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Seasonal patterns of myositis-specific and myositis-associated autoantibodies in Italy
Seasonal patterns of myositis autoantibodies

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ABSTRACT

Objective: Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of systemic autoimmune disorders affecting skeletal muscles but also other organs. There are different forms of IIM, each with peculiar clinical manifestations and prognosis. Accordingly, several autoantibodies have been described in IIM, with different prevalence in the different forms of the disease. The etiopathogenesis of IIM is still unclear, although environmental agents play certainly a role to trigger disease development in genetically predisposed individuals. Supporting this notion, some reports suggest that the incidence of IIM may be different throughout the year. In this work, we tested if the detection of autoantibodies typically observed in IIM has a seasonal pattern.

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Methods: We collected serological data from line immunoassays (LIA) performed on 4277 patients with suspected IIM from January 2018 to December 2020 in ten Italian hospitals. Myositis-specific and myositis-associated autoantibodies were evaluated by line-immunoassay.
Results: Our findings demonstrate that absolute numbers of anti-MDA5, anti-PM-Scl75, anti-Mi2b and anti-TIF1γ autoantibodies are more frequently detected in autumn-winter than in spring-summer. However, only anti-PM-Scl75 and anti-MDA5 display a similar pattern when analyzing frequencies of positive tests (for anti-PM-Scl75 100 positive tests and 2107 negative tests from September to February; 55 positive tests and 1903 negative tests from March to August, $p = 0.003$; for anti-MDA5 34 positive tests and 1983 negative tests from September to February; 17 positive tests and 1760 negative tests from March to August, $p = 0.051$).
Conclusions: These findings suggests that triggering agents promoting the development of these autoantibodies have a specific seasonal pattern.

Significance and innovation

- Among all MSA and MAA, anti-MDA5 and anti-PM-Scl75 autoantibodies are detected more frequently in autumn-winter than in spring-summer.

- Environmental agents promoting the development of these autoantibodies may have a seasonal pattern.

1. Introduction

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of systemic autoimmune diseases characterized by immune-mediated damage of skeletal muscles, but other organs can also be affected. Based on clinical features and histopathology, IIM are divided in four main subgroups: dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM) and immune necrotizing myositis (IMNM) [1]. In agreement with the heterogeneous nature of IIM, different myositis-specific autoantibodies (MSA) and myositis-associated autoantibodies (MAA) correlating with different disease subsets have been described. The identification of MSA/MAA is a rapidly evolving field. Indeed, after the identification of anti-Mi2 and anti-Jo1 antibodies in the early 1980s, a variety of MSAs has been identified. Anti-signal recognition particle (SRP) and anti-3-hydroxy-3-methylglutaryl CoA reductase (HMGCR) antibodies are specific to IMNM. Anti-Mi2, anti-transcription intermediary factor 1γ (TIF1-γ), anti-nuclear matrix protein 2 (NXP2), anti-melanoma differentiation-associated gene 5 (MDA5), anti-small ubiquitin-like modifier activating enzyme (SAE) antibodies are specific to DM [2,3]. Anti-aminoacyl-tRNA synthetase (ARS) antibodies, including anti-Jo1, are recognized as markers for anti-synthetase syndrome (ASS), characterized by myositis, interstitial lung disease (ILD), arthritis, Raynaud's phenomenon, fever, and mechanic's hands [4]. Further complicating this scenario, IIM can also occur in the context of other autoimmune manifestations, the so-called overlap syndrome. Anti-PM-Scl, anti-Ku, anti-U_1 ribonucleoprotein (RNP), anti-Ro52 and anti-RuvBL1/2 antibodies are frequently associated to IIM. MAA are not specifically detected in IIM patients but can routinely be observed, especially in the context of overlapping syndromes. Additionally, in the last years, several studies provided models for an improved clinical assessment of IIM progression [5,6].

Understanding the etiology and pathogenesis of IIM is certainly hindered by the heterogeneous nature of these diseases. However, the classification based on autoantibodies can allow the recruitment of more homogeneous groups of patients from an etiopathogenetic point of view, thus allowing to identify genetic and environmental risk factors. Indeed, exposure to triggering environmental factors in genetically predisposed individuals is the most likely pathogenetic mechanism. Among the identified environmental factors are infections, drugs, and ultraviolet light (UV) rays [7]. Case reports and population studies have identified associations between these environmental factors and the onset of specific myopathies. The association with sun exposure is known for DM. The geographical distribution of DM cases associated with anti-Mi2 antibodies, an enzyme involved in DNA repair from UV radiation damage, has a North-South gradient [8].

