

# Macrophagic myofasciitis

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[Abstract](#)

[Keywords](#)

[Introduction](#)

[Clinical manifestations of macrophagic myofasciitis](#)

[Diagnostic criteria](#)

[Etiology](#)

[Conclusion](#)

[References](#)

## Abstract

*A new inflammatory myopathy, called macrophagic myofasciitis, is being seen in increasing numbers in the principal French myopathology centers. Since its appearance in 1993, more than 100 cases have been collected, mainly in France, by the Group for the Study and Research of Acquired and Dysimmunity-Related Muscle Diseases (known by the French acronym GERMAD). The disease usually affects adults, with no sex predominance. Macrophagic myofasciitis generally becomes manifest as muscle pain (myalgias) of variable intensity, observed in 95% of the patients, usually associated with chronic debilitating fatigue (90%). Myalgias predominantly affect the limbs – notably the legs – and are often aggravated by exertion. Joint pain, primarily affecting the large peripheral articulations is noted in 50–60% of the patients and a moderate febrile syndrome in 30%. There are no cutaneous manifestations or digestive tract symptoms. The diagnosis is made based on histological examination of a surgical biopsy of the deltoid muscle including the fascia which shows the pathognomonic focal macrophage infiltrate. Complementary examinations are not always contributive: elevated muscle enzyme and creatine kinase levels are observed in 30%; a myopathic electromyogram tracing is obtained for less than 30%; gallium scintigraphy suggests abnormalities but they are non-specific. A toxic origin (aluminated vaccines) is suspected and led to the initiation of an epidemiological inquiry conducted by the French Medications Agency. Numerous epidemiological, clinical, fundamental and therapeutic study protocols are in progress, under the aegis of the GERMAD, in association with the Institute for Public Health Vigilance.*

## Keywords

Inflammatory myopathy, myalgia, chronic fatigue, joint pain, febrile syndrome

## Introduction

In 1998, the Group for the Study and Research of Acquired and Dysimmunity-Related Muscle Diseases (known by the French acronym GERMAD) reported the appearance of a new inflammatory myopathy, being observed more-and-more frequently in the principal French myopathy centers and called macrophagic myofasciitis. Since its appearance, more than 60 cases have been collected in France.

## Clinical manifestations of macrophagic myofasciitis

Chérin *et al.* analyzed the signs and symptoms of the first 22 individuals affected with macrophagic myofasciitis. These patients had been referred for a presumed diagnosis of inflammatory myopathy (polymyositis, polymyalgia rheumatica) or without such a suspicion (mitochondrial cytopathy, muscular

dystrophy, congenital fibromyalgia myopathy or chronic fatigue syndrome).

**Description of the first 22 adult patients with macrophagic myofasciitis**

Parameter	Value
Mean age (range)	43 years (25-70 years)
M/F sex ratio	1.3
Patients working in a hospital	n 7
prolonged stay in a tropical zone	n 4 (3 in Africa, 1 in India)
Onset of muscle manifestations	11.2 ± 8.7 months before diagnosis
Principal history	<ul style="list-style-type: none"> <li>• Immune disorder, 5</li> <li>• Myelodysplasia, 1</li> <li>• Ear, nose, throat carcinoma during treatment, 1</li> </ul>
Principal manifestations	<ul style="list-style-type: none"> <li>• Chronic moderate myalgias, sometimes aggravated by exertion and predominantly affecting the legs (91%)</li> <li>• Inflammatory or mixed arthralgias mainly affecting the large peripheral joints (60%)</li> <li>• Proximal motor deficit (40%)</li> <li>• Severe asthenia (55%)</li> <li>• Fever (32%)</li> <li>• No skin manifestations,</li> <li>• No signs of dermatomyositis or palpable induration</li> <li>• No digestive tract symptoms</li> </ul>

**Diagnostic criteria**

Surgical muscle biopsies including the fascia were taken from the deltoid. The specimen was divided into 3 parts: one fragment was immediately frozen, another was fixed and embedded in epoxy for electron microscopy, and the last was fixed and embedded in paraffin for standard histological (light microscopy) examinations. The resulting slides were systematically read by 3 independent muscle pathologists using the histological criteria defined during the 1997 GERMMAD meeting held for this purpose.

The never-before-described histological picture thus established was strictly identical for all 22 patients analyzed. This picture, perfectly stereotyped, enables easy distinction of idiopathic inflammatory myopathies, granulomatous myositides and Shulman type-2 panniculitis-fasciitis syndromes.

