Asian Journal of Immunology

Volume 8, Issue 1, Page 97-103, 2025; Article no.AJI.134974

An Alum Loaded Macrophage Driven Autoimmune Myopathy

IBRAHIM M S SHNAWA [a,b*]

[a] Department of Medical Biotechnology, College of Biotechnology, AL-Qasim Green University, Qasim, Babylon, Iraq.
[b] College of Nursing, University of Hilla, Babylon, Iraq.

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: https://doi.org/10.9734/aji/2025/v8i1164

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://pr.sdiarticle5.com/review-history/134974

Opinion Article

Received: 25/02/2025
Published: 03/05/2025

ABSTRACT

Immune mediated diseases and syndromes are rare and attributed at most to genetic and environmental interactions. Macrophagic Myofasciitis MMF is one of these syndromes sub-entities. In the present opinion the immunobiology of MMF was being reviewed. The molecular autoimmune mechanisms can be as follows; concurrent release of alum nano-molecules are taken up by macrophage persist in, combine with cellular proteins forming metalloprotein. It is now modified cellular protein in a modified macrophage which have DC marker, but still of macrophage morphology. Metalloprotein, when being extracellular on cellular burst or on diffusion to extracellular space will reach immune cells, in presence of; chronic induction, pathogenic allele, the HLA DR1 01 and the affected tissue microenvironment. Molecular mimicry, antigen bystander and/or epitope spreading response may operate and autoimmune tissue changes happened within continuum of granulomatous lesion developed in skeletal muscle at the injection site. Modified macrophage may migrate to regional lymph node and spleen the finally reach the brain. As a result, disturbance occurs in skeletal muscle functions and in brain cognition function.

**Corresponding author: E-mail: ibrahimshnawa3@gmail.com;*

Cite as: *SHNAWA, IBRAHIM M S. 2025. "An Alum Loaded Macrophage Driven Autoimmune Myopathy". Asian Journal of Immunology 8 (1):97-103. https://doi.org/10.9734/aji/2025/v8i1164.*

Keywords: Alum; allele; autoimmune; environment; genetics; granuloma; HLA; macrophage myopathy.

1. INTRODUCTION

Immuno-prophylactants are vaccines and sero-therpeutics. These standard biologics are helpful for prevention and therapy, both in man and animals. Vaccines and adjuvants so far they are helpful but they are associated with an adverse effects. Vaccine and adjuvant adverse effects can be ramified into; vaccine and adjuvant associated disease enhancement VADE and vaccine failure VF (Shnawa, 2017, 2023, Shnawa & ALKhafaji 2023). One of the known VADE is Shoenfeld syndrome SS (Shoenfeld et al., 2011). SS grouped five disease sub-entities as; i- Postvaccination with adjuvanated vaccine illness, ii-Macrophagic myofasciitis illness MMF, iii – sick building illness, iv-Gulf war illness and v - siliconosis. This syndrome sub-entity is a molecular immunogenetic disease with presentation of an autoimmune reactions. It is an inducive chronic rare syndrome associated with specific human leukocyte antigen haplotype (Calarelli et al., 2024). The objective of the present opinion paper was to tackle the immunobiology [Box one] of MMF.

BOX-One: Relevant Terminology (Abbas et al., 2015)
1. Anergy: A state of unresponsiveness to antigenic stimulation. Lymphocyte anergy is failure of T and/or B cell clones to react antigen and is a mechanism of maintaining immune tolerance to self antigens.
2. Antigen By- stander: Continued immune responses to infection modified proteins, an attendant inflammation allow exposure of autoantigens to immune responses. Theoretically, this could operate through T cell recognition resulting in help of potentially, B lymphocyte.
3. Clonal ignorance: A form of lymphocyte unresponsiveness in which self antigens are ignored by the immune system even though lymphocyte specific for their antigens remain viable and functional.
4. Clonal deletion: A mechanism of lymphocyte tolerance in which an immature T cell in the thymus or immature B cells in bone marrow undergoes apoptotic death as a consquences of recognizing self antigens.
5. Epitope spreading: In autoimmunity it is found that the development of immune responses to multiple epitopes as an autoimmune disease originally target one epitope progresses, likely caused by further breakdown in tolerance and release of additional tissue antigen due to self protein stimulated by the initial response.
6. Molecular Mimicry: A postulated mechanism of autoimmunity triggered by infection with a microbe that cross react with self antigen. Immune response to the microbe results in reactions with self tissue antigen.
7. Sequestrated Antigens: There are certain tissue niches in which their specific antigens are not recognized to immune system cells during the ontogeny of the individuals. Like, eye vetrus fluid, semen plasm, and synovial fluid when exposed to immune cells will be recognized as foreign.
8. Tolerance: unresponsiveness of adaptive immune system to antigen, as a result of inactivation or death of the antigen specific lymphocyte induced by the exposure to antigen.