Geographical distribution may also reflect the presence of environmental risk factors such as the presence of viruses. For example, in Japan, an aggregation of DM cases with anti-MDA5 antibodies has been described in areas adjacent to the KisoRiver, which has been hypothesized to be associated with a higher incidence of coxsackievirus B infections [9]. The association with viral infections has been proposed also to justify the seasonal pattern observed for IIM, that has been observed in many cohorts [10,11,12].

In this work, we evaluated the seasonality of MSA and MAA in Italy to understand if their incidence, and of the related diseases, displays differences in the different parts of the year, further supporting the role of environmental agents with a specific seasonal pattern.

2. Materials and methods

To assess if the incidence of MSA and MAA displays a seasonal pattern, we analyzed the serological data obtained from 4277 patients from January 2018 to December 2020 in ten Italian hospitals (Table 1). Patients were referred to diagnostic centers because of a suspected underlying IIM.

Peripheral blood samples were collected in tubes without anticoagulant and then centrifuged to obtain sera. Sera were maintained at 4 °C and tested within 3 days from collection. In all recruiting centers, detection of MSA and MAA was performed by using one of two commercially available line immunoassays (LIA) from Euroimmun (Lübeck, Germany): Euroline myositis antigen Profile 3 (Mi-2β, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro-52), Autoimmune

Table 1
Characterization of the study cohort by recruiting center and type of LIA used.

Recruiting Center	Number of recruited patients	Kit
Bergamo	428	Euroline myositis antigen Profile 3 (11 Ag)
Bologna	356	Autoimmune inflammatory myopathies 16 Ag
Brescia	193	Autoimmune inflammatory myopathies 16 Ag
Florence Careggi Hospital	996	Autoimmune inflammatory myopathies 16 Ag
Florence San Giovanni di Dio Hospital	1125	Autoimmune inflammatory myopathies 16 Ag
Ferrara	130	Autoimmune inflammatory myopathies 16 Ag
Genoa	458	Autoimmune inflammatory myopathies 16 Ag
Potenza	62	Autoimmune inflammatory myopathies 16 Ag
Siena	363	Autoimmune inflammatory myopathies 16 Ag
Trento	166	Euroline myositis antigen Profile 3 (11 Ag)

inflammatory myopathies 16 Ag (Mi-2α, Mi-2β, TIF1γ, MDA5, NXP2, SAE1, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro-52) (Supplementary Table 1). LIA were prepared and scanned with an automated system (EUROBlotOne, Euroimmun). Cut-off positivity was defined according to manufacturer's instructions.

Statistics was performed using Rayleigh test (for circular data) or with Chi-squared test (for frequencies). In both cases, a p value <0.05 was considered significant. Circular mean was calculated with the *circ_mean* function from pingouin package in Python.

Ethics committee approval was not required as the study was retrospective and utilized anonymized data.

3. Results

Overall, MAA (anti-Ro52, anti-Ku, anti-PM-Scl75 and anti-PM-Scl100) displayed higher absolute numbers (Fig. 1; Supplementary Figure 1) and frequencies (Fig. 2; Supplementary Figure 2) throughout the year, compared to MSA. Among MAA, anti-PM-Scl75 was prevalently detected in the fall-winter period, from September to February, with a circular mean in December (Fig. 1, $p = 0.002$). To test if this observation might have been influenced by variations in the total number of tests performed within the different months of the year, we calculated the ratios of positive/negative tests in the different seasons. This approach confirmed that anti-PM-Scl75 autoantibodies are detected more frequently in fall-winter than spring-summer (100 positive tests and 2107 negative tests from September to February; 55 positive tests and 1903 negative tests from March to August, $p = 0.003$) (Fig. 2). On the contrary, anti-Ro52, anti-Ku and anti-PM-Scl100 did not show a prevalence in a specific season (Supplementary Figures 1 and 2).

