	Myopathic	MMF
11/52/M	Myalgia, fatigue	Normal	12	Normal	MMF
12/47/M	Fatigue, myalgia, arthralgia	× 1.5	30	Normal	MMF

* CK = creatine kinase; ESR = erythrocyte sedimentation rate; EMG = electromyogram; MMF = macrophagic myofasciitis.

mild-to-moderate muscle weakness, which was diffuse in 3 patients and proximal in the lower limbs in 2 patients. Fever from 38°C to 39°C was noted in 2 patients (Table 1). No digestive or cutaneous manifestations were observed.

The EMG showed myopathy in 5 patients and neuropathy in 1. The serum CK concentration was high in 6 patients (1.5–5 times higher than normal).

Muscle biopsy findings. The deltoid muscle biopsy showed conspicuous infiltration of densely packed, large, rounded cells, with central, round nuclei that often contained nucleoli, and clear, slightly basophilic cytoplasm showing fine granular staining with PAS reagent. These cells were investigated by immunocytochemistry. They did not stain for desmin and smooth muscle actin, tested positive for the histiocyte marker CD68, and tested negative for the Langerhans' cell marker CD1a and for S100 protein. They were therefore identified as macrophages. No necrosis, epithelioid cells, giant cells, or mitotic figures were detected. The macrophage infiltrate was focal or multifocal in the epimysium, perimysium, and endomysium (Figures 1 and 2).

The lymphocytes present were mostly CD8+ T cells. CD4 T cells were rare, and neither CD20+ B cells nor plasma cells were found. CD45 lymphocytic cells were seldom observed in any of the muscle tissues. They appeared as isolated lymphocytes intermingled with macrophages or as small perivascular cuffs, close to or far from the macrophage infiltrate. Myonecrosis, perifascicular atrophy, and myopathic changes were inconspicuous or absent. Class I and class II MHC antigens were strongly expressed by macrophages and weakly by muscle fibers close to macrophage infiltrates. MHC molecules were not expressed by muscle fibers at some distance from the infiltrate.

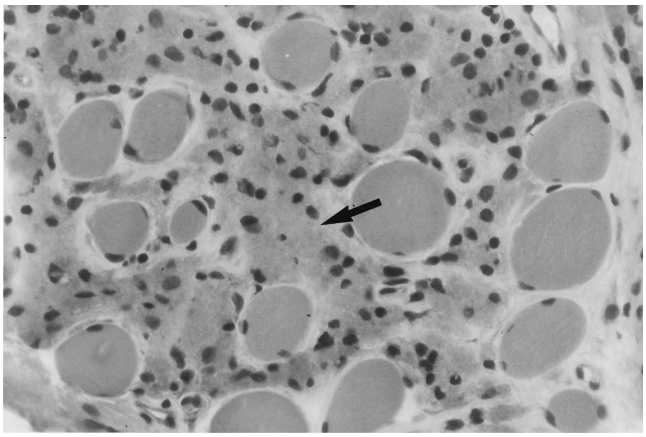

Figure 1. Findings on light microscopy of muscle biopsy tissue showing endomysial infiltration by contiguous nonepithelioid macrophages, with a large, finely granular cytoplasm (**arrow**). (Stained with hematoxylin and eosin; original magnification × 400.)

Figure 2. Findings on light microscopy of muscle biopsy tissue showing strong expression of the transferrin receptor TfR/CD71 by macrophages infiltrating the endomysium. (Stained with immunoperoxidase; original magnification × 240.)

TfR/CD71 was strongly expressed by infiltrating macrophages (Figure 2). TfR/CD71 expression was not observed in CD8+ and CD4+ T lymphocytes or muscle fibers. For all 4 patients with macrophages detected in Epon-embedded material, electron microscopy revealed abundant small aggregates of osmiophilic crystal structures, which were often bound by a distinct membrane, in the cytoplasm of macrophages. Viral and bacterial profiles were conspicuously absent.

In patient 1, a second muscle biopsy was performed on a tibialis anterior muscle. It showed ^{67}Ga uptake and mild lymphocyte infiltration, without macrophage infiltration.