2. MACROPHAGIC MYOFASCIITIS MMF CONCEPT

MMF is an uncommon immune mediated inflammatory disorder of muscle and is believed to be due to an alum in a vaccine combination exhibited persistence at the site of injection. The conditions characterized by diffuse myalgia, arthralgia and fatigue (Ravindran 2024, Dittmann 2000, Ieraeli et al 2011). It is a rare inflammatory condition that affect skeletal muscle and connective tissue characterized by infiltration of macrophages into muscle tissue, in which the affected subject presents local or systemic manifestation. The local manifestation can be an immune active lesion of granuloma, in a rare muscle disease characterized by; microscopic lesions found in muscle biopsies that showed infiltration of the muscle tissue by PAS positive macrophages in light microscope and alum crystal inclusion in electron microscopic studies and they are traced in epimysium, perimysium, prefascular endomysium with crystal lesion composed of aluminum salt (Tervaert et al, 2023, Gibson, 2024). Hence, aluminum containing vaccines have been implicated. MMF lesions result from aluminum hydroxide adjuvant hidden within the tissue with frequent steady state release of alum causing immune reactions (Watad et al., 2017, Santos et al 2018, Caldarelli et al., 2024).

3. TIMELINE

Knowing the past will in light the present and pin point directions to the future. So, the MMF timeline made in Table 1.

Table 1. Macrophagic Myofasciitis timeline

Achievement	Date	Reference
MMF was initially described as an emergency entity by Franch myo-pathologist. The reported in Lancet	1993,1998	Shivane et al., 2012 Amoura et al., 2000
Between 1993 and 1999 more than 50 cases of MMF have been described in France	1999	Amoura et al., 2000
MMF patient presents central nervous system disease	2001	Authier 2001
Long term persistence of vaccine driven alum in muscle	2001	Gherardi et al., 2011
MMF present local and systemic forms	2003	Papo 2003
Electron microscopic study of MMF lesion description	2003-2005	Shmgdi et al., 2005
Reporting MMF unrelated to vaccination	2005	Park et al., 2005
Experimental induction of MMF in rats.TH1 bias response, TH1/TH2 balance unchanged in norma lesion size	2006	Authier et al., 2006
MMF being prove of vaccine autoimmune related disease	2011	Israeli et al., 2011
Macrophage take up alum in tendon through fluerescent alum translocate to drainage lymph node then to blood, spleen and brain	2012	Gherardi & Authier 2012
MMF several reports in UK	2012	Shivahe et al., 2012
A report of an atypical presentation of MMF	2020	Dias et al., 2020
Al (OH)3 vaccine associated with MMF pseudo-lymph node and causing hypersensitivity	2020	Kim et al., 2020

4. IMMUNOBIOLOGY

Relatively, immune cells both naïve and active forms could be involved in immunobiology of MMF. Though the main player cells is the naïve and active macrophage. Autoreactive B cells are evidently involved, Autoreactive T cells are of unclear role. Modified macrophages of DC surface markers, modified morphology and modified function but still of macrophage morphotype are noted .TH1/Th2 are note changed and TH1 biased responses. These are the main immune-biological features of MMF as presented in the following paragraphs.

