Review

Environmental triggers for idiopathic inflammatory myopathies: unravelling the known and unknown

C. Cardelli[1,2], F. Trentin[3], F. Fattorini[1], M. Diomedi[1], E. Laurino[1], S. Barsotti[4], M. Mosca[1], L. Carli[1]

[1]*Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa;*
[2]*Department of Medical Biotechnologies, University of Siena;*
[3]*Rheumatology Unit, Azienda Sanitaria Friuli-Occidentale, Pordenone;*
[4]*Rheumatology Outpatient Clinic and Internal Medicine, Hospital of Livorno, Italy.*

*Chiara Cardelli, MD**
*Francesca Trentin, MD**
Federico Fattorini, MD
Michele Diomedi, MD
Elenia Laurino, MD
Simone Barsotti, MD, PhD
Marta Mosca, MD, PhD
Linda Carli, MD, PhD

**Contributed equally.*

Please address correspondence to:
Linda Carli
Reumatologia,
Dipartimento di Medicina Clinica e Sperimentale,
Università di Pisa,
via Roma 67,
56126 Pisa, Italy.
E-mail: 81clinda@gmail.com

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ABSTRACT

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of rare connective tissues diseases that usually share the common feature of immune-mediated muscle or lung injury. Whereas their pathogenesis is widely recognised as multifactorial, the specific triggers initiating their onset remain largely elusive. Factors such as infections, inhalants, or geoclimatic variables are implicated, yet due to the limitations inherent in studies involving small and non-homogeneous cohorts, findings often appear fragmented and inconclusive. This review endeavours to present the most updated evidence regarding the influence of environmental factors in determining the onset of IIM, with the aim of offering insight to optimise the routinary management of affected patients.

Introduction

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of acquired, rare connective tissue diseases that usually share the common feature of immune-mediated muscle or lung injury (1, 2). Distinct subgroups have been identified, including dermatomyositis (DM), polymyositis (PM), anti-synthetase syndrome (ASS), immune-mediated necrotising myopathy (IMNM), inclusion body myositis (IBM), and juvenile idiopathic inflammatory myositis (JIIM). In recent years, significant progress has been made in identifying myositis-specific (MSA) and myositis-associated (MAA) autoantibodies (1, 3, 4). These discoveries have revealed strong associations with the emergence of particular IIM phenotypes, each exhibiting distinct clinical course, prognoses, and response to treatment. This suggests a potential contributory role in the pathogenesis of these conditions.

However, the pathogenesis of IIMs is far more complex and involves genetic predisposition, which can influence both innate and adaptive immune system activation, as well as environmental triggers (5-7), such as infections, exposure to geoclimatic variables, pollutants, and drugs (6, 7). Numerous studies report a high prevalence of respiratory, gastrointestinal, or hospital-acquired infections preceding disease onset (8-10) and elevated antibody titres (both IgM and IgG) against various viruses in IIM patients (11-14). Additionally, there are several reports of IIMs occurring in patients with chronic infections such as HIV (15), HTLV-1 (16), and HCV (14). These findings suggest that acute, chronic, and latent infections may all contribute to the development of IIMs.

This narrative review will first focus on specific subgroups of IIMs (PM, DM, ASS, IMNM, IBM), followed by an exploration of recently discovered triggers of IIMs (graft-*versus*-host disease (GVHD), immune checkpoint inhibitors (ICIs) and SARS-CoV2 infection/vaccine). We deem these topics deserving of separate descriptions given their clinical significance.

Materials and methods

Keywords used for the Medline search were "myositis" OR "idiopathic inflammatory myopathies" AND "pathogenesis" OR "risk factors" OR "environment" OR "infections" OR "drugs" or "SARS-CoV2". Original studies, case reports and review articles published until February 22nd 2024 were considered. Papers on juvenile forms of the disease or in languages other than English were excluded.

Results

Dermatomyositis

The observation of seasonal trends in the onset of IIMs, particularly in certain clinical phenotypes, indicates a potential role for environmental factors such as infections or geoclimatic variables. Data from the United States regarding primary hospital admissions for DM indicated a significantly higher occurrence during spring and summer seasons (17). Moreover, muscular and cutaneous flares of DM were observed with a higher frequency in summer (18). In contrast, Nishina *et al*. noted a higher incidence of anti-melanoma differentiation-associated gene 5 (anti-MDA5) positive interstitial lung disease (ILD) cases between October and March (19).

