Identical Twins With Macrophagic Myofasciitis:
Genetic Susceptibility and Triggering by Aluminic Vaccine Adjuvants?

S. GUIS,1 J. P. MATTEI,1 F. NICOLI,2 J. F. PELLISSIER,3 G. KAPLANSKI,1 D. FIGARELLA-BRANGER,3 G. C. MANEZ,3 G. M. ANTIPOFF,1 AND J. ROUDIER4

Introduction
Macrophagic myofasciitis (MMF) is an inflammatory myopathy, recently described (1,2). Clinical symptoms include myalgias, arthralgias, muscle weakness, asthenia, and fever. Diagnosis is based on deltoid muscle biopsy that usually shows specific histologic abnormalities including infiltration of connective tissue structures by densely packed large and grossly rounded CD68+ histiocytes. These cells are characterized by central, round, and often nucleolated nuclei, and clear, slightly basophilic cytoplasm with fine PAS-positive granules (1). Aluminic vaccine adjuvants (3) as well as Tropheryma whippelii infection (4,5) have been recently suggested as possible etiopathogenic agents of MMF. We report 2 cases of MMF observed after hepatitis B vaccination in twin sisters. This observation illustrates the importance of the genetic background in MMF, and its possible triggering by aluminic vaccines.

Case report
Two 64-year-old identical twin sisters were referred to our department for possible rheumatoid arthritis. They had no family history of inflammatory disease. The first sister’s medical history was unremarkable until December 1993, 6 months after she received a third and final injection of hepatitis B vaccine (Engerix B vaccination, containing aluminic hydroxide, vaccination in April, May, and July, 1993) in the left deltoid. At this time, she began complaining of arthritis. On physical examination, arthritis involving both wrists and the proximal and distal interphalangeal joints of the hands and feet were noted. Arthritis was associated with myalgias and upper limb muscle weakness. She complained of dry eyes and mouth and of oral aphthae. Treatment with oral prednisone (5 mg/day) and methotrexate (20 mg weekly) proved ineffective. Neurologic examination revealed distal paresthesias and cramps affecting the 4 limbs, slight weakness of hand muscles, no pyramidal syndrome, and partial visual acuity loss. Sicca syndrome was confirmed by Schirmer’s test. Salivary gland biopsy showed Chisholm 3 grade, consistent with the diagnosis of Gougerot-Sjögren’s syndrome. Erythrocyte sedimentation rate (ESR) was 20 mm/hour, C-reactive protein was 30 mg/l. Serum creatine kinase and cerebrospinal fluid were normal. Antinuclear antibodies (ANA) were weakly positive (200 UI/ml) with spotted pattern. Anti-DNA, anti-SSA, anti-SSB, rheumatoid factor, and anticardiolipin antibodies were not detected. Serologic tests for hepatitis A, B, C, and parvovirus B 19 were negative. The patient typed as HLA–A01, A02, B13, B35, DRB1*01, DRB1*07. Electromyography showed a slight myogenic aspect. Radiographs of the hands, shoulders, wrists, ankles, and feet were normal. Technetium bone scan showed symmetric increased uptake of the main joints. Upper right limb muscle magnetic resonance imaging (MRI) showed general muscle atrophy. The morphology and chronology of the visual-, auditory-, motor-, and somaesthesic-evoked responses were normal, and cerebral MRI was normal. Esophago-gastro-duodenoscopy was normal with no evidence of PAS+/H11001+ cells on duodenal biopsies, the culture for Tropheryma whippelii in duodenal biopsies was negative. Diagnosis of MMF was obtained by histologic examination of biopsy sample of the left deltoid muscle, which showed stereotypical epi-, peri- and endomysial infiltrates of densely packed CD68+ macrophages twice associated T and B cells (Figure 1). Electron microscopic examination was not performed on this biopsy.