Alum nano-molecules may reach distant organs of the body including brain through the migration of the an alum loaded macrophage or though out diffusion process across the semipermeable membranes. This accompanied by an active liver detoxification of this chemical insult. Clearance of alum from the body have been found a species dependent process (Gherardi et al., 2019). Alum adjuvant induces humoral immune Th2 responses via primary and secondary response events in mice and mixed humoral and cellular responses in human being whereby vaccine adjuvant supports the activation of CD8 T cells but these cells does not differentiated to cytotoxic T cells (Hogen-Esch 2013). In an in-vitro culture system Al(OH)2 stimulate isolated macrophages that contains large and persistent intracellular crystalline inclusion, the “Alum Loaded Macrophage ”ALM.ALM exhibit phenotypical and functional modifications as they showed myeloid dendritic cell surface markers[HLADR high,/CD1a-/CD14-] and displayed potent ability to induce MHC restricted antigen specific memory response but kept macrophage morphology. This suggest a key role of ALM in relation to the alum-vaccine and important role in this memory response (Ann-Ceclle et al., 2004). The vaccine alum adjuvant formulation when applied into the muscle, months to years later, the alum persists hidden in the inoculation site. Then released frequently in a steady state manner leading to chronic induction of immune reaction in the application site Macrophages and to lesser extent lymphocytes accumulate in the injection site took up alum nano-molecules may be through pinocytosis. Local granulomatous response is initiated and developed. In continuum with this local reaction alum may combined with self cellular protein from metalloprotein. A modified self protein such as a metalloprotein of MMP initiated specific immune and autoimmune responses in presence of the pathogenic allele HLADR 1 01 and the activated

tissue microenvironment as a pathology system. The net result of such reactions is the production of myo-specific autoantibody and CD8+T cell predominantly existed along with modified macrophages in the lesions (Shnawa 2023). This alum loaded modified macrophages my migrate through out blood stream to lymph nodes, spleen and brain by this they may lead to skeletal muscle and cognitive disorders (Gherardi et al 2021).

MMF has been reported after contact with metals and /or vaccines.it is typically occurs in individuals with genetic predisposition like HLADRB1 andPTPN22.Such contact may initiate over-immune reaction of the immune system that propriates to production of autoantibodies and fully cause autoimmune disorder. MMF is a sub-entity of ASIA syndrome results from interaction between genetic and environmental factors with adjuvant through modulation receptors such as TLR, NLR and CLR triggering aberrant immune response prompting development of an autoimmune disorder (Caldarelli et al., 2024). Aluminum adjuvant is well known enhancer of TH2 responses. However, it has been suggested that Aluminum induces TH1 response in presence of other TH1 inducing compounds such as LPS or Rec. Influenza antigen, a bystander effect through which alum adjuvant trigger autoimmunity via activation of dormant autoreactive T lymphocyte in some individuals (Fan et al., 2022).

5. MMF AUTOIMMUNE MECHANISMS

In general autoimmune mechanisms are of classical and recent mosaic nature (Shnawa 2023). MMF autoimmune mechanisms composed of a paradigm of three heritability features and four govering etiology roles (Li et al., 2015). As mentioned in the following paragraphs;

Three main molecular mechanisms valid for explaining autoimmunity as; Tolerance, molecular mimicry and epitope spreading. Tolerance can be established through clonal deletion, anergy, clonal ignorance and regulatory T cell function (Perricon et al., 2019). The heritability of MMF has been well documented, quantified and exhibit three important features; I – all genetic diseases have strong genetic components, ii- relatively large numbers of risk alleles are shared between multiple autoimmune diseases and iii- the product of most of the autoimmune associated genes are parts of immunological pathways in particular T cell signaling, TNF signaling and innate immunity (Zherankova et al., 2009). The reaction of the immune system to an environmental stimuli, produce autoimmune disease should pass four governing roles in a stepwise manner and start with; i-foundation of predisposing genetic architecture representing autoimmunity, ii- chronic repeated skewed and biased responses over years yield pathological system, iii- the pathological system induces loss of immune tolerance and iv- adopting nocuous potentials (Li et al., 2015, Zherankova et al., 2009, Shnawa 2023). Hence, the proposed autoimmune mechanisms of the MMF are as follows;

The genome of MMF patients has strong genetic component which is the autoimmune associated genes that contains large numbers of risk alleles. The gene expression products of these risk alleles are parts of the immunological pathway. Alum Chronic repetitive induction over years face the genome of the patient leading to a pathological system. Such pathological system induces loss of tolerance. Then affected immune system adopt nocuous potentials [molecular mimicry, antigen bystander and/or epitope spreading] the autoimmune condition.