Then, we focused our analysis on MSA, namely: anti-EJ, anti-OJ, anti-PL7, anti-PL12, anti-Jo1, anti-MDA5, anti-Mi2a, anti-Mi2b, anti-NXP2, anti-SAE1, anti-SRP and anti-TIF1-γ. Among these, we found that the incidence of anti-MDA5 antibodies was significantly higher in the fall-winter period, with a circular mean in November ($p = 0.006$), while the circular mean of anti-Mi2b antibodies was observed in September ($p = 0.024$) (Fig. 1). Anti-TIF1-γ were instead mainly detected between September and December (circular mean in October, $p = 0.027$) (Fig. 1). When evaluating frequencies, anti-MDA5 autoantibodies confirmed their higher prevalence in the fall-winter period than spring-summer (34 positive tests and 1983 negative tests from September to February; 17 positive tests and 1760 negative tests from March to August, $p = 0.051$) (Fig. 2). Notably, the higher number of positive tests for anti-MDA5 autoantibodies in the fall-winter period was repeatedly observed in all the three years analyzed (2018–2020, Fig. 1). On the contrary, anti-TIF1-γ and anti-Mi2b did not show statistically significant differences when studying frequencies (78 positive tests and 1938 negative tests from September to February; 55 positive tests and 1721 negative tests from March to August for anti-TIF1-γ; 89 positive tests and 1846 negative tests from November to April; 61 positive tests and 1687 negative tests from May to October for anti-Mi2b; $p = 0.1$ and $p = 0.08$, respectively) (Fig. 2).

4. Discussion

IIM represent a heterogeneous group of inflammatory diseases mainly affecting skeletal muscles. Different forms of IIM have been described, with distinct clinical and histopathological features. In the last years, the discovery of MAA and MSA has contributed to the definition of clinical-serological groups, allowing a more homogeneous clustering of patients. However, despite this advancement, the current classification criteria of IIM do not consider the multitude of autoantibodies described in the context of IIM, focusing only on anti-Jo1. The occurrence of different types of autoantibodies in different forms of IIM can be the result of distinct pathogenic mechanisms sustaining disease development and progression. Indeed, the pathogenesis of the different forms of IIM is still far from being understood. As in all rheumatic diseases, also in the context of IIM it is currently believed that environmental agents can trigger disease development when acting on genetically predisposed subjects. Genetic risk factors have been detected both in HLA- and non-HLA-loci [7]. Regarding environmental agents, several studies have investigated associations with several factors including infections, foods and chemicals [7]. Some reports have also suggested that the incidence of distinct groups of IIM can exhibit a seasonal pattern, further supporting the role of environmental agents in disease development [12,13]. This finding has been demonstrated for anti-synthetase autoantibodies, exhibiting a peak in March-April in a study performed on patients from the US and Germany [14]. However, data on seasonal pattern of IIM are still controversial, depending also on the ethnical and geographical distribution of the analyzed populations.

Our study was prompted by the anecdotal observation of the onset of several anti-MDA5+ dermatomyositis during the autumn-winter. To formally test this hypothesis, we pooled the laboratory data from a large number of laboratories and extended to the full MSA/MAA panel, in order to possibly identify previously undetected patterns. For these reasons, in the current study we decided to evaluate the seasonal prevalence of MSA and MAA in an Italian cohort of patients.

The analysis confirmed that anti-MDA5 displayed the strongest seasonal pattern, with an accumulation in the fall-winter period. This finding was observed when analyzing absolute numbers, and just missed statistical significance when analyzing frequencies. Given the rarity of anti-MDA5 positive patients, our observation should be confirmed by larger studies. However, our findings are in agreement with previous data obtained in two Japanese studies, showing an increased incidence of anti-MDA5 autoantibodies in autumn and winter [9,15]. Accordingly, a Chinese study demonstrated among anti-MDA5 patients, symptoms onset was less common in summer [16]. A French study further proved that anti-MDA5 DM is less common in summer and is correlated with respiratory viral infections [17]. In this context, it is worth mentioning

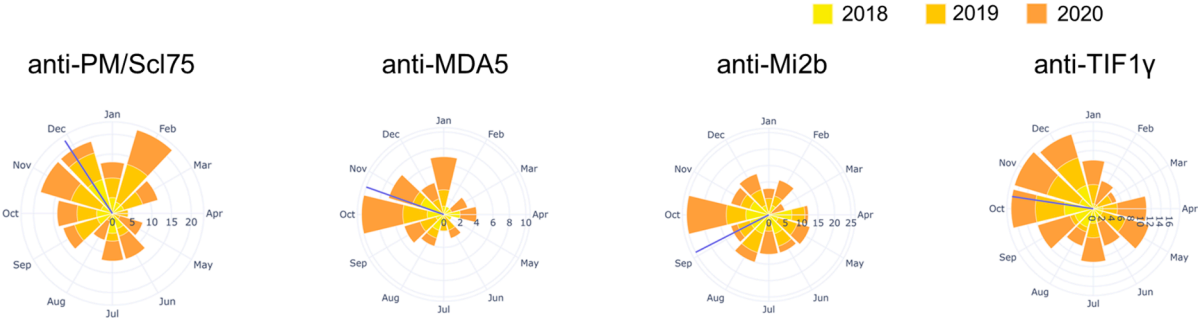

Fig. 1. Radar plot of positive LIA tests for each MSA and MAA in the different months of the year. Data are reported as absolute numbers of positive tests, colored by year (2018 yellow, 2019 dark yellow, 2020 orange). The blue line represents the circular mean. Statistics was calculated with Rayleigh's test. $P < 0.05$ was considered significant.