Among different geoclimatic variables, the ultraviolet (UV) radiation intensity seems to be a primary determinant of DM development, as observed in both Chinese and North American populations (20, 21). This association was additionally supported by data coming from the MYOVISION registry (22). Moreover, a linear positive correlation was observed between irradiance and the synthesis of anti-Mi2 autoantibodies (20). In an *in vitro* study (23), both UV exposure and ionising radiations were linked to an upregulation of the Mi2 subunit of the nucleosome remodelling and deacetylase (NuRD) complex in keratinocytes, suggesting that UV light could increase antigen presentation following DNA damage. Interestingly, the association between UV exposure, anti-Mi2 antibodies production and DM onset seems more significant in women (22) and in Caucasians (21). Lastly, UV radiation has been shown to not only trigger the onset of DM but also exacerbate disease flares (24). These data are corroborated by the observation that sunburns often precede the onset of DM (22).

Geographical latitude could also be associated with DM onset. In particular, an increased incidence of DM was observed going from northern to southern countries; a similar trend was found for the positivity of anti-transcription intermediary factor 1-γ (anti-TIF1γ) autoantibodies (25). Accordingly, the distribution of HLA-DRB1*07:01 and HLA-DQB1*02 was negatively associated with latitude gradient (26). Nonetheless, this relationship could derive from the increasing intensity of UV radiation towards the equator (6).

A prolonged exposure to certain aerosolised inorganic dusts has also been associated with the development of systemic autoimmune diseases, including IIMs. The first report of a causal association between silica exposure and DM onset was published in 1995 (27). The association between exposure to dust during military service and the risk of autoimmune diseases was investigated by Ying *et al*. Among 438,086 Afghanistan and Iraq military veterans, 55 (0.01%) developed IIMs (28). Unfortunately, the paper does not specify the subtypes of IIMs that were observed. In a nested case-control study (29, 30), nearly 16,000 rescue and recovery workers exposed to World Trade Center dust were monitored over a 12-year period. The dust in question contained potentially harmful components, including a mixture of pulverised cement, glass fibres, silica, asbestos, lead, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, polychlorinated furans, and dioxins; 14% of patients who developed a systemic autoimmune disease were diagnosed with IIMs, including two cases of DM. Even the exposure to mold, birds or pillow feathers seemed to increase the risk of DM (31).

In support of the hypothesis of an infectious trigger in DM onset, Megremis *et al*. (32) found that patients with anti-TIF1γ autoantibodies had higher titres of antibodies against several viral families, including Coronaviridae, Poxviridae, Herpesviridae and Orthomyxoviridae. Ichimiya *et al*. (33) reported increased levels of antibodies against streptococcal recombinant M12 protein in DM patients. Furthermore, Martini *et al*. (34) discovered a homologous aminoacidic region shared between this protein and the myosin heavy chain of human skeletal muscle in JDM patients, indicating a plausible mechanism of molecular mimicry.

In 2008, Seidler *et al*. (35) conducted a review of case reports on drug-induced IIMs, revealing that more than half were associated with the use of hydroxyurea. Particularly noteworthy was its association with the onset of clinically amyopathic DM (CADM), with pathognomonic cutaneous lesions in just under 80% of cases. The majority of patients also had underlying pathologies, most frequently neoplasms. In most cases, clinical improvement was observed after discontinuation of the drug.

The intake of certain herbal-based weight loss supplements has been linked to the development of DM or CADM (36). Interestingly, the authors observed higher levels of proinflammatory cytokines such as TNFα, IFNα and IFNβ following stimulation of peripheral blood mononuclear cells with those herbal-based supplements.

