

Macrophagic myofasciitis and vaccination: Consequence or coincidence?

Tânia Santiago · Olinda Rebelo · Luís Negrão ·
Anabela Matos

Received: 19 February 2014 / Accepted: 3 June 2014 / Published online: 13 June 2014
© Springer-Verlag Berlin Heidelberg 2014

Abstract Macrophagic myofasciitis (MMF) characterized by specific muscle lesions assessing long-term persistence of aluminum hydroxide within macrophages at the site of previous immunization has been reported with increasing frequency in the past 10 years. We describe clinical and laboratory findings in patients with MMF. We did a retrospective analysis of 16 cases observed in our Neuropathology Laboratory, between January 2000 and July 2013. The mean age of the 16 patients was 48.8 ± 18.0 years; 80.0 % were female. Chronic fatigue syndrome was found in 8 of 16 patients. Half of the patients had elevated creatinine kinase levels, and 25.0 % had a myopathic electromyogram. Thirteen patients received intramuscular administration of aluminum-containing vaccine prior to the onset of symptoms. MMF may mirror a distinctive pattern of an inflammatory myopathy. The vaccines containing this adjuvant may trigger MMF in some patients.

Keywords Macrophagic myofasciitis · Myopathy · Aluminum hydroxide · Vaccination · Fatigue chronic syndrome

T. Santiago (✉)
Rheumatology Unit, Centro Hospitalar e Universitário de
Coimbra, Praceta Prof. Mota Pinto, 3000-075 Coimbra, Portugal
e-mail: tlousasantiago@hotmail.com

O. Rebelo
Neurology Unit, Neuropathology Laboratory, Centro Hospitalar e
Universitário de Coimbra, Coimbra, Portugal

L. Negrão · A. Matos
Neurology Unit, Neuromuscular Outpatient Clinic, Centro
Hospitalar e Universitário de Coimbra, Coimbra, Portugal

Introduction

Macrophagic myofasciitis (MMF) is an uncommon aluminum-induced myopathic syndrome reported for the first time in France in 1998 [1]. This syndrome is characterized by specific muscle lesions assessing long-term persistence of aluminum hydroxide within macrophages at the site of previous immunization [2]. Recently, MMF was categorized under a common syndrome entitled “Autoimmune/Inflammatory Syndrome Induced by Adjuvants” [3].

Electron microscopy, microanalytical studies, experimental procedures, and an epidemiological study demonstrated that the lesion is due to persistence for years, at the site of injection, of an aluminum hydroxide adjuvant used in vaccines against hepatitis A virus, hepatitis B virus, and tetanus toxoid [3]. This adjuvant is known to potently stimulate the immune system and to shift the immune responses toward a Th-2 profile. It is plausible that persistent systemic immune activation represents the pathophysiologic basis of MMF.

Over 400 cases of MMF have been described in the literature [4]. Most of the cases of MMF recognized so far are from France, and isolated cases have been recorded in the USA and other European countries [5–7]. The present study was conducted to determine clinical and laboratory findings in patients with MMF.

Materials and methods

All patients with biopsy-proven MMF, between January 2003 and July 2013, from our Neuropathology Department were included in the study.

MMF was diagnosed on the basis of evidence of (1) well-circumscribed sheets of densely packed, large,