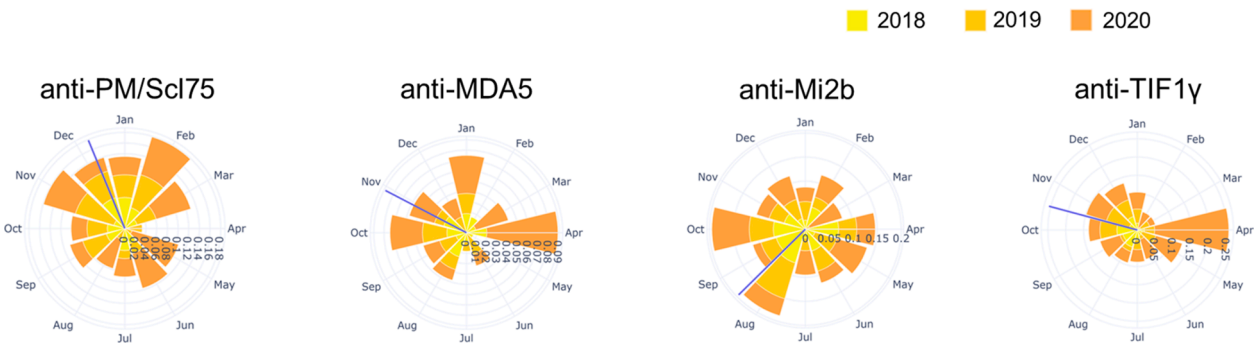

Fig. 2. Radar plot of the frequency of positive LIA tests for each MSA and MAA in the different months of the year. Data are reported as ratios, calculated between positive and total tests performed, and colored by year (2018 yellow, 2019 dark yellow, 2020 orange). The blue line represents the circular mean. Statistics was calculated with Chi-squared test. $P < 0.05$ was considered significant.

that MDA5 is a cytosolic viral RNA sensor, that induces innate responses and cytokine production. It has been suggested that RNA viral infections can induce MDA5 expression and its release upon virus-mediated cell lysis, followed by autoantibody production [18]. Therefore, anti-MDA5 autoantibodies can either be bystander products or display also pathogenic properties, as suggested by the direct correlation between their serum concentration and disease activity [19]. Our finding that anti-MDA5 autoantibodies are mainly detected in the fall-winter period may support the role for viral infections in this autoimmune process, as viral circulation in the general population is sustained in these seasons.

Among MAA, we found that anti-PM-Scl75 autoantibodies have a higher prevalence in the fall-winter period. Anti-PM-Scl75 autoantibodies are directed against the 75 kDa fraction of the PM/Scl macromolecular complex [20]. Initial data identified the 100 kDa subunit as the main target of autoantibodies. However, more recently it has been demonstrated that also the 75 KDa fraction can be targeted [20]. There is still paucity of data about clinical implications of anti-PM-Scl75 autoantibodies. The finding that their detection occurs mainly in the fall-winter period can suggest that triggering environmental agents are mainly present in these seasons, though confirmatory studies need to be performed. It should be acknowledged that concerns have been raised regarding the specificity of the line blot used in our study for anti-PM-Scl75 autoantibodies [21,22]. In agreement, some reports suggest that patients should only be regarded as positive if they test positive for both the PMScl100 and the PMScl75 subunits [21,22]. We did not find any specific seasonal pattern for samples positive for both anti-PM-Scl75 and anti-PM-Scl100 antibodies (data not shown). However, our study was not aimed and powered to evaluate assay performances.