Anti-synthetase syndrome

A seasonality has also been observed in the onset of ASS, which, in non-black patients, seemed more frequent during March and April (37). This finding was corroborated by Leff *et al*. (38), who observed muscle weakness started more frequently between February and July, with a peak in April for patients with anti-Jo1 antibodies. Even if more rarely than observed for DM, Scalabrini *et al*. found sunburns could also favour juvenile forms of ASS (39). Similarly to anti-TIF1γ, the incidence of anti-synthetase autoantibodies also showed a negative correlation with the latitude (25).

The identification of ASS as a separate entity is more recent than that of DM or PM, with which it may also share some clinical features; this, especially in older studies, could lead to an underestimation of ASS prevalence. Indeed, Yang *et al*. (40) described patients with IIM onset after an exposure to silica had a significant higher prevalence of mechanic's hands, Raynaud's phenomenon and ILD, all signs that typically tend to cluster in ASS.

In 2013, a study from Spain showed significantly higher exposure to biological or mineral dusts, gases or fumes in patients who developed ASS than other IIMs. Interestingly, when compared with the evolution of other forms of ASS, a more consistent improvement in FVC was registered after avoiding the

noxious agent (41, 42). Abrasive agents have also been described as triggering factors for pulmonary inflammation (43).

Additionally, cases of ASS developed after the exposure to mold or bird feathers were also described; in some instances, these patients were initially diagnosed with hypersensitivity pneumonitis, as positivity to anti-Jo1 antibodies was only later detected in the disease course (31, 44).

Moreover, a large North American population study of IIM patients (45) observed that Caucasian ever-smokers individuals exhibited a higher likelihood of having anti-Jo1 or other anti-synthetase autoantibodies. Tobacco smokers had a greater susceptibility to develop ILD compared to non-smokers, but this difference did not reach statistical significance. The duration of smoking exposure correlated with a 2% increase in the risk of ILD for each pack-year. The presence of the HLA-DRB1*03:01 allele in Caucasian ever-smokers amplified the risk of PM, ILD or ASS, while reduced the prevalence of anti-TIF1γ autoantibodies, suggesting a potential influence of genetic background on the tobacco-related risk of IIMs (45).

Taken together, these data underline a connection between airborne exposure and the onset of ASS, corroborating the hypothesis that autoimmunity in ASS may originate in the lungs and the respiratory tract.

The hypothesis that infections can trigger ASS is supported by a significant homology found between histidyl-tRNA synthetase (Jo1) and alanyl-tRNA synthetase (PL12) and proteins isolated from EBV, adenovirus or influenza virus, thus sharpening the concept of molecular mimicry (46).

Additionally, Quintero-Puerta and colleagues (47) observed a significant difference in lung microbiome composition between anti-Jo1 positive and negative ASS patients. Specifically, the genus Veillonella was found in lower abundance in patients with anti-Jo1 and the grade of abundance showed a positive correlation with an increase in lymphocytes and eosinophils count and a negative correlation with macrophages levels, thereby confirming the interplay between infectious agents and autoimmunity.

Three cases of ASS, two of which with anti-Jo1 positivity, were reported after IFNα therapy (48-50). A review of IIM cases developed after the use of anti-TNFα agents showed that most patients had an ASS phenotype; clinical symptoms generally improved after drug discontinuation (51).

Inclusion body myositis

IBM is an acquired, late-onset inflammatory myopathy, with both inflammatory and degenerative pathogenesis. Chronic viral infections linked to IBM encompass HIV, HTLV-1 and HCV.

HIV-positive individuals with myositis may initially exhibit early-onset at a young age, markedly elevated CK levels or proximal weakness that improves with treatment. However, over time, they may progress to develop an IBM-like myositis (52-54). Similarly, there exist multiple documented cases of HTLV- (55, 56) and HCV-associated IBM (14, 57, 58).

A proposed hypothesis suggests that the prolonged presence of viral infection perpetuates immune stimulation, leading to T-cell exhaustion.

The observation of cases of IBM after a long-term use of imatinib (59) is limited to a few case reports.

Immune-mediated necrotising myopathy

IMNM was identified as distinct from PM in the early 1990s. Three subtypes of IMNM are recognised (60): anti-signal recognition particle (anti-SRP) autoantibody positive IMNM (61); anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) autoantibody positive IMNM; anti-SRP/HMGCR negative IMNM.

