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Prevalence of other connective tissue diseases in idiopathic inflammatory myopathies

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Abstract

We sought to determine the prevalence of additional connective tissue diseases (CTDs) in patients with idiopathic inflammatory myopathies (IIM), and to study the muscle biopsy patterns in various clinico-serologic subsets of myositis. We undertook a retrospective cohort study of 648 patients with a histological diagnosis of IIM. The following was determined from the South Australian Myositis Database: presence of associated CTDs, histological details and presence of myositis-specific (MSA) or myositis-associated (MAA) antibodies. Among patients with IIM, a significantly greater proportion had systemic sclerosis 32/648 (4.9%) than mixed connective tissue disease (12/648, $p = 0.003$), primary Sjogren's syndrome (12/648, $p = 0.003$), systemic lupus erythematosus (10/648, $p < 0.001$) or rheumatoid arthritis (6/648, $p = 0.0001$). Polymyositis was the most common IIM diagnosis regardless of the presence or absence of CTD. MSA/MAA was more commonly detected in those with systemic sclerosis than those with IIM alone (OR 5.35, $p < 0.005$). The higher prevalence of SSc (compared with other CTDs) in IIM, together with the more frequent detection of autoantibodies in this group, suggests that these conditions may be linked.

Keywords Myositis · Systemic sclerosis · Scleroderma · Myositis overlap · Connective tissue disease

Introduction

Idiopathic inflammatory myopathies (IIM) comprise systemic autoimmune disorders characterized by proximal weakness, raised serum creatine kinase (CK) levels and histological evidence of muscle inflammation [1]. The main subtypes are polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM) and necrotizing myopathy (NM), each distinguished by characteristic muscle histology.

An autoimmune contribution to the pathogenesis of IIM is supported by the presence of myositis-associated (MAA) (anti-Ro, -PMScl, -Ku, -U1RNP) and myositis-specific autoantibodies (MSA) (anti-Jo1, -PL7, -PL12, -OJ, -EJ, -Mi2, -SRP) [2–4] and an association with the 8.1 ancestral haplotype (HLA-A1, B8, DRB3*0101, DRB1*0301, DQB1*0201) which predisposes to many autoimmune connective tissue diseases (CTDs) [5]. Myositis also occurs in certain CTDs such as systemic sclerosis (SSc) and mixed connective tissue disease (MCTD) [6–8] and it may also occur in the context of "overlap myositis" in patients with other rheumatic diseases such as rheumatoid arthritis, primary Sjogren's syndrome or systemic lupus erythematosus Antinuclear antibodies (ANA) are more commonly detected in patients with IIM with concurrent CTDs [9, 10], although comparisons of autoantibody prevalence in IIM populations with and without CTDs have not been extensively studied. These features of autoimmunity raise the possibility that other autoimmune CTDs may be more prevalent among patients with IIM.

Not only does the coexistence of IIM with other CTDs suggests shared underlying immunopathogenetic mechanisms, but also the diagnosis of another CTD in patients with IIM may have clinical implications, for example the relative contraindication for high-dose corticosteroids in patients with systemic sclerosis (SSc).

Herein, we sought to determine the prevalence of other CTDs in a well-characterized cohort of patients with

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biopsy-proven IIM and further to study the muscle biopsy patterns in various clinico-serologic subsets of myositis.

Methods

The South Australian (SA) Myositis Database is a registry of 648 adult patients with biopsy-proven IIM identified subsequent to 1980, approved by the Research Ethics Committees of the teaching hospitals in SA and in particular by the Human Research Ethics Committee of the Royal Adelaide Hospital (Protocol Number 051012). Patient demographics, clinical features, CK levels and serology including ANA, autoantibodies to extractable nuclear antigens (ENA), MAA and MSA, use of medications including statins and the presence of malignancy were recorded. The presence of CTDs including SSc, MCTD, primary Sjogren's syndrome (pSS), systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) was recorded. The database was searched for patients with IIM between 1980 and 2013.

Autoantibodies to ENA are analysed by commercial ELISA (Euroline ENA Profile 5, Euroimmune AG, Germany) and in-house counterimmunoelectrophoresis. These include antibodies to nRNP/Sm, Sm, U1RNP, Ro52/Ro60, SSB/La, Scl-70, PM-Scl100, Jo-1, CENP B and nucleosomes. Testing for MSA/MAA by line immunoblot (Euroline Myositis Profile 3, Euroimmune AG, Germany) identifies autoantibodies to Ro52, Mi-2, Ku, PM-Scl75, PM-Scl100, Jo-1, SRP, PL-7, PL-12, EJ and OJ. Antibody tests were done on stored sera at the time of patient recruitment to the database.

