Rheumatoid myositis, myth or reality? A clinical, imaging and histological study

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Abstract

Rheumatoid myositis (RM) is still poorly characterized, albeit the concept of muscle involvement in rheumatoid arthritis (RA) is well-recognized as being driven by a wide range of causes including inflammation, drugs, impaired joint flexibility, sedentarism. Objective: To describe clinical, serological, imaging and histological pattern of RM. Materials and Methods: This is a retrospective study on eight RM selected from a cohort of one hundred and three consecutive rheumatoid arthritis – 1987 American College of Rheumatology criteria – which were systematically screened for the evidence skeletal muscle involvement. Data collected in all enrolled patients included clinical, serological, imaging and histological pattern of RM. Results: Routine muscle histology indicated both non-specific muscle fiber damage (changes in fiber size and internal structure; pleomorphic mitochondria, dilated sarcotubular system, multiple internal or subsarcommal nuclei; abnormal fiber types distribution: trend towards type II; atrophy; degenerative/regenerative modifications) and the presence of inflammatory deposits in all patients (mild to moderate, patchy B- and T-cells infiltrates, mainly perivascular and endomysial, but also in the perimysial region classified as polymyositis-like deposits). High levels of serum muscle enzymes, abnormal EMG (short duration, small amplitude, polyphasic motor unit action potentials) without insertionals activity and fibrillations, active inflammation on both Doppler ultrasound and MRI were commonly reported. Conclusions: Traditional analysis of muscle biopsy specimens (Hematoxylin–Eosin, modified Gomori trichrome staining) is faraway unsatisfactory, only documenting changes in muscle fibers size, architecture, internal structure, and, possibly, detecting perivascular, perimysial or endomysial inflammatory deposits. Upcoming research should address the value of muscle imaging for the diagnosis and evaluation of treatment response and muscle function in rheumatoid myositis.

Keywords: myositis, rheumatoid arthritis, muscle imaging, muscle biopsy.

Introduction

While progress seems to have been made in raising the knowledge about idiopathic inflammatory myopathies, there is still a vast need for understanding the pathologic pathways of inflammatory myopathies associated with other autoimmune rheumatic disorders including rheumatoid arthritis, lupus, scleroderma and Sjögren’s syndrome [1, 2].

Rheumatoid myositis is typically described as immune inflammatory infiltrates associated with variable degrees of skeletal muscle damage occurring in patients with rheumatoid arthritis [1–5]; although it shares certain clinical and laboratory features with idiopathic myositis, particularly with polymyositis, rheumatoid myositis remains a greatly under-diagnosed and under-treated disease, even in the era of new diagnostic tools – such as magnetic resonance imaging with or without spectroscopy, computed tomography, muscle ultrasound – to facilitate the identification of individuals with rheumatoid arthritis and secondary muscle involvement [1, 2, 6, 7].

Moreover, a systematic review of the literature indicates that rheumatoid myositis is still poorly characterized [3–5, 8–14], albeit the concept of muscle involvement in rheumatoid arthritis was firstly recognized in early 60s as being driven by a wide range of causes including inflammation (systemic, articular, muscular), medication (corticosteroids, antimalarials, cyclosporine), impaired joint flexibility as well as sedentarism [1, 2, 9].

The objective of our study was to describe clinical, serologic, imaging and histological pattern of rheumatoid myositis.

Materials and Methods

We performed a retrospective analysis of the muscle involvement in eight patients diagnosed with rheumatoid myositis; cases were identified among a cohort of one hundred and three consecutive rheumatoid arthritis – 1987 modified American College of Rheumatology (ACR) criteria – which were systematically screened for the evidence skeletal muscle involvement.

Data collected in all enrolled patients included clinical signs and symptoms related to muscle involvement (myalgia, weakness, muscle atrophy), muscle enzymes (creatine kinase, CK; lactic dehydrogenase, LDH), electromyography (EMG), ultrasonography (conventional, color Doppler), magnetic resonance imaging (MRI) and muscle biopsy as well.

Muscle biopsy

Open muscle biopsy of the left deltoid was performed only in patients with positive skeletal muscle involvement as supported by conservative approaches. We adapted the protocol proposed by Agrawal et al. [14]; the biopsy specimen was divided into two parts: (i) one was put in
10% buffered formalin; paraffin-embedded sections were prepared in longitudinal and transverse axis and stained with Hematoxylin–Eosin (HE) and Gömöri trichrome; and (ii) the other part was cooled in liquid nitrogen (-170°C) for cryostat sections; histoenzymatic reactions were done on five microcryostat sections using Adenosine Triphosphate pH 4 and 4.6. Further, our protocol included an initial exam performed in light microscopy for the HE-stained sections and modified Gömöri trichrome staining, and a second step of enzymologic exam (acid ATP-ase).