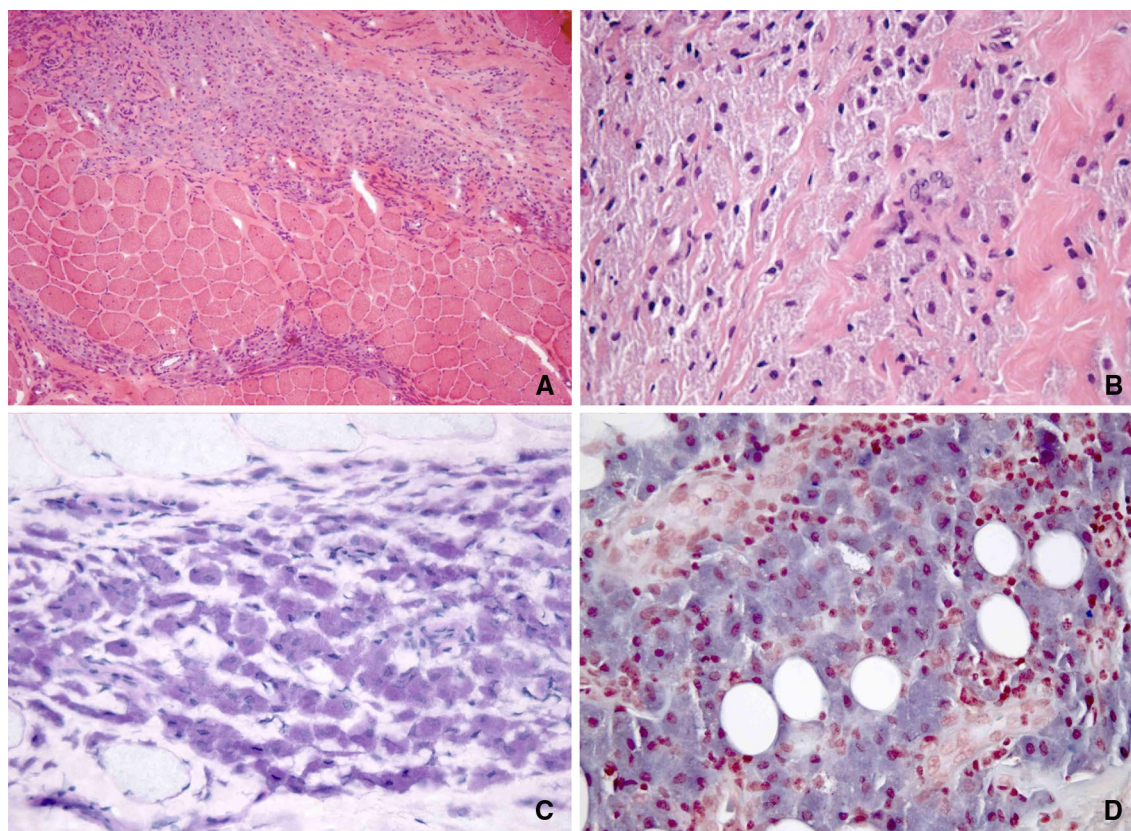


Fig. 1 Deltoid muscle biopsy of patients with MMF (light microscopy). **a** $\times 50$, Hematoxylin and eosin, macrophagic perifascicular infiltrate; **b** $\times 400$, hematoxylin and eosin, macrophagic perifascicular

infiltrate in detail; **c** $\times 400$, extensive infiltration of PAS-positive diastase resistant; **d** $\times 400$, aluminum-containing macrophages (in purple) stained by aluminum–beryllium staining

nonepithelioid macrophages with a finely granular, periodic acid-Schiff-positive content in the connective structures of the muscle, perimysium, and epimysium (Fig. 1a–c), (2) lymphocytic infiltrates intermingled with macrophages, (3) absence of significant muscle injury, and (4) macrophages with intracytoplasmic aluminum stained by the technique of aluminum–beryllium (*Solocromo-Azurina*) (Fig. 1d).

Medical records were retrospectively examined for age, gender, age at diagnosis, initial symptoms, laboratory findings (including creatine kinase levels, aldolase, autoimmunity), and electromyographic results. All patients were evaluated by a Neurologist at the time of diagnosis of their muscle disease. In addition, in each patient, we determined by telephone interview the history of immunization.

Results

Clinical and laboratory findings in 16 patients with MMF are summarized in Table 1. Of the 16 patients, 80 % were female. The mean age of patients was 48.8 years (range 27–85 years). Delay elapsed from first symptoms to biopsy was 51.9 months (3–180 months).

Table 1 Clinical and laboratory findings in 16 patients with macrophagic myofasciitis

Age (years) ^a	48.8 \pm 18.0
Gender (female) ^b	13/16 (80)
Age at diagnosis/biopsy (years) ^a	44.9 \pm 18.1
Symptom duration before diagnosis (months) ^a	64.8 \pm 60.3
Myalgia/myopathy/muscle weakness ^b	9/16 (56.3)
Arthralgia ^b	2/16 (12.5)
Responsive to steroids ^b	1/5 (20.0)
Associated diagnosis	
Chronic fatigue syndrome ^b	8/16 (50.0)
Dermatomyositis ^b	2/16 (12.5)
Others ^b	6/16 (37.5)
History of vaccination ^b	13/16 (81.3)
Delay between vaccination and symptoms (months) ^b	51 (3–192)
Abnormal laboratory findings	
CK levels >145 U/ml ^b	8/16 (50.0)
Aldolase >7.6 U/L ^b	2/4 (50.0)
EMG (myopathic) ^b	4/9 (44.4)

CK creatine kinase, EMG electromyogram

^a Values shown as mean \pm standard deviation

^b Values shown as *n* (%)

This group of 16 patients was referred with the presumptive diagnosis of chronic fatigue syndrome (CFS) [8], dermatomyositis [2], myasthenia gravis or muscle dystrophy or metabolic myopathy or migraine (one each). Two patients had their diagnosis in progress. Their symptoms included myalgias (10/16), marked asthenia (10/16), muscle weakness (10/16), and arthralgia (2/16). Six of 13 patients had a positive ANA screening with a speckled pattern in 4 and a homogeneous pattern in two patients. Abnormal laboratory findings included elevated creatinine kinase levels in half of the patients, aldolase elevated in 12.5 % (2/16), and a myopathic electromyogram in 25.0 % (4/16) of the patients.