6. MMF IMMUNE FEATURES (Li et al., 2015, Zherankova et al., 2009, Shnawa 2023)

The major immune features of MMF can be pointed out in the followings;

i -Rare immune mediated disease

ii – It is of an Inducive and constitutive nature.

iii – Adjuvant-Alum driven.

iv-Alum form metalloprotein a modified self protein.

v-MMF macrophage appeared to useLC3 associated phagocytosis to alum vaccine, and secret pain inducing molecules (Masson et al., 2024).

vi- Modified self protein, antigen bystander and/or molecular mimicry in presence of HLADR 1a 01 haplotype induce autoimmune response.

vii-The nature of the autoimmune response in mice is humoral while in man is mixed humoral and cellular.

viii-Alum modified macrophage adopt new surface marker DC cells but they still of macrophage morphology. Such macrophage is believed to have a role in memory response.

ix-TH1/TH2 balance found stable, but with bias TH1 response.

x-Local muscle lesion nature is granulomatous.

xi-The immune whole mark of ongoing reactions leads to functional problems in skeletal muscles and in cognition.

7. DISEASE ENTITY

The MMF is a rare macrophage driven myopathy. It stands as a molecular immunogenetic condition with an autoimmune presentation linked to HLADR 1a 01 susceptibility haplotype. MMF is grouped within the Shoenfeld's Syndrome (Shoenfeld et al., 2011).

8. LABORATORY IMMUNOLOGY

Patient's blood samples collect for the systemic humoral and cellular investigation. The humoral for check of myo-specific autoantibodies and for macrophage and T cell subsets. Biopsy sample for detection of the local cellularity nature of the granulomatous tissue reactions. Electron microscopic preparation from the lesion to elucidate the alum crystallization in cells. Immune laboratory animal model can be prepared to recheck the founding in man.

9. LABORATORY ANIMAL IMMUNE MODELS

Several number of laboratory animal models have been tempted by specialist workers in this field (Ruiz et al., 2017, Colafrancesco et al., 2013). MMF lesions have been reproduced in; mice, rat, rabbit, monkeys and sheep by IV and IM routes. IV associated with rapid elimination. While, rabbit IM injection elimination lasts four weeks post injection (Gherardi et al., 2019). In an experimental animal setting, fluorescent nano-tagged alum within the phagocyte have shown translocation of alum from the site of injection through blood circulation to the regional lymph nodes, spleen then to brain (Gherardi & Authier 2012). Spurg-Dully and Lewis rat injected with 10ul of Al(OH)3 adjuvant vaccine and watched over one year for the appearance of the lesions and the possible reduction of their sizes per time elapse. Shrinkage of the lesion size happened over time. Humoral Th2 and B cell immune responses mounted.TH1/Th2 balance. The function of cytotoxic T cell interferes with alum clearance process (Authier et al., 2006).

10. ANIMAL IMMUNE MODEL SUGGESTION

A group of 18 Spurg-Dully rats will be elected and grouped into three groups each of six. One sham saline control, one for alum solution a lone and one with vaccine -alum adjuvant. Rats of the three groups IM injected, and will follow up to score the lesions and possible reduction over time elapse. The formed lesions will be subjected to histopathological evaluations in month wise manner for six months.

11. FACT SHEET (PARK ET AL., 2019, ISRAELI ET AL., 2011, CRUZ-TAPIAS ET AL 2013)

Terminology: Macrophagic Myofasciitis.

Disease Nature: Rare immune mediated liked to HALADR1*01 susceptibility haplotype.

Onset Duration:3 months to eight years.

Inducer: Vaccine-Alum formulation, or unknown

Tissue Lesion Nature: Local sterio-typed immunologically active lesion.

Histology: Tissue sections from biopsy made, stained with PAS searching for cellularity.