The histopathological study addressed the following parameters: changes in the individual architecture of the muscle fibers; changes in fiber size; changes in fiber-type distribution; changes in internal structure (sarcolemmal nuclei and/or mitochondria); signs of muscle fiber degeneration and/or regeneration; mononuclear cell reaction meaning the presence and distribution of inflammatory infiltrates in skeletal muscle.

All patients attended a single rheumatology center (Clinical Rehabilitation Hospital, Iassy, Romania) during a four-year period (2000–2004), while muscle biopsy analysis was done in “Victor Babes” National Institute for Research and Development in Pathology and Biomedical Sciences, Bucharest, Romania.

The study received the local ethical committee approval and all patients given written informed consent before their enrollment.

Statistical analysis was done using SPSS-13 software package, \( p<0.05 \).

\section*{Results}

\subsection*{Clinical, serological evaluation}

Clinical, serum muscle enzymes and muscle imaging data were available in all studied cases. Rheumatoid myositis affected mainly women (female/male ratio of 8:1), with an average age of 51.28±10.93 years, average disease history 8.23±2.95 years and an average of 3.41±2.54 years between RA diagnosis and onset of clinical symptomatic muscle disease; all patients had moderate disability (functional class II), the majority were under Methotrexate and none of them took corticosteroids during the last 12 months prior to our study.

Muscle signs and symptoms with a proximal and symmetrical pattern were reported in all patients as follows: muscle pain in seven cases and weakness in six cases; no patient presented with muscle atrophy. Average CK levels were 196.25±53.12 U/L (116–265 U/L), ranging from normal levels (two cases) up to a maximum of 1.5 times the upper normal limit (six cases). However, LDH was in normal range for the majority of patients, with an average value of 392±120.36 U/L (210–589 U/L).

Electromyography of the deltoid and quadriceps muscles revealed variable degree of short duration, small amplitude and polyphasic motor unit action potentials, strongly suggestive for a myopathic pattern in seven cases; however, spontaneous muscle activity was not demonstrated. Only one patient had a neurogenic pattern.

Conventional myosonography showed focal homogenous area of increased muscle echogenicity in the majority of patients, while only in one case no abnormalities were detected. In addition, we reported increased Doppler signal in six cases, suggesting that active inflammation of the skeletal muscle is a common ultrasound finding in patients with myositis in RA.

The ability of MRI to diagnose myositis was studied in all cases using short tau inversion recovery (STIR) and T2-weighted sequences of the deltoid and quadriceps muscles; evidence of pathologic MRI was seen in all cases including abnormal high signal intensity in T2 and STIR with a diffuse and moderate pattern suggesting active inflammatory changes which are very characteristic for initial steps of myositis; fatty infiltration as well as muscle atrophy were more prevalent in the proximal muscles of the lower limb, particularly suitable for detecting chronic myositis. Furthermore, no calcinosis and subcutaneous change were detected in our patients.

\subsection*{Histopathological evaluation}

Routine muscle histology demonstrated both muscle fiber damage and the presence of inflammatory deposits in all patients (Table 1, Figures 1–3).

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<thead>
<tr>
<th>No.</th>
<th>Fibers size variability</th>
<th>Type I atrophy</th>
<th>Type II atrophy</th>
<th>Nuclear changes</th>
<th>Degeneration/ regeneration</th>
<th>Cellular reaction</th>
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Muscle fiber damage

We reported marked physiological variability in all cases with either grouped or individual atrophic fibers in five cases as well as moderate hypertrophic fibers in other three. Furthermore, type IIb fibers become more frequently atrophic (three cases) as compared with type I fibers (two cases). In other two patients, we found a specific “irritate” aspect of the muscle fibers defined as increased mitochondrial number and pleomorphic mitochondria as well, particularly in the subsarcolemmal level (“en coup d’ongle”); myelin figures and multiple internal nuclei were detected in three cases.

Abnormal high level of type I fibers was also evident on ATP-acid stained sections in more than half (five) cases. Although degenerative and/or regenerative signs were reported in the majority of cases (six patients), only minor signs were demonstrated.

Inflammatory deposits

Mild mononuclear (B- and T-lymphocytes, rare macrophages) inflammatory infiltrates, with a characteristic single layer distribution typically located in the perivascular region were demonstrated in the majority of cases (six patients); however, no signs of fibrinoid necrosis and vascular endothelial cell damage.
Minor endomysial polymyositis-like inflammation was also found in six cases, mainly lymphocytes and rare macrophages, invading non-necrotic muscle fibers. Finally, discrete perimysial inflammatory deposits were demonstrated in up to four subjects. All cases were defined by patchy inflammatory infiltrate. No fibrotic change was identified in studied cases. The distribution of muscle fiber types based on different histoenzymatic reactions showed no specific changes.

