Cancer-associated myositis before and after the COVID-19 pandemic onset: a changing trend

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Abstract

Objective

During the COVID-19 pandemic, there was a significant impact on the management of non-COVID-19 related diseases, potentially increasing the incidence of paraneoplastic syndromes such as cancer-associated myositis (CAM).The aim of this study is to determine the incidence of CAM in our cohort before and after the COVID-19 pandemic onset.

Methods

We included patients with idiopathic inflammatory myopathy (IIM), diagnosed between June 2016 and June 2023. The patients were divided into two groups according to the date of IIM diagnosis.

Results

We included 132 patients; 65.1% (n=86) were diagnosed prior to and 34.9% (n=46) after the COVID-19 pandemic. The most common IIM was dermatomyositis (DM) before and after the COVID-19 pandemic onset (p=0.750). The most frequent myositis-specific antibody (MSA) before the COVID-19 pandemic was anti-Mi2 (15.1%). After the COVID-19 pandemic onset, anti-TIF1γ was the most common MSA (21.7%), with a significantly higher relative prevalence (p=0.006). The incidence of CAM was significantly higher after the COVID-19 pandemic onset (11 vs. 3 new cases, p<0.002). Patients with CAM more frequently had anti-TIF1γ-positivity (p<0.001) and a diagnosis after the pandemic (p=0.001) than non-CAM-IIM patients. No significant differences were found regarding vaccination status or previous COVID-19 infection in CAM and non-CAM-IIM patients. Diagnosis after the COVID-19 pandemic was an independent predictor of CAM among IIM patients (OR 0.012, 95% CI 0.000–0.400, p=0.013), regardless of age, sex or previous COVID-19 infection.

Conclusion.

There was a significant increase in the incidence of CAM after the COVID-19 pandemic. IIM diagnosis after the COVID-19 pandemic was an independent predictor of CAM.

Key words

cancer, COVID-19 pandemic, inflammatory idiopathic myopathies

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Introduction

Cancer-associated myositis (CAM) occurs in up to 13.0% of patients with IIM. Older age, male sex, antibodies against transcription intermediary factor 1-γ (anti-TIF1γ), nuclear matrix protein NXP2 (anti-NXP2) (1, 2) and immune-mediated necrotising myopathies, either seronegative or HMG-CoA-positive (3, 4) are associated with an increased risk of malignancy.

The COVID-19 pandemic has significantly impacted the management of non-COVID-19-related diseases. The delay in cancer diagnosis potentially increased the incidence of paraneoplastic conditions (5, 6), such as CAM.

With this work, we aimed to determine the CAM incidence in our cohort before and after the onset of the COVID-19 pandemic.

Methods

We included adult IIM patients according to the European Alliance of Associations for Rheumatology (EULAR)/ American College of Rheumatology (ACR) 2017 classification criteria, diagnosed between June 2016 and June 2023. The patients were divided according to the date of IIM diagnosis, before (June 2016 to December 2019) and after the COVID-19 pandemic (January 2020 to June 2023) onset. CAM was defined as the occurrence of neoplasia within three years (before or after) of the IIM diagnosis (7). Data regarding the occurrence and timing of CAM, COVID-19 infection and vaccination were retrieved from the Rheumatic Diseases Portuguese Registry (Reuma.pt) (8). No data on anti-SARS-CoV-2 antibody response after vaccination was available, as our centre followed the health policy guidance in our country regarding this procedure.

Differences between groups were assessed using chi-square, Fisher's exact, or Mann-Whitney tests. We considered likely associations when $p<0.100$ and definite associations when $p<0.050$. Binomial logistic regression was used to find independent predictors of CAM. Moderate collinearity was considered for variation inflation factors (VIF) between 1 and 5, and strong collinearity for VIF higher than 5. Whenever moderate or strong collinearity was identified between explanatory variables, one of the collinear variables was excluded from the multivariate model. SPSS version 26 was used for statistical analysis.

