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Contracturing granulomatous myositis in a patient with rheumatoid arthritis: a case report

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Abstract (up to 150 words),

Contracturing granulomatous myositis is a rare myopathy in which patients present with flexion contractures of the upper limbs in addition to slowly progressive muscle weakness and pain. Whether it represents a distinct nosological entity remains a point of discussion. We present a patient with isolated granulomatous disease of the muscle that responded very well to intravenous immunoglobulins after treatment failure of corticosteroids and methotrexate.

1. Introduction

Granulomatous myositis is a myopathy associated with non-specific epithelioid granulomas in striated muscle. In a large review of a muscle biopsy database only 63 of 27301 muscle specimens (0.2%) interpreted over a 26-year period displayed intramuscular granulomas [1]. This rare entity is most frequently related to sarcoidosis, but other uncommon causes have been reported, including an idiopathic form (after exclusion of systemic disorders known to cause similar myopathological abnormalities) [2]. Whether contracturing granulomatous myositis (CGM) represents a separate disease remains obscure. We report on a female patient with a very illustrative presentation and a marked therapeutic response on intravenous immunoglobulins (IVIg).

Key words

Myositis

Granulomas

Contractures

2. Case Report

A 60-year-old Caucasian woman was admitted to the hospital with a rapidly progressive loss of strength in both upper and lower limbs and unexplained weight loss. Her medical history was notable for primary ciliary dyskinesia due to dynein deficiency, seropositive rheumatoid arthritis (RA) diagnosed 21 years before admission for which she had been receiving six-monthly infusions of two times 1000 mg rituximab for seven years, and lentigo maligna (complete resection). Rituximab was stopped two months prior due to neutropenia. Physical examination revealed a symmetrical, predominantly proximal muscle weakness of Medical Research Council (MRC) grade 4/5 in upper and lower limbs. Additionally, finger flexor weakness and striking contracture of these muscles – reminiscent of Bethlem myopathy – was noticed as well as induration of both forearms (figure 1). There was no finger extensor weakness and passive finger extension was not possible. Furthermore, bilateral scapular winging was visible and neck flexion was noticeably weakened, while neck extension was preserved (MRC-scoring in table 1). There was no dysphagia or muscle fatiguability, neither sensory deficits or pyramidal tract signs. Rheumatologic evaluation on admission showed symmetrical polysynovitis of the carpal and metacarpal joints and pitting edema in both legs. Nerve conduction study did not show a neuropathy and EMG indicated a non-irritative myopathy.

Blood tests revealed a persistent (albumin-corrected) hypercalcemia (3.36 mmol/L, reference range 2.15 – 2.58 mmol/L), hypoparathyroidism (9.5 ng/L, reference range 15.0 – 65.0 ng/L) and spontaneously elevated 1,25-dihydroxy-vitamine D (93.2 ng/L, reference range 19.9 – 79.3 ng/L) with a normal 25-dihydryoxy-vitamin D. Additionally, a markedly raised angiotensin-converting enzyme (ACE) was noted (130 U/L, reference range 8 – 52 U/L) while C-reactive protein (CRP), sedimentation rate, protein electrophoresis, serum light

chains and thyroid stimulating hormone (TSH) were all within normal limits. Urine sample showed hypercalciuria (23.9 mmol/24h, reference range 2.5 -7.5 mmol/24h).

The clinical presentation was most suggestive of a myopathic process, albeit with a normal creatine kinase (CK) of 111 U/L and negative myositis antibodies panel (Mi-2α, Mi-2β, TIF1γ, MDA5, NXP2, SAE1, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro-52). Biochemistry however implied a granulomatous disease. Whole body FDG-PET did show a marked involvement of skeletal muscles, including the forearm flexors (figure 2). A muscle biopsy of the right deltoid revealed widespread inflammatory features with inflammatory infiltrates, often perivascular and localised to the endomysium and perimysium with presence of multiple non-necrotizing granulomas (figure 3). Marked sarcolemmal MHC class I expression was noted, as well as the presence of numerous necrotic muscle fibres and regenerating muscle fibres. Systemic sarcoidosis and tuberculosis were ruled out by whole-body FDG-PET, skin biopsy and bronchoscopy with alveolar lavage for Löwenstein–Jensen culture.

A histopathological diagnosis of granulomatous myositis (GM) was established, resulting in a clinicopathological diagnosis of contracturing granulomatous myositis (CGM). The patient was then started on methylprednisolone 64 mg daily tapered down to 8 mg and subcutaneous methotrexate (MTX) 15 mg weekly while rituximab was discontinued. This initial regimen had no effect on her symptoms after three months. Thereafter, monthly infusions with intravenous immunoglobulins (IVIg) at a dose of 0.4 g/kg were associated with both clinical (MRC-scoring in table 1) and biochemical response; ACE levels dropped down to 20 U/L. The contractures of the finger flexors disappeared (fig 1B).