All biopsies were assessed in a single laboratory employing well-validated histological, immunohistochemical and ultrastructural criteria [11, 12] and were subject to peer review. Biopsies were subjected to routine stains for MHCI, MHCII and the membrane attack complex (MAC). Conditions in which inflammatory infiltrates may cause confusion (e.g. dystrophies) were excluded. The histological criteria used for PM and IBM are endomysial inflammatory cell infiltration by lymphocytes and macrophages, polyfocal polyphasic muscle fibre necrosis and lymphocytic invasion of MHC1 expressing non-necrotic muscle fibres (CD 8 positive T-cells) as well as prominent MHC1 sarcolemmal and sarcoplasmic immunoreactivity of non-necrotic fibres. IBM is distinguished from PM by "rimmed vacuoles" associated with 15–20 nm filamentous inclusions on electron microscopy, COX-deficient fibres, mitochondrial abnormalities and amyloid deposits. In DM, there is often perifascicular atrophy with or without perivascular and perifascicular chronic inflammatory cell infiltration (predominantly B-lymphocytes but also CD4 + cells) and deposition of MAC. A diagnosis of "myositis—not otherwise specified (MNOS) is used when there is chronic inflammation in the absence of the sufficient features to enable a diagnosis of DM/PM/IBM/NM. NM is characterized by myofibre necrosis with a paucity of inflammatory infiltrates.

Statistical analysis

Comparisons between groups were made utilizing the Fisher's exact test (two-tailed), and p values < 0.05 were considered significant.

Results

Of 648 patients with IIM, a concurrent CTD was present in 72 (11.1%).

The overwhelming majority of patients (89%) with IIM had no concurrent diagnosis of CTD (Table 1). Among IIM patients with concomitant CTD, SSc (Group 2) was the most common (32/648; 4.9%) and occurred significantly more frequently than the next most prevalent CTD, namely MCTD (Group 3) (12/648, 1.9%, $p = 0.003$). Collectively, other CTDs (Group 4) occurred in a small minority of patients [28/648 (4.3%)] and individually occurred significantly less frequently than SSc: pSS (12/648, 1.9%, $p = 0.003$), SLE (10/648, 1.5%, $p < 0.001$) and RA (6/648, 0.9%, $p = 0.0001$).

We next determined the prevalence of concurrent CTDs in the different subsets of IIM. An overlap syndrome with another CTD was seen in 7/43 (16.3%) patients with MNOS, 8/54 (14.8%) patients with DM, 30/212 (14.2%) patients with PM, 6/77 (7.8%) patients with NM and 7/160 (4.4%) patients with IBM. Patients with MNOS, DM and PM were all significantly more likely to have an associated CTD than patients with IBM ($p < 0.02$).

PM was the most common IIM subtype in all four groups. In comparing the distribution of IIM subtypes within our four groups, only two significant differences were found: patients with IIM alone (Group 1) were more likely to have IBM compared to those with concurrent SSc (Group 2) (OR 5.43, 95% CI 1.28–22.97); $p = 0.01$); and patients with MCTD (Group 3) were almost nine times more likely to have

Table 1 Prevalence of connective tissue disease in patients with idiopathic inflammatory myopathies

Patient groups ($n = 648$)	Prevalence, n (%)
IIM alone (Group 1)	576 (88.9)
IIM and SSc (Group 2)	32 (4.9)
IIM and MCTD (Group 3)	12 (1.9)
IIM and other CTD (Group 4)	28 (4.3)

IIM idiopathic inflammatory myopathy, *SSc* systemic sclerosis, *MCTD* mixed connective tissue disease, *CTD* connective tissue diseases

PM compared to those with SSc (Group 2) (OR 8.75, 95% CI 1.64–46.75; $p < 0.01$).

Unsurprisingly, antinuclear antibodies were more frequently detected in IIM patients who had concurrent CTD (42/49) than those without (73/193), $p < 0.0001$.

MSA/MAA was more commonly detected in IIM patients with SSc than those with IIM alone (OR 5.35, $p < 0.005$). Anti-PM-Scl (OR 14.76 [4.10–53.14], $p < 0.001$), anti-Scl70 (OR 47.75 [4.79–476.51], $p < 0.0001$), anti-centromere (OR 30.56 [2.68–348.65], $p = 0.01$) and anti-Ro52 (OR 8.00 [3.13–20.78], $p < 0.001$) antibodies occurred more commonly in those with concurrent SSc than in patients without CTD.