Results

Demographic data

One hundred thirty-two patients were included, mostly females (n=97, 73.5%), with a median age of 50.0 years (IQR 26.8) at the time of the IIM diagnosis. Most patients were diagnosed before the pandemic onset (n=86, 65.1% *vs*. n=46, 34.9%).

Demographic and clinical characteristics before and after the COVID-19 pandemic onset

Age (median 50.0 (IQR 23.0) *vs*. 50.0 (IQR 30.5) years; $p=0.124$) and sex (n=67, 77.9% *vs*. n=30, 65.2% females; $p=0.116$) were not significantly different between groups.

The most common IIM subtype was DM, before and after COVID-19 pandemic (n=38, 44.2% *vs*. n=19, 41,3%, $p=0.750$), followed by anti-synthetase syndrome (n=16, 18.6% *vs*. n=8, 17.4%, $p=0.863$), polymyositis (n=14, 16.3% *vs*. n=6, 13.0%, $p=0.621$), overlap syndrome (n=10, 11.6% *vs*. n=6, 13.0%, $p=0.812$), mixed connective tissue disease (n=7, 8.1% *vs*. n=4, 8.7%, $p=0.912$) and immune-mediated necrotising myopathy (n=1, 1.2% *vs*. n=3, 6.5%, $p=0.087$).

The manual muscle testing (MMT, 76±6 *vs*. 75±9, $p=0.330$), and the modified skin disease activity score (DAS skin, 0.9±1.4 *vs*. 1.0±1.4, $p=0.321$) at disease presentation, were not statistically different between groups. Organ involvement, such as skin (n=55, 63.9%, *vs*. n=28, 60.7%, $p=0.827$), lung (n=30, 34.9%, *vs*. n=11, 23.9%, $p=0.266$), heart (n=5, 5.8%, *vs*. n=1, 2.2%, $p=0.382$), and joint (n=34, 39.5%, *vs*. n=14, 30.4%, $p=0.466$), were also similar.

Autoantibodies before and after the COVID-19 pandemic onset

The most common MSA before the pandemic was anti-Mi2, and there was a likely decrease in its prevalence