Immunology: Determination of myo-specific autoantibodies in patients sera.

Lesion Description: Infiltration of epimysium, perimysium, and perivascular endomysium with alum loaded PAS positive macrophage accumulation at the site of injection. Muscle necrosis is typically absent, spars CD8 T cells and minimal myofiber damage the lesion is of granulomatous nature (Gherhardi, Authier 2003).

Chemical Analysis: Chemical microanalysis and atomic laser spectrophotometery reveals alum crystals within the macrophage.

Systemic Reactions: Skeletal muscle and cognitive disorders (Israeli et al., 2011, Park et al., 2019).

Age Prevalence: All ages.

12. CONCLUSION

MMF is an alum loaded macrophage driven autoimmune myopathy a syndrome sub-entity. It is linked with specific HLA haplotype susceptibility and grouped within Shoenfeld syndrome. MMF Immunobiology and autoimmune mechanisms, immune features and factsheet were issued.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

Abbas, A. K., Lichtman, A. H., & Pillai, S. (2015). *Cellular and molecular immunology* (8th ed.). Elsevier Saunders, Canada, 465–492.

Amoura, Z., Costedoat, N., Maisonobe, T., et al. (2000). Familial macrophagic myofasciitis. *Ann. Rheumatic Disease*, *59*(11), 926.

Anne-Ceclle, et al. (2004). Aluminum hydroxide adjuvant induces macrophage differentiation toward specialized antigen presenting cell type. *Vaccines*, *22*(23–24), 3127–3155.

Authier, F.-J. (2001). Central nervous system disease in patients with macrophagic myofasciitis. *Brain*, *124*(5), 974–983.

Authier, F.-J., Sauvates, S., Chrisolv, C., et al. (2006). $AL(OH)_3$-adjuvant vaccine induce macrophagic myofasciitis in rat it influences by the genetic background. *Journal of Neuromolecular Disorder*, *16*(5), 547–557.

Caldarelli, M., Rio, F., Giambra, V., et al. (2024). ASAI Syndrome: State of art and future prespectives. *Vaccines*, *12*, 1183. https://doi.org/10.3390/vaccines12101183

Colafrancesco ,S., Agmon-Levin, N., Perricone, N, Shoenfeld, Y. (2013). Unraveling the soul of autoimmune disease:pathogenesis, diagnosis and treatment adding dowels to the puzzle.Immunologic Research,56,200-205

Cruz-Tapias, P., Agmon-Levin, N., Israeli, E., et al. (2013). Autoimmune-inflammatory syndrome induced by adjuvant ASIA-animal model a proof of concept. *Current Medical Chemistry*, *20*(32), 4030–4036. https://doi.org/10.2174/09298673113209990253

Dias, R, Raquel ,F.,Diogo,R,,,,Cartlas, V.(2020).Macrophagic myofasciitis: A typical presentation for a rare disease with challenging approach. Rheumatologia ,58(3),167-172.

Dittmann, S. (2009). Macrophagic myofasciitis clinical signs in human and animals associated with minerals, trace element and rare earth elements, 2022.

Fan, J., Jin, S., Gilmartin, L., et al. (2022). Advances in infectious disease vaccines adjuvants. *Vaccines*, *10*, 1120.

Gherardi, R. K. (2011). Macrophagic myofasciitis assess long term persistence of vaccine derive aluminum hydroxide in muscle. *Brain*, *124*(9), 1821–1831.

Gherardi, R. K., & Authier, F.-J. (2003). Aluminum inclusion MMF: Recently identified condition. *Immunology Allergy Clininic*.

Gherardi, R. K., & Authier, F.-J. (2012). Macrophagic myofasciitis characteristic and pathophysiology. *Lupus*, *21*(2), 184–189.

Gherardi, R. K., Crepeaux, G., & Authier, F. (2019). Myalgia, chronic fatigue syndrome following immunization: Macrophagic myofasciitis in man and animals. Studies support linkage to aluminum adjuvant persistence and diffusion into immune system. *Autoimmunity Review*, *18*, 691–705.

Gibson, C. M. (2024). Macrophagic myofasciitis. *WikiDOC*.