The occurrence of anti-HMGCR myopathy shows a significant correlation with the presence of the class II major histocompatibility complex (MHC) allele DRB1*11:01 and with exposure to statin medications. This suggests that the condition arises when genetically predisposed individuals increase the expression of HMGCR, especially following statin exposure (62). However, the prevalence of statin exposure among patients with anti-HMGCR myopathy varies depending on the demographic composition of the cohort. Interestingly, statins are naturally present in certain foods and dietary supplements, including oyster mushrooms, red yeast rice, or Pu-erh tea. These alternative sources of statins are commonly consumed in Asian cuisine, suggesting that the relatively weaker association between anti-HMGCR myopathy and medical statin exposure in Asian cohorts may be attributed to increased exposure to these dietary sources of statins (62).

Viral infections are also believed to be a potential trigger for IMNM. This is supported by evidence pointing to a seasonal pattern in the development of anti-SRP myopathy, with a peak incidence noted in November (38), possibly linked to upper respiratory tract viral infections.

Polymyositis

With the better understanding of IMNM, IBM, overlap myositis and ASS, pure PM now appears to be less common than previously thought and remains a diagnosis of exclusion. The bulk of existing literature on environmental triggers of PM is outdated, which may lead to potential bias due to the inclusion of other types of IIMs in the studies.

As for other types of IIMs, many infectious agents have been proposed as initiating factors, including Coxsackie viruses, parvoviruses and enteroviruses, but data are controversial (63). HIV can trigger a PM-like myositis (15), often accompanied by IBM features, as discussed above. PM associated with HTLV-1 is infrequent and usually limited to endemic areas (16, 64, 65). The observation of PM cases after chickenpox and mumps infection (66) is limited to a few case reports. The North-Eastern United States exhibited a higher prevalence of myositis cases (67), coinciding with a region known for elevated Lyme disease incidence; however, the study lacked serological analysis. Further research is needed to ascertain whether there is an association or whether it is merely coincidence.

Six cases of PM, two of which anti-Jo1 positive, were also recorded among res-

cue and recovery workers exposed to World Trade Center dust (29).

Several cases of PM have also been observed in patients treated with interferon (50, 68-71), statins (72) and D-penicillamine (6). Additionally, there are over twenty case reports of PM occurring during anti-TNF therapy (51), mainly in patients diagnosed with rheumatoid arthritis. Improvement of IIM after anti-TNF discontinuation (with the concomitant use of other immunosuppressants) was reported in 94% of cases. Interestingly, in some instances, MSAs (anti-Jo1, anti-PL7, anti-PL12) or MAAs (anti-U1RNP) were already present before the initiation of anti-TNF therapy. It is plausible that these patients presented with incomplete forms of IIMs or MCTD, which might have been worsened or, at the very least, not effectively treated with anti-TNF therapy.

Graft-versus-host disease-associated myositis

GVHD is a severe complication of haematopoietic stem cell transplantation, wherein immunocompetent T lymphocytes from the graft attack the immunodeficient recipient's tissue, leading to damage, especially in the skin and internal organs. Although the occurrence of muscle and nervous tissue damage is rare, myositis has been reported in 0.06-0.54% of transplanted patients (73-75). This subtype of myositis shares similarities with PM, but histological analysis reveals a diffuse infiltration of macrophages (76, 77). Additionally, MSAs are usually negative (74, 75).

Immune checkpoint inhibitors-associated myositis

In recent years, it has come to light that ICIs can trigger a new variant of myositis in cancer patients, referred to as ICI-myositis (78). The pathogenesis of autoimmune adverse events in the context of ICIs treatment is still not completely understood. Whether immune-related adverse events could stem from a sudden and intense activation of pre-existing or newly induced autoimmunity is still debated.

According to a meta-analysis, ICI-myositis is rare, as occurred in 0.38% of treated patients and is more prevalent in patients treated with PD-1/PD-L1 inhibitors compared to anti-CTLA-4 agents (79). Muscle biopsies typically reveal the presence of T-cells and macrophages, with minimal infiltration of B-cells (80). Nearly half of the patients develop features typical of myasthenia gravis, such as diplopia and ptosis, and/or myocarditis (79, 81). Conversely, another 18% exhibit a skin rash resembling that observed in DM (79). In the presence of a pre-existing cancer diagnosis, it may be challenging to distinguish between true ICI-induced myositis and IIM associated with malignancy: the presence of MSAs and/or MAAs supports IIM diagnosis instead of ICI-myositis (82).