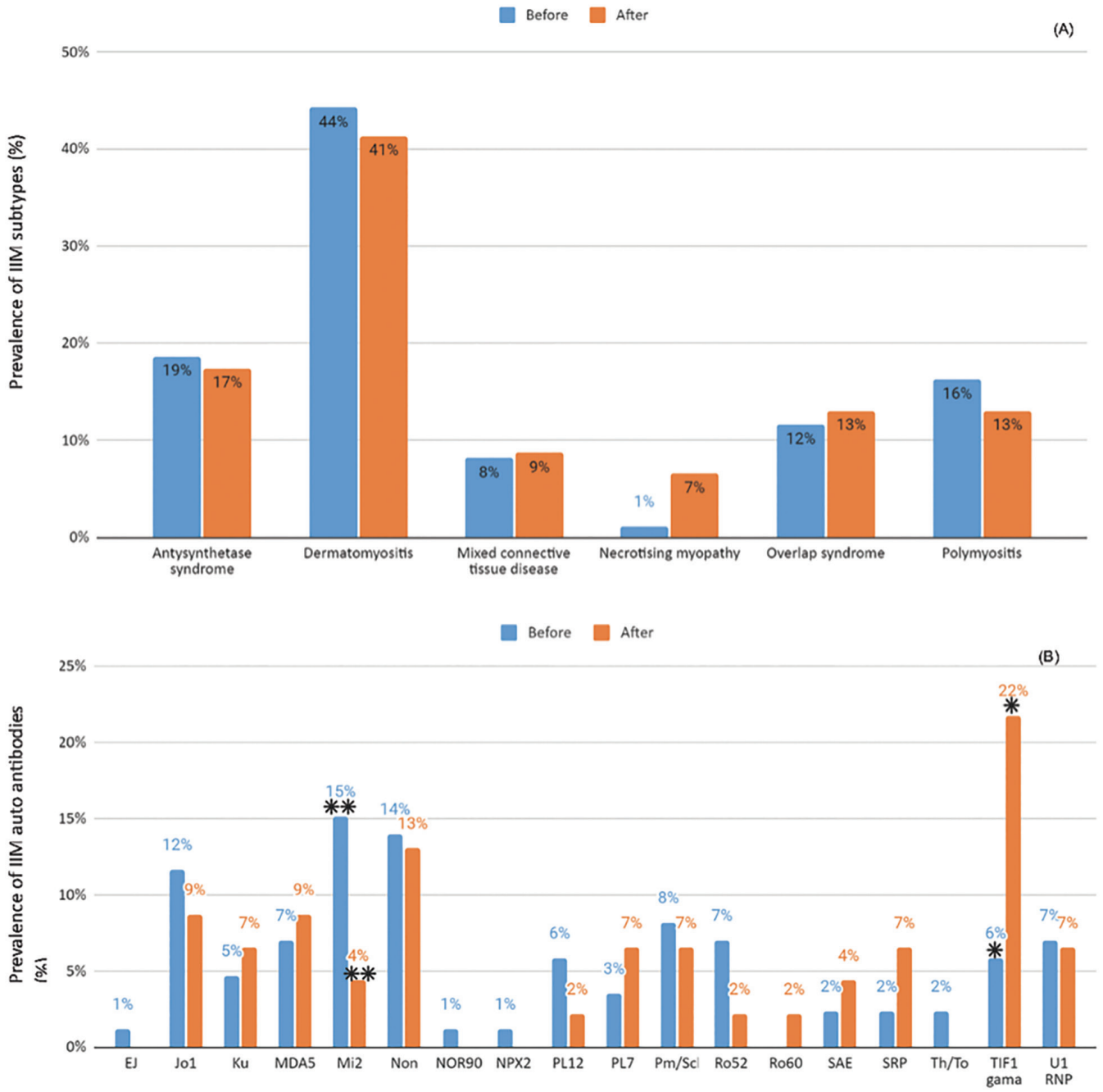

Fig. 1. Prevalence of IIM subtypes (**A**) and autoantibodies (**B**) before and after COVID-19 pandemic onset. Asterisks mark the variables with a likely (*) or definite (**) difference in prevalence before and after COVID-19 pandemic onset.

(n=13, 15.1% *vs*. n=2, 4.3%, *p*=0.063) after the COVID-19 pandemic. After the COVID-19 pandemic onset, anti-TIF1γ became the most common MSA, with a definite increase in its prevalence (n=5, 5.8% *vs*. n=10, 21.7%, *p*=0.006) compared to the pre-pandemic period. The second most common autoantibody before and after the pandemic was anti-histidyl tRNA synthetase (anti-Jo1, n=10, 11.6% *vs*. n=4, 8.7%, *p*=0.602), followed by anti-Pm/Scl (n=7, 8.1 % *vs*. n=3, 6.5%, *p*=0.738), anti-melanoma differentiation-associated gene 5 (anti-MDA5, n=6, 7.0% *vs*. n=4, 8.7%, *p*=0.722), anti-Ro52 (n=6, 7.0% *vs*. n=1, 2.2%, *p*=0.241), anti-U1 ribonucleoprotein RNP (anti-U1RNP, n=6, 7.0% *vs*. n=3, 6.5% *p*=0.921), anti-alanyl-tRNA synthetase (anti-PL12, n=5, 5.8% *vs*. n=1, 2.2%, *p*=0.339), anti-Ku DNA-binding protein (anti-Ku, n=4, 4.7% *vs*. n=3, 6.5%, *p*=0.648), anti-threonyl-tRNA synthetase (anti-PL7, n=3, 3.5% *vs*. n=3, 6.5, *p*=0.425), anti-small ubiquitin-like modifier-1 activating enzyme (anti-SAE, n=2, 2.3% *vs*. n=2, 4.3%, *p*=0.518), anti-signal recognition particle (anti-SRP, n=2, 2.3% *vs*. n=3, 6%, *p*=0.229), antiaminoacyl tRNA synthetase antibody (anti-EJ, n=1, 1.2% vs n=0, 0%, *p*=0.463), anti-NPX2 (n=1, 1.2% *vs*. n=0, 0%, *p*=0.463), anti-Ro60 (n=0, 0% *vs*. n=1, 2.2%, *p*=0.170), anti-Th/To (n=2, 2.3% *vs*. n=0, 0%, *p*=0.297) and anti-nucleo-