Gallium scan results. *Macrophagic myofasciitis*. In all MMF patients, global scintigraphy showed significantly higher levels of ^{67}Ga uptake in muscle and para-articular areas than that found in soft tissues and in normal controls. In MMF patients, Ga uptake was detected predominantly in the limb muscles and joints. There was no specific axial fixation. Two patients had ^{67}Ga uptake in the lacrimal gland, 2 had uptake in the respiratory tract, 1 had uptake in the breast, and 1 in the kidney (Table 2).

The fascia showed homogeneous linear ^{67}Ga uptake, and were therefore easily distinguished from the subcutaneous tissue. In patients with myalgia, ^{67}Ga uptake by muscle was greater in the lower limbs (1 patient with high-level muscle uptake and 10 patients with clear muscle delineation compared with soft tissue background) than in the upper limbs (no patients with high-level muscle uptake, 7 patients with clear muscle delineation, and 5 patients with slight muscle delineation compared with soft tissue background) (Table 2). In the lower limbs, ^{67}Ga uptake slightly predominated in the legs (Figure 3). Muscle ^{67}Ga uptake was bilateral, symmetric, and homogeneous. There was no predominance of ^{67}Ga uptake among the upper limb muscles.

Articular ^{67}Ga uptake also predominantly affected the lower limbs. Knees, hips, and ankles were more involved than shoulders, elbows, and wrists (Table 2). Fixation appeared mainly periarticular, and synovial uptake was not observed.

The bronchoalveolar lavage findings in the patients with ^{67}Ga uptake in the respiratory tract were normal. In the patient with ^{67}Ga uptake in the kidney,

Table 2. Results of ^{67}Ga scintigraphy in macrophagic myofasciitis*

	Upper limb						Lower limb						
	Muscle			Joint			Muscle		Joint				
Patient	Deltoid	Arm	Forearm	Shoulder	Elbow	Wrist	Thigh	Leg	Hip	Knee	Ankle	Back	Other
1	2+	2+	1+	2+	1+	2+	3+	2+	3+	2+	3+	1+	None
2	1+	1+	1+	1+	ND	1+	1+	2+	2+	2+	ND	0	Lacrimal, breast
3	2+	2+	1+	2+	ND	2+	1+	2+	2+	2+	1+	1+	None
4	1+	1+	1+	1+	1+	1+	2+	2+	2+	2+	2+	0	None
5	2+	2+	1+	1+	ND	1+	2+	2+	2+	2+	ND	0	Lacrimal
6	1+	1+	1+	1+	2+	1+	2+	2+	3+	3+	ND	0	Kidney
7	1+	2+	1+	1+	1+	1+	1+	2+	2+	2+	1+	1+	Respiratory tract
8	1+	1+	1+	1+	1+	1+	1+	2+	2+	2+	1+	0	None
9	1+	1+	1+	2+	1+	1+	2+	1+	2+	2+	1+	0	None
10	2+	1+	1+	1+	1+	1+	1+	1+	1+	1+	1+	0	None
11	2+	2+	1+	1+	1+	1+	1+	2+	1+	1+	ND	0	None
12	1+	2+	1+	1+	1+	1+	2+	1+	1+	2+	1+	0	Respiratory tract

* The semiquantitative scale used was as follows: 0 = no significant difference between soft tissue background and muscle and joint uptake of gallium-67 (^{67}Ga); 1+ = slight delineation of muscle or joint uptake; 2+ = clear delineation of muscle or joint uptake; 3+ = high-level muscle uptake (or joint uptake) of ^{67}Ga. ND = not done.