In an attempt to better understand the dominant pathological processes in patients with IIM in the context of CTD, we determined the presence or absence of various muscle histopathological features in patients with IIM alone and those with CTD (Table 2). Compared with patients with IIM and CTD (Groups 2–4), patients with IIM alone (Group 1) had more polyphasic muscle fibre necrosis and lymphocyte invasion of myofibres.

The higher prevalence of SSc compared with other CTDs in IIM prompted us to determine whether the histopathological features of patients with IIM/SSc (Group 2) were distinct from those with IIM with other CTDs (Group 3, 4). There was less frequent polyphasic and polyfocal myofibre necrosis and less fibre regeneration compared with patients with IIM/MCTD (Group 3) ($p < 0.05$). Polyfocal and polyphasic muscle fibre necrosis was seen in almost all patients in Group 3 (10/12 for both) compared with 15/31 and 14/31, respectively, in Group 2. There were no differences in comparisons with those with other CTDs (Group 4).

Discussion

By studying the clinical, pathological and serological characteristics of a large cohort of patients with a definitive histological diagnosis of IIM, we have shown that SSc is the most prevalent associated CTD in patients with a primary diagnosis of IIM, and, interestingly, lymphocytic infiltration of myofibres occurs less frequently in patients with IIM and SSc This, together with the higher prevalence of autoantibodies suggests a shared underlying immunopathogenetic mechanism linking these two rare autoimmune CTDs.

Only a few studies, with small patient numbers, have previously examined IIM patient populations for overlapping CTDs including SSc (Table 3); the collective prevalence of CTD varied between 14.1% and 52.4% (9–10, 14–17). Among patients with IIM, 4.4–7.7% have been reported to have concurrent SSc [9, 10, 13–15], with some reports suggesting this to be the most common CTD in patients with IIM, consistent with the findings of the present study.

Studies to date [9, 10, 13–16] have utilized the Bohan and Peter criteria for a diagnosis of IIM, and notabl, these criteria do not recognize IBM and NM. The inclusion of patients with a "probable" diagnosis of IIM according to these criteria means some may not have had histological confirmation of disease, hence the potential for misclassification of disease, and inclusion of non-uniform patient populations. Furthermore, the subclasses of CTD determined in these studies to date [9, 10, 13–16] were not consistent, e.g. Hausmanowa-Petrusewicz et al. included

Table 2 Histopathological features in idiopathic inflammatory myopathy patients with and without connective tissue disease

Histological finding	No CTD (Group 1), $n = 524$ (%)	CTD (Groups 2–4), $n = 67$ (%)	p value
Polyfocal muscle fibre necrosis	323 (61.6)	33 (49.3)	0.063
Polyphasic muscle fibre necrosis	320 (61.1)	32 (47.8)	**0.047**
Segmental necrosis with macrophage myophagia	229 (43.7)	24 (35.8)	0.24
Basophilic fibre regeneration	284 (54.2)	38 (56.7)	0.79
Rimmed vacuoles	196 (37.4)	17 (25.4)	0.06
Vacuoles non-rimmed	131 (25.0)	11 (16.4)	0.13
Perifascicular atrophy	54 (10.3)	8 (11.9)	0.83
Lymphocyte invasion of muscle fibres	278 (53.1)	24 (35.8)	**0.009**
Perivascular interstitial lymphocyte invasion	288 (55.0)	42 (62.9)	0.24
MHCI	255 (48.7)	32 (47.8)	0.90
MHCII	182 (34.7)	26 (38.8)	0.59
CD45	262 (50.0)	29 (43.3)	0.36
CD68	264 (50.4)	31 (46.3)	0.60

Statistically significant p values are in bold

Group 1 idiopathic inflammatory myopathy alone, *Group 2* idiopathic inflammatory myopathy and systemic sclerosis, *Group 3* idiopathic inflammatory myopathy and mixed connective tissue disease, *Group 4* idiopathic inflammatory myopathy and other connective tissue diseases, *MHC* major histocompatibility complex

Table 3 Previous studies assessing idiopathic inflammatory myopathy populations for overlapping connective tissue disease and the comparison with the present study