A history of vaccination was available for 13 of 16 patients. All 13 patients had received intramuscular administration of aluminum-containing vaccine prior to the onset of muscular symptoms, and the delay from the last vaccination to the first manifestations ranged from 3 to 192 months (mean 51 months).

Discussion

In our retrospective study, we described 16 cases of MMF. This condition was more common in female adults and associated with CFS, a complex multidimensional condition in which fatigue can manifest in multiple forms including disabling fatigue [8].

Some authors highlighted a possible mechanism whereby vaccination involving aluminum-containing adjuvants could trigger the cascade of immunological events that are associated with autoimmune conditions including CFS and MMF [8]. The immune adjuvant effect of aluminum has been recognized for several decades [8, 9]. Adjuvants increase innate and adaptive immune responses. In addition, they may function as delivery systems by creating depots that trap antigens at the site of infection, providing slow release in order to continue the stimulation of the immune system, thus enhancing the antigen persistence at the injection site and increasing recruitment and activation of antigen-presenting cells (depot's effect) [9]. Aluminum-containing adjuvants stimulate the activation of dendritic cells, lymphocytes, macrophages, uric acid, and intracellular Nalp3 inflammasome system [9].

Thus, adjuvants increase the local reaction to antigens (e.g., at the site of infection) and subsequently the release of chemokines and cytokines, such as IL-1 and IL-18.

Moreover, 15–20 % of the MMF cases are associated with an autoimmune disease or a neuromuscular disorder such as MS-like demyelinating disorders, Hashimoto's thyroiditis, dermatomyositis, myasthenia gravis, and inclusion body myositis [10, 11]. The coexistence with dermatomyositis is rare, the precise relationship between these two

conditions is unknown, and it has been suggested an individual susceptibility to developing muscle disease [12].

The link between symptoms and pathology in cases of MMF is not fully understood, but animal studies have demonstrated widespread systemic distribution of aluminum-containing macrophages following vaccination [4]. Affected patients may have myopathic pattern on electrophysiology and raised creatine kinase [4].

Permanence time of aluminum hydroxide in human muscle has not been established despite of its long use in vaccines [9]. Phagocytized aluminum hydroxide increases survival of macrophages and synergizes the effects of monocyte colony-stimulating factor and granulocyte/monocyte colony-stimulating factors. Some aluminum-containing macrophages accumulate locally, while others migrate to regional lymph node [8].

Antigen presentation at the injection site is assessed by the presence of lymphocytes and plasma cell infiltrates in the zone of macrophages, creating the immunogenic granuloma.

Time elapsed from last vaccination to histological detection of MMF could be very long, and this may depend on inter-subject variation in the clearance process of aluminum [13]. In a large series of MMF cases, all had been immunized 3 months–8 years before muscle biopsy with aluminum-containing vaccines [3]. In our retrospective study, there was an unusually long duration between vaccination and the onset of symptoms (3 months–16 years). Although it is not possible to prove a causal link, the presence of persistent aluminum-containing macrophages and typical symptoms supports a diagnosis of MMF.

Cognitive dysfunction and multiple sclerosis-like disorders have also been documented in a subgroup of patients with MMF [12].

We point out that cases of MMF can be diagnosed without any relation to alum-containing vaccination [14], suggesting that other causes unrelated to vaccination need to be investigated in the pathogenesis of MMF.

Why is there a discrepancy between the wide application of aluminum-containing vaccines and the limited number of MMF cases reported in the literature?

Firstly, it seems that a genetic predisposition influences the occurrence of MMF. Two studies have implicated the HLA-DRB1 typing as a predictor of an increased risk for development of MMF [15]. Moreover, a significantly increased frequency of HLA-DRB1 was observed in patients with MMF compared with controls [16].

Secondly, we hypothesized that other factors, including drugs, environmental and toxic factors, may influence the clinical manifestations of MMF [3]. Thirdly, the degree of local macrophage infiltration in the muscle may also influence the clinical manifestations.

Consequently, we suggest that patients with myalgia, marked asthenia, muscle weakness, chronic fatigue should

be carefully checked for a history of aluminum-containing adjuvants in vaccines, and if there is consistent chronology, a muscle biopsy to search for MMF at the site of injection should be considered, even many years after onset of symptoms.