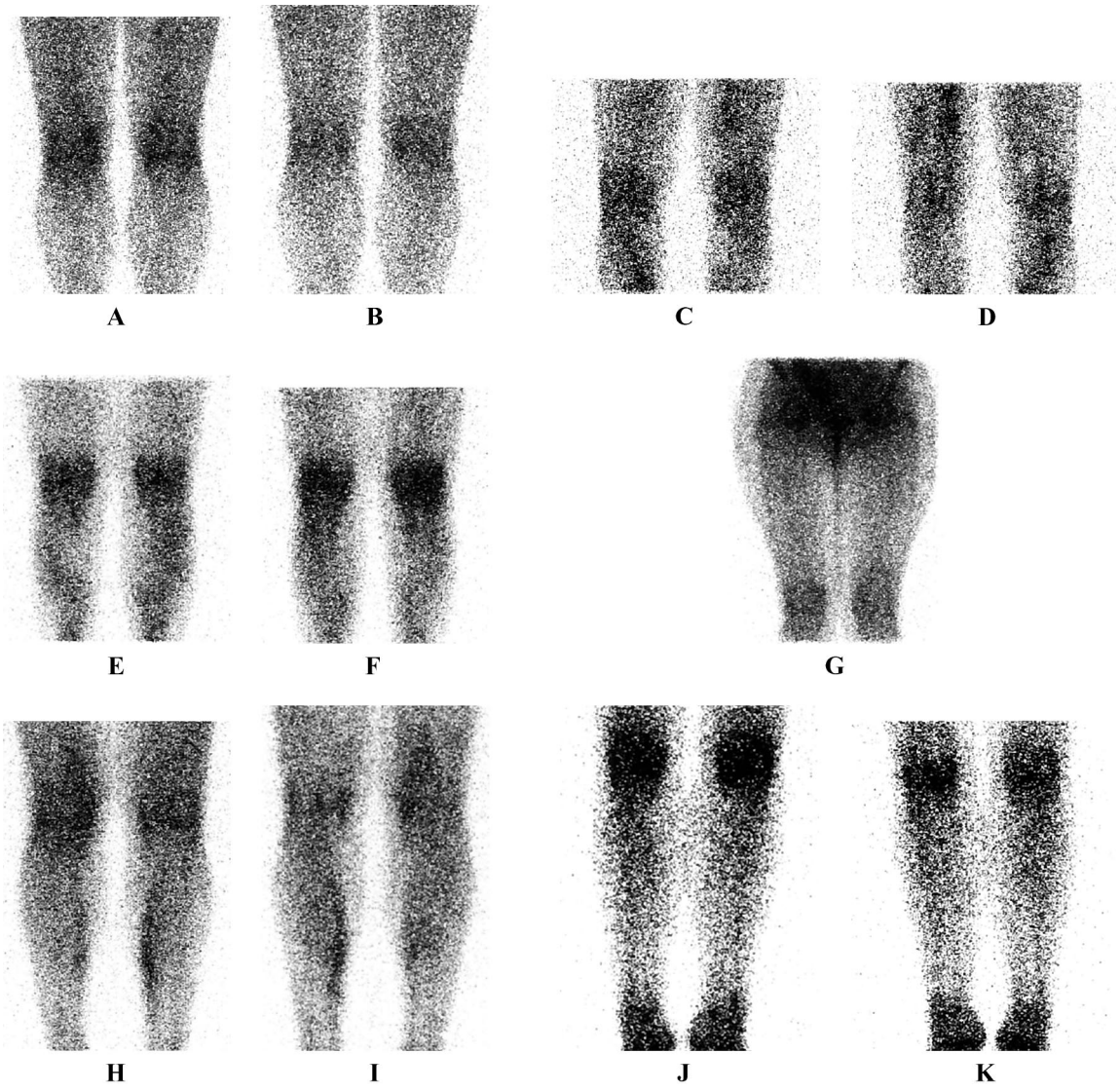

Figure 3. Anterior **(A, C, E, H,** and **J)** and posterior **(B, D, F, G, I,** and **K)** views of the lower limbs of patients with macrophagic myofasciitis (MMF) and control patients, obtained by scintigraphic imaging with citrate gallium-67 (^{67}Ga). **A** and **B,** Normal control patient with mediastinal non-Hodgkin's lymphoma, showing low-level synovial uptake. **C** and **D,** Muscular sarcoidosis control patient, showing heterogeneous and asymmetric muscle uptake. **E** and **F,** Polymyositis control patient, showing heterogeneous and symmetric muscle uptake. **G,** MMF patient 2, showing delineation between diffuse uptake of ^{67}Ga in muscles and subcutaneous background activity (pelvis and thighs). **H** and **I,** MMF patient 11, showing macroscopic bilateral ^{67}Ga uptake in muscular bundles. **J** and **K,** MMF patient 10, showing para-articular hyperactivity (knees and wrist) and moderate linear uptake in muscles.

surgery revealed a benign kidney tumor (oncocytoma). Mammography in the patient with breast ^{67}Ga uptake was inconclusive as to the cause.

Controls. In patients with lymphoma or fibromyalgia, there was no muscle or articular ^{67}Ga uptake. In lymphoma patients, Ga uptake was detected in the lymph nodes (7 patients), liver (2 patients), bone marrow (2 patients), spleen (1 patient), and mediastinum (1 patient). In all fibromyalgia patients, ^{67}Ga scintigraphy scans gave negative results, with muscle and articular ^{67}Ga uptake similar to that in the soft tissue background.