	Number of patients	Diagnostic criteria used	IIM subtype included	Total OS (%)	SSc OS (%)	MCTD OS (%)	RA OS (%)	SLE OS (%)	PSS OS (%)	Other OS (%)
Hochberg et al. (1986)	76	Bohan and Peter	DM/PM only	18 (23.7)	5 (6.6)	n/a	n/a	7 (9.2)	6 (7.1)	n/a
Hausmanowa-Petrusewicz (1997)	84	Bohan and Peter	DM/PM only	44 (52.4)	4 (4.8)	3 (3.6)	n/a	3 (3.6)	n/a	34 (40.5)*
Troyanov et al. 2005	100	Bohan and Peter	DM, PM, CTD, CAM	31 (31)	n/a	n/a	n/a	n/a	n/a	n/a
Ramesha et al. (2010)	68	Bohan and Peter	DM/PM/IBM	20 (29)	3 (4.4)	3 (4.4)	7 (10.2)	6 (8.8)	n/a	1 (1.5)
Vansca et al. (2010)	169	Bohan and Peter	DM/PM only	39 (23)	13 (7.7)	n/a	12 (7.1)	5 (3.0)	9 (5.3)	n/a
Aguila et al. (2014)	220	Bohan and Peter	DM/PM only	31 (14.1)	15 (6.8)	Excluded	7 (3.2)	9 (4.1)	n/a	n/a
Maundrell et al.	648	Muscle biopsy	DM, PM, IBM, NM, MNOS	72 (11.1)	32 (4.9)	12 (1.8)	6 (0.9)	10 (1.5)	12 (1.9)	n/a

CAM cancer-associated myositis, *DM* dermatomyositis, *IBM* inclusion body myositis, *NM* necrotizing myopathy, *MNOS* myositis not otherwise specified, *IIM* idiopathic inflammatory myopathy, *MCTD* mixed connective tissue disease, *OS* overlap syndrome, *PM* polymyositis, *PSS* primary Sjogren's syndrome, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *SSc* systemic sclerosis

*Includes 21 patients with scleromyositis and 13 patients with non-specific CTD

"scleromyositis" defined as the coexistence of myopathy and features of SSc and found this to be the most common overlap CTD in their population, with 21/84 patients having this diagnosis [9].

In the large IIM cohort studied herein, SSc was the most frequently associated CTD. Patients with IIM/SSc were five times more likely to have MSA or MAA. Anti-PM-Scl, as well as anti-Scl70, anti-centromere and anti-Ro52, was more frequently detected in this group, confirming a known association between IIM/SSc overlap and anti-PM-Scl [17]. Clinicians should be vigilant for a diagnosis of SSc in those with IIM who have one of these antibodies, especially in those with polymyositis. Anti-Ro52 antibodies, in particular, are commonly associated with many autoimmune diseases [18].

Anti-Ku autoantibodies, though originally described in SLE, SSc and RA [19], have subsequently been associated with IIM and overlap syndromes, in particular with SSc; 14 of 625 patients with SSc had anti-Ku antibodies, and these patients had more frequent joint and muscle involvement [20]. Another study of 207 IIM patients showed that anti-Ku antibodies were associated with overlapping rheumatic diseases (not further specified), arthritis and interstitial lung disease [21]. Herein, we demonstrated an association between anti-Ku antibodies and IIM/SSc overlap, suggesting the potential utility of this autoantibody to detect this subset of patients.

On comparing muscle histopathology, the only differences identified were that patients with IIM alone had more frequent polyphasic myofibre necrosis and endomysial lymphocytic invasion. This may suggest that the entity of IIM/CTD overlap is less dependent upon MHC1-dependent cytotoxic T cell responses than IIM alone.

The more frequent detection of polyfocal and polyphasic muscle fibre necrosis in patients with myositis and MCTD, compared with IIM/SSc, suggests this subset of disease is more active with more necrosis and regeneration, although this needs further investigation.

A limitation of this study is the relatively low numbers of patients tested for antibodies to ENA and MSA/MAA. This largely reflects the time period over which patients were recruited, prior to the availability of these tests. The low numbers do limit the interpretation of autoantibody associations, although we note we have replicated previously reported results. Furthermore, antibodies to the more newly recognized MSA, such as antibodies directed to MDA-5, TIF1-gamma and NXP2, were not available for testing at the time of the study. Patients are recruited to the database by referral from treating specialists from multiple centres across South Australia, hence there is potential for inconsistency in reporting CTD. We also acknowledge the potential for underreporting of patients with IIM/SSc. While patients with SSc may have IIM, they are even more likely to have

a bland myositis for which investigations such as muscle biopsy may be omitted; the investigation of prevalence of myositis in a large cohort of patients with SSc will be of interest.

These limitations acknowledged, we have utilised the largest cohort of well-characterized IIM patients reported to date to investigate the prevalence of concurrent CTD. The high prevalence of SSc in patients with IIM suggests that vigilance for a diagnosis of SSc in patients with IIM, especially those with anti-Pm-Scl, anti-Scl70, anti-centromere and anti-Ro52 antibodies, is warranted.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest and no disclosures.

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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