Our data provide some novel hints that also anti-Mi2b and anti-TIF1-γ autoantibodies can display a seasonal pattern. Anti-Mi2b antibodies show a peak in September, at the end of summer in Italy. An association between UV and DM with anti-Mi2 autoantibodies has already been described. Several studies have demonstrated a higher incidence of the disease in populations with increased exposure to solar radiation [8,23,24]. Mi2 is a component of the Mi2/NuRD complex, involved in the maintenance of chromatin structure for cell cycle progression [25] and it can be rapidly upregulated in keratinocytes following UV exposure [26]. The finding that anti-Mi2b autoantibodies preferentially develop at the end of summer in a country like Italy with a high solar exposure in summer can further support this hypothesis. Our data show that anti-TIF1-γ autoantibodies instead peak in October. There are currently no other reports showing a seasonality for the incidence of this type of autoantibodies, but it has been shown a latitudinal gradient, with lower incidence far from the Equator [27].

Our study has some limitations. The time between the onset of symptoms and the execution of the test is unknown since the clinical manifestations of IIM can be acute or chronic. For acute onset we can assume that the patients refer to the clinician as soon as possible. However, for chronic disease diagnostic delay is probably too heterogeneous.

Additionally, we did not have access to final diagnosis, which precludes definite conclusions about the real seasonal incidence of IIMs.

Regarding our methodological approach, it should be stated that to date, immunoprecipitation is considered the reference method to identify MSAs and MAAs. However, it is an impractical method for widespread diagnostic use, as it is relatively expensive, has a low throughput and requires specialized facilities along with staff expertise. As a result, the availability of immunoprecipitation for diagnostic purposes is limited to a handful of specialized centers worldwide and commercially available immunoblots offer the rapid detection of MSAs and MAAs at low cost and without the need for specialists. Although LIAs are widely used in routine diagnostics, some concerns have been raised regarding the sensitivity and specificity of these tests, particularly with regard to certain MSA specificities, and false positive rates may also be unacceptably high [28]. This observation does not apply to anti-MDA5 detection, that displays overall good performances [29].

Finally, it should be mentioned that patients were enrolled for this study between 2018 and 2020. This period was characterized by the emergence of COVID-19 pandemic, which has been associated to increased development of autoimmune phenomena, including anti-MDA5 autoimmunity [30,31]. In our cohort, we did not find differences in autoantibody frequencies before and after COVID-19 emergence. However, it should be considered that the strict implementation of health and social measures significantly restricted SARS-CoV-2 circulation in 2020 in Italy, while maximal diffusion in the population was observed in later years with novel viral variants. Accordingly, also in the study by David and colleagues the maximal increase in anti-MDA5 positive tests during the COVID-19 pandemic was observed in 2021 [31].

In conclusion, we demonstrate here in an Italian cohort that some MAA and MSA have a specific seasonal pattern, which further may suggest the importance of environmental factors in the breakage of immune tolerance.

CRediT authorship contribution statement

Boaz Palterer: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Alessio Mazzoni:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Maria Infantino:** Writing – review & editing, Methodology, Conceptualization. **Roberto Semeraro:** Writing – review & editing, Methodology, Data curation. **Mariangela Manfredi:** Writing – review & editing, Methodology, Data curation. **Giampaola Pesce:** Writing – review & editing, Methodology, Data curation. **Brunetta Porcelli:** Writing – review & editing, Methodology, Data curation. **Lucia Terzuoli:** Writing – review & editing, Methodology, Data curation. **Gaia Deleonardi:** Writing – review & editing, Methodology, Data curation.

Giulia Previtali: Writing – review & editing, Methodology, Data curation. **Maria Grazia Alessio:** Writing – review & editing, Methodology, Data curation. **Emirena Garrafa:** Writing – review & editing, Methodology, Data curation. **Sara Ghisellini:** Writing – review & editing, Methodology, Data curation. **Michela Boni:** Writing – review & editing, Methodology, Data curation. **Pierluigi Anzivino:** Writing – review & editing, Methodology, Data curation. **Teresa Carbone:** Writing – review & editing, Methodology, Data curation. **Maria Cristina Sacchi:** Writing – review & editing, Methodology, Data curation. **Maria Concetta Sorrentino:** Writing – review & editing, Methodology, Data curation. **Ignazio Brusca:** Writing – review & editing, Methodology, Data curation. **Nunzia Rita Tarricone:** Writing – review & editing, Methodology, Data curation. **Anna Ghirardello:** Writing – review & editing, Methodology, Data curation. **Francesco Annunziato:** Writing – review & editing, Methodology, Data curation. **Paola Parronchi:** Writing – review & editing, Methodology, Data curation. **Nicola Bizzaro:** Writing – review & editing, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare no competing interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imlet.2024.106966.

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