In polymyositis patients, symmetric, but heterogeneous, ^{67}Ga uptake was observed in the muscles, but not in the fascia. In patients with sarcoidosis, ^{67}Ga

uptake was detected in the lung and/or mediastinal lymph nodes (10 patients), lacrimal and salivary glands (3 patients), superficial lymph nodes (2 patients), joints (2 patients), muscle (1 patient), and spleen (1 patient). In the patient with muscle sarcoidosis confirmed by biopsy, muscle ^{67}Ga uptake was nodular and heterogeneous, with no uptake by the fascia. In 2 patients with specific articular manifestations, the joints showed characteristic synovial ^{67}Ga uptake.

DISCUSSION

In this study, all of the patients with MMF confirmed by muscle biopsy were found to have ^{67}Ga uptake in the muscles and articular areas at a level above that of the soft tissue and normal controls. Diagnostic muscle biopsy was performed on the deltoid muscle in all patients, but ^{67}Ga uptake and myalgia, the most frequent presenting symptom of MMF, predominantly affected the lower limbs. The fascia showed homogeneous linear ^{67}Ga uptake. Periarticular regions were enhanced, whereas synovial areas were not. The number of nonsymptomatic locations and visceral involvement appeared minimal. Patterns of ^{67}Ga uptake similar to those observed in MMF have been reported in the active phases of other inflammatory muscle diseases, such as polymyositis and dermatomyositis (20). Indeed, some MMF patients were initially referred with a presumptive diagnosis of fibromyalgia, but none met the ACR criteria for fibromyalgia (19) and all lacked the tender points characteristic of this disease.

The results of ^{67}Ga scintigraphy in fibromyalgic patients whose muscle biopsy findings were normal were similar to those in normal controls (lymphoma patients without muscle symptoms). This suggests that ^{67}Ga scintigraphy could be performed to support the indications of the muscle biopsy in patients with purely myalgic syndromes. Open biopsy of the deltoid muscle and its fascia was necessary to establish a diagnosis of MMF in our patients. The myopathologic features of MMF are easily distinguishable from idiopathic inflammatory myopathies (21) such as dermatomyositis, polymyositis, and inclusion body myositis, and from the so-called fasciitis-panniculitis syndromes (5) such as Shulman's disease, Spanish toxic oil syndrome (22), and adulterated L-tryptophan–associated eosinophilia-myalgia syndrome (23,24). In these disorders, macrophages do not predominate in the inflammatory infiltrates, except in the rare condition of dermatomyositis with marked macrophage activation (25). In contrast, abundant macrophages are typically found in sarcoid and sarcoid-like granulomatous myopathies (26). Unlike those in sarcoid granulomatas, however, the macrophages infiltrating muscle connective tissue in MMF do not have an epithelioid appearance, do not form giant cells, and are not organized into nodules. The pattern of ^{67}Ga uptake in sarcoidosis was different from that observed in MMF patients. Unlike that in MMF patients, ^{67}Ga uptake in sarcoidosis patients was nodular and heterogeneous in muscle, was not detected in fascia, and was suggestive of synovial involvement in joints, as previously reported (13,17). The difference in ^{67}Ga uptake between MMF and polymyositis patients was less clear.

MMF is a poorly understood condition that is rapidly becoming more common in France and is occasionally detected in other developed countries. It has been brought to the attention of the Centers for Disease Control and Prevention (Atlanta, GA) and is the object of a national epidemiologic survey by the Institut de Veille Sanitaire (Saint-Maurice, France). Diagnosis is based strictly on the findings of deltoid muscle biopsy, in which there is typical evidence of infiltrates of large macrophages with PAS+ cytoplasmic inclusions, corresponding to osmiophilic crystals on electron microscopy examination (1,2). The condition is usually recognized in patients with diffuse arthromyalgia and asthenia, sometimes associated with central nervous system manifestations. Skeletal muscle symptoms are steroid responsive. No noninvasive investigations of significant diagnostic value for MMF have been reported before (3). This study suggests that ^{67}Ga scintigraphy may be useful for distinguishing MMF from fibromyalgia and sarcoidosis.

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