In a recent multicentric study (83), unsupervised clustering identified three distinct transcriptomic subsets within ICI-myositis: ICI-DM, ICI-MYO1 and ICI-MYO2. ICI-DM encompassed patients with DM and anti-TIF1γ autoantibodies, who, similarly to DM patients, exhibited overexpression of type I interferon-inducible genes. ICI-MYO1 patients displayed highly inflammatory muscle biopsies and included all patients who developed co-existing myocarditis and ocular symptoms. The serum of some patients in this group tested positive for anti-acetylcholine receptor (anti-AChR) or anti-striated muscle antibodies. ICI-MYO2 consisted of patients with predominant necrotising pathology and low levels of muscle inflammation. Activation of the type II interferon pathway was observed in both ICI-DM and ICI-MYO1 subsets. Unlike other types of myositis, all three subgroups of ICI-myositis patients exhibited overexpression of genes associated with the IL-6 pathway.

One of the most important causes of death in ICI-myositis is respiratory failure, but the underlying pathogenetic process is not entirely clear: autopsy cases seem to suggest that active myositis of the diaphragm driven by cytotoxic T lymphocytes results in life-threatening respiratory failure (84).

COVID-19 and myositis

There is an amount of data supporting a liaison between COVID-19 and IIMs. An increased prevalence of MSAs and/or MAAs after SARS-CoV2 infection or vaccination was observed by different authors (85). Accordingly, a higher frequence of IIMs diagnosis has been registered since the COVID-19 era and IIM flares have also been described (86). Moreover, IIMs-ILD may strictly resemble COVID-19 pneumonia and organ damage is strongly associated with endothelial dysfunction and vasculopathy in both conditions (87). Finally, immunosuppressive therapies such as baricitinib have proven to be effective in the treatment of both pulmonary conditions (88).

A possible explanation for this fascinating link could rely upon the fact that some of the most typical MSAs and MAAs, particularly anti-MDA5, anti-synthetase and anti-Ro52, are directed against antigens that could be involved in viral replication, viral proteins synthesis or host defence against viruses, resulting in the activation of type I interferon and NF-κB pathways, that are known to be involved in the pathogenesis of IIMs. Reasonably, some other complex interplays are needed to obtain the overt clinical picture of an inflammatory myositis, possibly related to the genetic background (89).

Data from a systematic review did not

Table I. Conclusions and clinical practice points.

- IIMs with ILD could derive from an immune response against environmental factors primarily affecting the lungs.
- Patients should avoid modifiable environmental risk factors (such aas smoking or sun exposure).
- Patients should be sensitised about a possible clinical worsening of IIM after infections or sun exposure, to allow an earlier identification and an earlier treatment of eventual disease flares.
- Further studies are needed to better explain the interrelation between infections (COVID-19 in particular) and IIMs.
- Rheumatologists should share their clinical decisions with patients, to optimise their adherence to both pharmacological and behavioural therapies.

confirm a causal link between SARS-CoV2 infection and IIMs, however temporal associations have been reported and there are potential pathogenetic similarities between these two conditions that deserve further exploration (90).

A stimulating perspective for rheumatologists could be to follow-up patients who have developed MSAs or MAAs after SARS-CoV2 infection or vaccination, to clarify how antibody titres might vary, to identify which factors might trigger the onset of IIMs, and to determine which subjects might be more predisposed to develop these diseases.

Conclusion

The rarity and clinical heterogeneity of IIMs poses challenges in establishing robust evidence on the key environmental factors involved in their pathogenesis. Nevertheless, as outlined in Table I, the data presented in this review may offer insights into certain concepts that could prove valuable in clinical practice. To fill the lack of knowledge about this issue, longitudinal multicentric studies, together with basic science investigations, should be planned to elucidate the interplay between genetics and environment in fostering these complex autoimmune diseases.

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