The twin sister had a similar clinical presentation with bilateral arthritis of wrists, shoulders, temporomandibular joints, hands, and ankles. She received prednisone (15
mg/day), hydroxychloroquine (400 mg/day), and methotrexate (20 mg/week). Her medical history was unremarkable except for mild asthma and high blood pressure. On admission, she reported peripheral arthritis with myalgias. Neurologic examination showed distal paresthesias and cramps of the 4 limbs, severe weakness of the hand muscles, hyperreflexia of the right upper limb, right Hoffmann’s sign, and normal plantar reflexes urgency of micturition. The symptoms had started 7 months after intramuscular hepatitis B vaccination in the left deltoid (Engerix B containing aluminic hydroxide, vaccination in December 1995, February, and July 1997). ESR was 30 mm at one hour. Serum creatine kinase was normal. ANA, anti-DNA, anti-SSA, anti-SSB, rheumatoid factor, and antiacardioliopin antibodies were negative. Serologic tests for hepatitis A, C and parvovirus B19 were negative. Hepatitis B serology confirmed the vaccination status, specifically the absence of hepatitis B surface, anti-hepatitis B core and anti-hepatitis B e antigens, and the presence of anti-hepatitis B surface antibodies. The patient typed as HLA–A01, A02, B13, B35, DRB1*01, DRB1*07. Schirmer’s test was positive. Electromyography showed myogenic aspect. Radiographs of the hands, shoulders, wrists, ankles, and feet were normal. MRI of the superior right limb muscles showed a diffuse muscle atrophy. Evoked potentials and brain MRI were normal. Esophago-gastro-duodenoscopy was normal and cultures for *Tropheryma whippellii* in duodenal biopsies were negative. Once again, muscle biopsy of the left deltoid muscle confirmed the diagnosis of MMF.

**Figure 1.** Deltoid muscle biopsy (light microscopy, serial sections, original magnification × 125) demonstrating macrophagic myofasciitis in patient 1. A, inflammatory infiltrates of adipose tissue of fascia (fasciitis) by macrophages notably large in size and lymphocytes (Hematoxylin and eosin stained). B, immunoreactivity of CD68+ showing large predominance of macrophages. C, immunoreactivity of CD3+ mononucleated cells corresponding to T cells. D, immunoreactivity of DBB42 antibody showing B cells.

### Discussion

We report cases of MMF affecting twin sisters, which occurred 6–7 months after hepatitis B vaccination. In both cases, clinical symptoms were remarkable because of the importance of arthritis associated with muscle involvement. Laboratory tests showed slight inflammation, and normal muscle enzyme levels. Remarkably, although both twin sisters had had complete hepatitis B vaccination, only the second had developed antibodies to the hepatitis B surface antigen. Indeed, the HLA–DRB1*07 allele, which both twins expressed, is associated with poor humoral responses to hepatitis B vaccination (6). Thus, antibody responses to hepatitis B surface antigen may not be crucial to the development of MMF.

Conversely, the role of vaccines containing aluminum hydroxide in the pathogenesis of MMF has been recently suggested (3). Despite the fact that histologic abnormalities are present only at the site of vaccination, systemic symptoms are generally observed. However, there is a discrepancy between the wide usage of aluminum hydroxide-containing vaccines (especially anti hepatitis B vaccines) and the very limited number of MMF cases reported so far. We did not perform electron microscopy on muscle biopsies to check for aluminium inclusions in macrophages. This report suggests that additional factors, perhaps genetic, may influence the occurrence of MMF. Aluminum hydroxide may trigger unusual muscle inflammatory infiltrates in patients with increased susceptibility to inflammatory disease or decrease macrophages’ capacity for aluminum hydroxide digestion. The nature of the predis-
posing genetic factor is unknown. HLA–DRB1*01, which was found in both sisters (identical twins) could be a potential candidate. Thus, our observation suggests that aluminic vaccinations may trigger MMF on the HLA–DRB1*01 genetic background.

REFERENCES