**Discussion**

Our study provided updated information about the status of skeletal muscle in rheumatoid arthritis. Both traditional (serum muscle enzymes, muscle biopsy) and new approaches (muscle MRI, conventional and Doppler ultrasound) in diagnosing rheumatoid myositis were available in all studied patients facilitating the full description of muscle involvement.

Traditional light microscopy analysis of HE-stained sections indicated non-specific damage of skeletal muscle in all eight cases comprising the following key facts: changes in fiber size and internal structure (pleomorphic mitochondria, dilated sarcotubular system, multiple internal or subsarcommaal nuclei), abnormal distribution of fiber types (a trend towards type II fibers) and atrophy, degenerative as well as regenerative modifications.

Additionally, inflammatory changes were identified in the majority of patients; mild to moderate and patchy, immune infiltrates (B- and T-cells) were mainly reported in the perivascular and endomysial region, but also in the perimysial region classified as polymyositis-like deposits. All these findings were suggestive of myositic muscle involvement and were consistent with the data described earlier in the literature [3, 5, 8–14].

It is clear that muscle involvement in rheumatoid arthritis represents a well-recognized extra-articular manifestation, multiple factors contributing to the development of muscle disease: pro-inflammatory cytokines such as TNF-α and IL-1 acting not only in articular but also in muscle environment with subsequent damage of muscle and abnormal muscle metabolism, chronic corticosteroids starting from 10 mg daily, sedentary lifestyle, and impaired joint flexibility as well [1, 2, 9].

However, the literature indicates only few studies documenting the status of muscle in rheumatoid arthritis [3, 4, 9, 14–18]; we have already reported data from our cohort of patients providing new insights into the pathogenesis based on the immunohistochemical assessment of skeletal muscle [9].

It is important to point out that rheumatoid myositis has apparent similarities with polymyositis comprising clinical, serological and EMG pattern [1, 6, 7]. Muscle biopsy remains the only investigation clearly supporting the presence of muscle involvement in rheumatoid myositis; as rheumatoid myositis is typically moderate and patchy, affecting mainly proximal muscle in a symmetrical and bilateral manner [3, 9, 14], multiple section analysis is currently needed in order to diagnose the disease [3, 14].

Points of agreement between our findings and facts frequently suggested in the literature are based on epidemiologic, clinical and biological parameters in rheumatoid myositis.

Despite the relative common muscle involvement in RA, rheumatoid myositis represents a rare disorder, occurring in up to 8% of our cases.

Myositis occurs early during RA course, in patients with active disease, particularly in those with increased ESR and acute phase reactants. As mentioned in literature, at least two other RA settings are potentially associated with myositis, such as active RA with systemic involvement and high serum CK levels, as well as rheumatoid vasculitis [3, 8, 9, 12, 15].

Additionally, we demonstrated impaired serum muscle enzymes (CK, LDH), changes in the normal EMG with a specific myopathic pattern, abnormal muscle ultrasound and MRI; as expected, modifications of these diagnostic tools reflected the activity or chronicity of the myositic process. Thus, we reported high average levels of serum muscle enzymes (particularly for CK and LDH) in the
majority of cases, ranging between normal levels accounting for chronic myositis to 1.5 times the upper normal limit in active disease.

Unlike polymyositis, rheumatoid myositis was characterized by abnormal EMG (short duration, small amplitude, polyphasic motor unit action potentials) without insertional activity and fibrillations supporting data already published [4, 9, 17].

Moreover, as expected, no significant differences between active (inflammatory edema) and chronic (fibrosis) myositis were detected with conventional muscle ultrasound [6, 7]; furthermore, color Doppler revealed hypervascularization of the affected muscles meaning acute inflammation. Although, the key role of Doppler and power Doppler ultrasound is well recognized in rheumatology, especially for inflammatory joint and tendon pathology, the level of significance for diagnosing and monitoring muscle pathology remains still unclear [1, 2, 6, 7].

Finally, the MRI abnormalities of the muscle in patients with rheumatoid myositis (e.g., inflammation in T2 and STIR sequences) along with the gaps in literature confirm that a dearth of data exists in this field [6, 7]. Thus, the picture of MRI status in the settings of myositis occurring in rheumatoid arthritis needs to be clarified.

Conclusions

Rheumatoid myositis generally defined as inflammatory infiltrates with variable degrees of skeletal muscle injury, which develop in patients with rheumatoid arthritis, represents a distinct entity with a specific clinical, biological, imaging and histological pattern. Traditional analysis of muscle biopsy specimens (Hematoxylin–Eosin, modified Gömöri trichrome staining) is faraway unsatisfactory, only documenting changes in muscle fibers size, architecture, internal structure, and, possibly, detecting perivascular, perimysial or endomysial inflammatory deposits. Upcoming research should address the value of muscle imaging for the diagnosis and evaluation of treatment response and muscle function in rheumatoid myositis.

References