3. Discussion

Here, we report on a patient showing a treatable myopathy with finger flexor contractures as a particularly rare presentation of granulomatous myositis (GM), which is an inflammatory myopathy most commonly associated with sarcoidosis and tuberculosis, but may also be seen in a wide variety of other etiologies (i.e. lymphoma, thymoma-myasthenia gravis, inflammatory bowel disease, cryofibrinogenemia). Firstly, a point of discussion remains whether GM can also present in isolation as an idiopathic form or if this form constitutes an exceptional manifestation of sarcoidosis without systemic features [2]. A very rare variant of GM is CGM, in which patients present with flexion contractures of the upper limbs in addition to slowly progressive muscle weakness and pain. To present day only a few cases of CGM have been reported in the literature, most of which were attributed to an underlying sarcoidosis [3]. Indeed, there were no significant pathological differences between these entities, but much like the discussion on idiopathic GM it has been suggested that CGM constitutes a separate clinical entity distinct from sarcoidosis since there were little to no systemic symptoms of sarcoidosis in the aforementioned cases [4]. In this regard, a presentation of CGM similar to our case was ascribed to sarcoidosis based on both evidence of granulomatous myositis as well as vitamin D–calcium dysregulation, the latter of which they considered to be an end-organ sarcoid involvement [5]. However, this vitamin D dysregulation, as also documented in our patient, is generally regarded upon as a phenomenon of granulomatous disease and in no way pathognomonic for sarcoidosis [6]. Indeed, sarcoidosis remains a diagnostic odyssey, which is never fully secured since no infallible tests or diagnostic criteria exist. Additionally, other inflammatory myopathy subtypes might also present with contractures, particularly in case of overlap with GM, as described for sporadic inclusion-body myositis (sIBM) [1]. **We therefore propose CGM to be a general subtype of an inflammatory myositis with a specific differential diagnosis which might include**

an 'idiopathic' variant. As a rule of thumb we advise to consider an underlying myositis when confronted with contractures even with a normal CK level, and the finding of granulomas on muscle biopsy could help narrow down its differential diagnosis.

Secondly, a possible association between CGM and therapy-resistant RA cannot be fully excluded in our case. Of late, a report of a middle-aged woman with progressive proximal weakness and biopsy-proven granulomatous myositis was published for which they suggested a separate entity being IgG4-related myositis due to the numerous IgG4+ plasma cells [7]. Interestingly, her medical history was also notable for a longstanding (seronegative) RA and her condition worsened while being treated with rituximab. However, this patient's diagnosis of RA was considered "highly equivocal", no elevation of IgG4 could be detected our case and IVIg did not improve her condition. Nonetheless, these findings might suggest possible association of granulomatous myositis with other conditions such as RA and IgG4-related illness which raises questions about treatment options. Indeed, current literature only mentions first-line steroids followed by methotrexate and barely any evidence in favour of third-line treatments (e.g. IVIg, therapeutic monoclonal antibodies) [8]. This wild variety of possible underlying etiologies and associations might possibly explain why IVIg with its pleiotropic effect resulted in amelioration unlike rituximab, corticosteroids and methotrexate. It would be highly insightful to study the effect of IVIg in a larger cohort of patients with granulomatous myositis. IVIg are increasingly used in (refractory cases of) other inflammatory myopathy subtypes [9].

Finally, we would like to stress the relevance of performing diagnostic muscle biopsies in as this tool risks being increasingly omitted from the routine workup of suspected (inflammatory) myopathies.

Further documentation of rare CGM cases is indispensable, as this is an extremely rare manifestation of a disorder which might constitute a specific treatable entity where IVIg might be a highly effective therapy.

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Declaration of competing interest

None.

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FIGURE LEGENDS

Figure 1. Finger flexor contractures

(A) Finger flexor contractures before treatment. (B) Resolution of contractures after treatment with corticosteroids, methotrexate and intravenous immunoglobulines

Figure 2. Muscle biopsy findings

(**A, B**) Hematoxylin and eosin (H&E) staining showed myopathic features with presence of numerous inflammatory infiltrates and formation of granulomas. (**C**) Gomori-trichrome staining showing a non-necrotizing granuloma. (**D**) Most inflammatory cells are CD68-immunoreactive histiocytes.

Figure 3. Findings on FDG-PET imaging

Marked ^{18}F-FDG-uptake in the skeletal muscles of both upper and lower arm.

TABLES

Table 1. MRC scoring before and after treatment with intravenous immunoglobulins

	BEFORE	AFTER
Neck flexion	4/5	4/5
Neck extension	5/5	5/5
Shoulder abduction	4/5	4/5
Elbow flexion	4/5	5/5
Elbow extension	4/5	5/5
Wrist extension	5/5	5/5
Finger flexion	4/5	5/5
Finger extension	5/5	5/5
Hip flexion	4/5	4/5
Knee extension	4/5	5/5
Knee flexion	4/5	5/5
Ankle dorsiflexion	5/5	5/5
Ankle plantar flexion	5/5	5/5

MRC testing before and after treatment with IVIg and tapering of corticosteroids.