Hogen-Esch, H. (2013). Mechanism of immunpotentiation and safety of aluminum adjuvant. *Frontiers of Immunology*, *3*. https://doi.org/10.3389/fimmu.2012.00406

Israeli, E., Agmon-Levin, N., Blank, M., & Sheonfeld, Y. (2011). Macrophagic myofasciitis a vaccine alum autoimmune related diseases. *Clinical Review of Immunology*, *41*(2), 163.

Kim, H., Lim, Y., Kang, J., et al. (2020). Macrophagic myofasciitis pseudolymph node caused by aluminum adjuvant. *Science Reports*, *10*, 11834.

Li, Y. R., Zhao, S. D., Branield, J. P., et al. (2015). Genetic sharing and heritability of pediatric age onset of autoimmune disease. *Nature Communication*, *61*, 1–10.

Masson, J.-D., Badran, G., Gherhardi, R. K., et al. (2024). Wide spread myalgia and chronic fatigue: Phagocytosis from macrophagic myofasciitis patients exposed to aluminum oxyhydroxide-adjuvanted vaccine exhibits specific inflammatory, autophagy and mitochondrial responses. *Toxics*, *12*, 491. https://doi.org/10.3390/toxics12070491

Papo, T. (2003). Macrophagic myofasciitis focal or systemic. *Joint Bone Spine*, *70*(4), 242–245.

Park, J.-H., Na, K.-S., Paik, S.-S., & Yoo, D.-H. (2005). Macrophagic myofasciitis unrelated to vaccination. *Journal of Rheumatology*, *24*(1), 65–67.

Perricon, C., & Sheonfeld, Y. (2019). *Mosaic of autoimmunity: The novel factors of autoimmune diseases*. Academic Press.

Ravindran, T. (2024). Macrophagic myofaciitis; causes, symptoms, and treatment. *Cliniq: The Virtual Hospit*

Ruiz, J. T., Lujan, L., Blank, M., & Seonfeld, Y. (2017). Adjuvant and vaccine induced autoimmunity, animal models. *Environmental Autoimmunity*, *56*, 55–65.

Santos, D. S., Santo, A., & Rebelo, C. (2018). Macrophagic myofasciitis: Challenging diagnosis. *British Medical Journal: Case Reports*. https://doi.org/10.1136/bcr2018

Sheonfeld, Y., & Agmon-Levin, N. (2011). ASIA – Autoimmune-Inflammatory Syndrome induced by adjuvant. *Journal of Autoimmunity*, *36*(11), 4–8.

Shingdi, M., Pamplette, R., Hughes, J., et al. (2005). Macrophagic myofasciitis associated with vaccine derived alumium. *Medical Journal of Australia*, *163*(3), 145–146.

Shivane, A., Hilton, D. A., Moat, R. M., et al. (2012). Macrophagic myofasciitis: A report of second case from UK. *Neuropathology Applied Neurology*, *38*, 711–716.

Shnawa, I. M. S. (2017). Vaccine allied biologics. *International Journal of Vaccination and Immunization*, *2*(2), 13–19.

Shnawa, I. M. S. (2023). Vaccine and adjuvant mediated autoimmunity. *Journal of Pharmaceutical Research International*, *35*(24), 42–48.

Shnawa, I. M. S., & AlKafaji, A. J. (2023). SARS-CoV-2 vaccine adverse effects. *Pharmaceutical Negative Results*.

Tervaert, J. W. C., et al. (2023). Autoimmune inflammatory syndrome induced by adjuvant ASIA. *Autoimmunity Review*, *22*(6), 103287.

Watad, A., Sarif, K., & Sheonfeld, Y. (2017). The ASIA syndrome: Basic concept. *Mediterranean Journal of Rheumatology*, *28*(2), 64–69.

Zherankova, V., Van Diemen, C. C., & Wijmenga, C. (2009). Detecting shared pathogenesis from shared genetics of immune related diseases. *Nature Reviews Genetics*, *10*, 586–594.

Peer-review history:
The peer review history for this paper can be accessed here:
https://pr.sdiarticle5.com/review-history/134974