Conclusion

Macrophagic myofasciitis is a relatively new condition characterized mainly by post-vaccination inflammatory muscle disorder systemic manifestations and a distinctive pathological pattern on muscle biopsy. On the basis of the accumulated data, this immune-mediated condition that may be triggered by exposure to alum-containing vaccines, in patients with a specific genetic background, and the temporal association may be manifested from a few months up to 15 years.

Conflict of interest None.

References

- Gherardi RK, Chérin P (1998) Macrophagic fasciitis: a new entity. Groupe d'études et recherche sur les maladies musculaires acquises et disimmunitaires (GERMMAD) de l'association française contre les myopathies (AFM). *Rev Med Interne* 19:617–618
- Gherardi RK (2003) Lessons from macrophagic myofasciitis: towards definition of a vaccine adjuvant-related syndrome. *Rev Neurol (Paris)* 159:162–164
- Perricone C, Colafrancesco S, Mazor RD, Soriano A, Agmon-Levin N, Shoenfeld Y (2013) Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: unveiling the pathogenic, clinical and diagnostic aspects. *J Autoimmun* 2013(47):1–16. doi:10.1016/j.jaut.2013.10.004
- Gherardi RK, Authier FJ (2012) Macrophagic myofasciitis: characterization and pathophysiology. *Lupus* 21:184–189. doi:10.1177/0961203311429557
- Polido Pereira J, Barroso C, Evangelista T, Fonseca JE, Pereira da Silva JA (2011) Macrophagic myofasciitis: a case report of autoimmune/inflammatory syndrome induced by adjuvants (ASIA). *Acta Reumatol Port* 36:75–76
- Barros SM, Carvalho JF (2011) Shoenfeld's syndrome after pandemic influenza A/H1N1 vaccination. *Acta Reumatol Port* 36:65–68
- Shivane A, Hilton DA, Moate RM, Bond PR, Edean A (2012) Macrophagic myofasciitis: a report of second case from UK. *Neuropathol Appl Neurobiol* 38:734–736. doi:10.1111/j.1365-2990.2012.01293.x
- Exley C, Swarbrick L, Gherardi RK, Authier FJ (2008) A role for the body burden of aluminium in vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome. *Med Hypotheses* 2009(72):135–139. doi:10.1016/j.mehy.2008.09.040
- Perricone C, Colafrancesco S, Mazor RD, Soriano A, Agmon-Levin N, Shoenfeld Y (2013) Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: unveiling the pathogenic, clinical and diagnostic aspects. *J Autoimmun* 47:1–16. doi:10.1016/j.jaut.2013.10.004
- Authier FJ, Cherin P, Creange A, Bonnotte B, Ferrer X, Abdelmoumni A et al (2001) Central nervous system disease in patients with macrophagic myofasciitis. *Brain* 124(974e):83
- Migita K, Ueda-Nakata R, Masuda T, Miyashita T, Koga T, Izumi Y, Ichinose K, Ezaki H, Ito M, Motomura M, Eguchi K (2010) Macrophagic myofasciitis associated with rheumatoid arthritis. *Rheumatol Int* 30(7):987–989. doi:10.1007/s00296-009-1015-3
- Lazaro E, Doutre MS, Coquet M, Bouillot S, Beylot-Barry M, Beylot C (2005) Coexistence of dermatomyositis and macrophagic myofasciitis. *Presse Med* 26(34):438–440
- Peter G, des Vignes-Kendrick TC, Eickhoff TC, Fine A, Galvin V, Levine MM, Maldonado YA, Marcuse EK, Monath TP, Osborn JE, Plotkin S, Poland GA, Quinlisk MP, Smith DR, Sokol M, Soland DB, Whitley-Williams PN, Williamson DE, Breiman RF (1999) Lessons learned from a review of the development of selected vaccines. National Vaccine Advisory Committee. *Pediatrics* 104(4 Pt 1):942–950
- Park JH, Na KS, Park YW, Paik SS, Yoo DH (2005) Macrophagic myofasciitis unrelated to vaccination. *Scand J Rheumatol* 34:65–67
- Guis S, Mattei JP, Nicoli F, Pellissier JF, Kaplanski G, Figarella-Branger D, Manez GC, Antipoff GM, Roudier J (2002) Identical twins with macrophagic myofasciitis: genetic susceptibility and triggering by aluminic vaccine adjuvants? *Arthritis Rheum* 15(47):543–545
- Guis S, Pellissier JF, Nicoli F, Reviron D, Mattei JP, Gherardi RK, Pelletier J, Kaplanski G, Figarella-Branger D, Roudier J (2002) HLA-DRB1*01 and macrophagic myofasciitis. *Arthritis Rheum* 46:2535–2537