Table I. Neoplasia and IIM characterisation before and after the onset of the COVID-19 pandemic.

IIM date of diagnosis	Sex	Age	IIM	Neoplasia date of diagnosis	Neoplasia	MSA
June 2016 – December 2019	F	57	Polymyositis	2017	Ovary	-
	F	87	DM	2019	Colon	TIF1γ
	F	50	DM	2021	Breast	TIF1γ
January 2020 – June 2023	F	67	DM	2022	Lung	TIF1γ
	F	37	DM	2020	Breast	PL7
	F	45	DM	2019	Haematological	SAE
	F	81	Polymyositis	2021	Colon	Mi2
	M	88	Necrotising myopathy	2021	Colon	-
	M	76	DM	2023	Lung	TIF1γ
	M	60	DM	2023	Gastrointestinal – non-specified	TIF1γ
	F	50	DM	2023	Breast	TIF1γ
	F	69	Polymyositis	2021	Thymus	-
	F	50	DM	2023	Breast	TIF1γ
	M	67	Polymyositis	2020	Prostate	-

DM: dermatomyositis; IIM: inflammatory idiopathic myopathy; MSA: myositis-specific autoantibodies; PL7: anti- threonyl tRNA synthetase; SAE: anti-small ubiquitin-like modifier-1 activating enzyme; TIF1γ: anti-transcription intermediary factor 1-γ.

lus-organising region 90 (anti-NOR90, n=1, 1.2% *vs*. n=0, 0%, *p*=0.463), (the last two presented in patients with overlap syndromes with myositis) (Fig. 1).

Cancer-associated myositis

Fourteen patients, 50% females, with a mean age of 57.0±15.6 years at the time of the IIM diagnosis, had CAM. Cancer was diagnosed within 5.0±7.5 months of the diagnosis of IIM. Gastrointestinal and breast cancer (with no BRCA1 or BRCA2 mutations) were the most frequent followed by lung, prostate, thymus and haematological cancers (Table I).

The most common IIM subtype was DM (n=9, 64.3%), followed by polymyositis (n=4, 28.6%). The most common MSA was anti-TIF1γ (n=7, 50.0%). CAM patients more frequently had anti-TIF1γ antibodies (n=7, 50.0% *vs*. n=8, 6.9%, *p*<0.001) than non-CAM IIM patients. There was no significant variation in anti-TIF1γ prevalence among CAM patients before and after COVID-19 (n=2, 66.7% *vs*. n=5, 45.5%, *p*=0.838).

Impact of the pandemic in the prevalence of cancer-associated myositis

There was a significantly higher proportion of CAM after the COVID-19 pandemic onset (n=11, 23.9% *vs*. n=3, 3.5% *p*<0.002). The proportion of patients with anti-SARS-CoV2 vaccination (n=3, 27.8% and n=16, 45.7%, *p*=0.946) or SARS-CoV2 infection (n=1, 9% *vs*. n=7, 20% *p*=0.577) before IIM diagnosis was not statistically different between CAM and non-CAM IIM patients.

Having an IIM diagnosis after the pandemic onset (OR 6.348, 95%CI 1.915–21.041, *p*=0.003) was an independent predictor of CAM among IIM patients, regardless of age at diagnosis (OR 1.057, 95% CI 0.998–1.119, *p*=0.058), sex (OR 1.046, 95% CI 0.189–5.791, *p*=0.959) or previous COVID-19 infection (OR 0.896, 95% CI 0.081–9.955, *p*=0.896). Vaccination status was not included in the multivariate model due to moderate collinearity (VIF 2.2) with previous COVID-19 infection.