**Histology of the muscle biopsy**

- Presence of an infiltrate composed of periodic acid-Schiff (PAS)+, non-epithelioid cells with large, finely granulated cytoplasm, and

expressing major histocompatibility complex (MHC) class II molecules

- Minor myocytes damage
- Absence of markers of the Langerhans' cell line (CD1a-, S100)
- Presence sometimes of a discrete lymphocytic infiltrate, predominantly CD8+ T cells or several scattered lymphocytes
- Rare CD4+ T cells
- Absence of CD20 B cells, plasmacytes or white blood cells
- Centripetal extension from the fascia to the underlying muscle, either focal or multifocal, sometimes with perivascular infiltrates. The subcutaneous panniculus adipose tissue is often infiltrated as well
- No focal necrosis or regeneration, perifascicular atrophy, epithelioid cells, giant cells, Michaelis-Gutmann intracytoplasmic inclusions, foreign particles or bodies
- Ziehl-Neelsen, auramine O, and Gram stains are negative
- No myocyte expression of MHC class I, in contrast to polymyositis
- No deposits of membrane-attack complexes (C5b-C9) in the endomysial capillaries, like those seen in dermatomyositis.

**Results of complementary examinations**

- Elevated muscle enzymes and creatine kinase (CK) in 50% of the patients
- Elevated erythrocyte sedimentation rate over 40 mm/1st hour in 35%
- The different serological tests performed did not indicate an evolving disease and the search for different autoantibodies was negative
- The electromyogram indicated a myopathy in less than 30% of the patients.

Other investigations did not prove contributive: chest radiography, electrocardiogram, echocardiography, respiratory function tests, abdominal radiography without contrast medium, lumbar puncture, endocrine profile, tumor markers.

Magnetic resonance imaging of muscle, performed in 8 patients, demonstrated abnormalities of the fascia giving a scalloped appearance in only 1. T1, T2 and T1 sequences with fat suppression and/or gadolinium injection did not show any anomalies of the muscle signal. Gallium-67 is a metal ion that binds to the transferrin receptor of activated cells, notably lymphoid cells and macrophages. Some patients with macrophagic myofasciitis underwent gallium scintigraphy which seems to have given interesting results.

## Etiology

Two etiopathological hypotheses are currently favored to explain this new disease: either a toxic or infectious origin.

### **Hypothesis of a toxic origin**

The possibility of a toxic origin was first suggested because the last three myopathies individualized were caused by a toxic substance: zidovudine myopathy, adulterated Spanish oil syndrome and the eosinophilia-myalgia syndrome; the last two have been linked to aniline derivatives. Within the framework of macrophagic myofasciitis, the hypothesis of a toxic origin is currently being investigated with search for substances toxic to muscle. Indeed, the disease is the object of a French national epidemiological study being conducted in collaboration with the Institut de Veille Sanitaire (InVS; Institute for Public Health Vigilance). Each patient was interviewed directly by the medical epidemiologist in order to fill out a detailed questionnaire, established by InVS and GERMMAD, with the objective of identifying a factor, particularly environmental, common to all patients affected by this disease and their potential predisposing factor(s). In addition, the nature of the cytoplasmic inclusions seen in macrophagic myofasciitis is being evaluated with microprobes, X-ray analysis and atomic spectrometry, to look for toxic substances incompletely digested by the macrophage system and perhaps responsible for triggering the disease. It should also be noted that 6 of our patients were taking hydroxychloroquine, a substance that inhibits macrophage secretion of interleukins (IL)-1a and -6, thereby interfering with the phagocytotic properties of these cells.

### **Hypothesis of an infectious origin**

The other etiology currently advanced for macrophagic myofasciitis is that of infectious histiocytosis. Infectious histiocytoses seem to be the consequence of the incapacity of the macrophagic system to complete the digestion of certain microbial agents after phagocytosis, thereby inducing a true macrophage-overload disease.

In light of the histological appearance of the muscle tissue, Whipple's disease with muscle tropism was first suggested for one of our first patients, but this site was the source of controversy in the literature. However, no patient had the digestive tract symptoms, the search for PAS+ macrophages in the lamina propria of the gastrointestinal tract was negative, as was polymerase chain reaction (PCR) search for *Trophirema whippellii* in digestive tract and muscle biopsies from our patients, thereby eliminating Whipple's disease. The search for a

microbial agent, especially an intracellular bacterium, in muscle tissues of patients with macrophagic myofasciitis by PCR and amplicon sequencing is underway, along with the search for altered cellular immunity which could favor the persistence of a chronic intramacrophage infection by microorganisms exhibiting low virulence (low expression of the alpha chain of the type 3 receptor of complement (or CD11b) at the surface of mononuclear leukocytes, defective monocyte production of IL-12, defective T-lymphocyte synthesis of interferon-gamma (IFN $\gamma$ )).

## Conclusion

Macrophagic myofasciitis represents a new entity emerging within the context of inflammatory myopathies and fasciitides. It does not correspond to any of the previously described histiocytoses or any known macrophage-overload disease. The clinical manifestations of macrophagic myofasciitis are not very specific and the diagnosis can only be established on a surgical biopsy with fascia. This disease was reported to the Centers for Disease Control (CDC) in Atlanta, GA, USA, and is the object of a French national epidemiological inquiry conducted by the InVS, GERMMAD and the Société Nationale Française de Médecine Interne (SNFMI). Numerous fundamental, clinical and epidemiological studies are in progress. It is strongly recommended that all new cases be reported to and histologically evaluated by the GERMMAD.

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