SARS-CoV2 infection

There were eight SARS-CoV2 infections (17.4%) amongst the 46 patients diagnosed with IIM after the onset of the pandemic. Only one of those patients (2.1%) had COVID-19 prior to the IIM diagnosis, and it occurred 240 days before the IIM diagnosis presenting as a mild disease. There were no IIM flares after the SARS-CoV2 infection in patients with established disease at the time of the infection.

Anti-SARS-CoV2 vaccination

In most cases, IIM diagnosis preceded anti-SARS-CoV2 vaccination (n=27, 59.0% of the patients diagnosed after the onset of the pandemic). On the other hand, 19 patients (41.0%) had an IIM diagnosis after at least one dose of an anti-SARS-CoV2 vaccine. Of these, three patients (15.8%) had been vaccinated with one dose, seven (36.8%) with two, eight (42.1%) with three, and one (5.3%) with four doses of an anti-SARS-CoV2 vaccine at the time of IIM diagnosis. The first, second, and third doses were administered, on average, 193.0±250.0, 160.0±238.0, and 91.0±160.0 days before the IIM diagnosis. Disease onset in the only patient with four vaccine doses administered before IIM, occurred 105 days after the fourth dose administration. The Pfizer® BNT162b2 mRNA vaccine was the most common (n=14, 73.7%), followed by Moderna® (n=3, 15.8%) and Janssen® (n=2, 10.5%).

Discussion

In our cohort of 132 patients, there was a significant increase in the incidence of CAM since the COVID-19 pandemic started. Paralleling the increase in the prevalence of CAM, anti-TIF1γ positivity also became significantly more prevalent after the COVID-19 pandemic and we interpret this as a direct consequence of the upsurge of CAM. There was no association with a specific type of cancer. There was no difference in IIM severity before and after the COVID-19 pandemic. No significant difference was found in vaccination status or previous SARS-

CoV2 infection when comparing CAM and non-CAM IIM patients. Additionally, IIM diagnosis after the COVID-19 pandemic onset was an independent predictor of CAM, irrespective of age, sex or COVID-19 infection.

COVID-19 infection and anti-SARSCoV2 vaccination were suggested to be associated with new-onset IIM (9). On a molecular level, the cytokine storm that occurs in some COVID-19 patients may lead to autoimmune phenomena, such as IIM, mainly due to molecular mimicry (10). In our cohort, COVID-19 infection was not associated with an increased incidence of IIM. Only one patient had a confirmed COVID-19 infection before IIM diagnosis.

Vaccines also involve several immunological events and may facilitate autoimmune phenomena. These have been reported with several vaccine mechanisms (11). Regarding SARS-CoV2 vaccination, several case reports suggested a temporal relation between the AstraZeneca® AZD1222 viral vector vaccine, the Moderna® mRNA-1273, and Pfizer® BNT162b2 mRNA vaccine administrations and IIM onset (12, 13). However, a retrospective study from Italy, based on IIM patients mainly vaccinated with the Pfizer® BNT162b2 mRNA vaccine, did not find an increase in IIM relapse after vaccination (14). In our cohort, COVID-19 vaccination was not associated with increased incidence of IIM.

A group in Israel reported an increased incidence of CAM in an IIM cohort after the COVID-19 pandemic onset (15). Our results confirm this observation and provide new data supporting that this trend is not directly related to COVID-19 infection nor anti-SARS-CoV2 vaccination, contrarily to some case reports. In fact, our observations suggest that the increased incidence of CAM after the pandemic onset may be related to worse management of non-COVID-19-related healthcare conditions, namely cancer screening and early diagnosis. Further research using data from larger international cohorts may confirm this trend.

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