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Case report

Immunoglobulin (Ig)G-4 related myositis – A new entity?

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Abstract

Immunoglobulin (Ig)G4-related disease is an uncommon systemic autoimmune disorder characterized by infiltration of IgG4$^+$ plasma cells in different organs and elevated levels of IgG4 in peripheral blood. So far, only one case of myositis with abundant IgG4$^+$ plasma cells has been reported and classified as 'polymyositis'. We present an unusual case of chronic inflammatory myopathy in a context of rheumatoid arthritis. Severe granulomatous myositis, featuring abundant IgG4$^+$ plasma cells was identified in two skeletal muscle biopsies within a five-year-interval. We suggest this entity to be a new subtype of immunoglobulin G4-related disease: IgG4-related myositis, while there were no diagnostic criteria fulfilled for the known idiopathic inflammatory myopathies.

Keywords: IgG4- related disease; Myositis; Granuloma; Eosinophils.

1. Introduction

IgG4-related diseases (IgG4-RD) are rare disorders with many organs characteristically involved. Typically, infiltration of organs can lead to pancreatitis, retroperitoneal and mediastinal fibrosis, sialadenitis and orbital inflammation) [1–4]. Multiple organ involvement with typical combinations is the rule, but affection of single organs has been described [5]. In peripheral blood, IgG4 levels are usually elevated and eosinophilia can appear. Comprehensive diagnostic criteria include characteristic clinical presentation (organ involvement), elevated serum levels of IgG4, and histopathological examination [6]. Thus, to definitively confirm the diagnosis, tissue analysis is of high value. Recently, a case of myositis with abundant IgG4$^+$ plasma cell infiltration has been described [7]. Interestingly, abundance of IgG4$^+$ plasma cells has been noticed as a non-specific finding in the context of polymyositis [7]. In this context, we present a challenging and unusual case of chronic, therapy-refractory myositis featuring abundant IgG4$^+$ plasma cells, identified in two skeletal muscle biopsies within a five-year- interval. Diagnostic criteria for any of the known idiopathic inflammatory myopathies were not fulfilled we classify this entity to be a new subtype of IgG4RD with single organ involvement that we delineate 'IgG4-related myositis' [8]. The patient provided written consent for publication of these data, and the ethical committee of the Charité – University hospital has approved the study (EA2/163/17).

2. Case report

A now 54-year-old female patient was diagnosed with rheumatoid arthritis (RA) at the age of 21 years due to arthralgia in her hands but without neuromuscular complaints. Glucocorticoid and methotrexate (MTX) therapies were started; she received gold between the age of 21 and 23 years and MTX between the age of 41 and 48 years. She complained about progressive muscle weakness of her thighs since age

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48 years. A first muscle biopsy, taken at that time was classified as 'granulomatous myositis'. Refractory disease lead to administration of rituximab at the age of 48 and 52 years (cumulative dose 4 g), and intravenous immunoglobulins at the age of 52 and 53 years (cumulative dose 80 g), and of cyclophosphamide at the age of 53 (4 g cumulative dose), none of which could prevent progression.

At present, she showed severe weakness of her biceps, triceps, quadriceps, iliopsoas and erector spinae muscles (2–3/5 according to medical research council (MRC) scale), being unable to perform full back erection. Physical examination was otherwise unremarkable, including absence of swollen or painful joints. We did not observe any skin change, lung fibrosis, or other significant findings in lung and abdomen CT scans.

Laboratory analysis revealed mildly elevated levels of creatine kinase (205 U/L, normal range (N): < 167 U/L), myoglobin (107 μg/L, N: 25–58 μg/L), troponin (88 ng/L, N: < 50 ng/L), lactate dehydrogenase (379 U/L, N: 135–250 U/L), liver enzymes (2-4-fold elevated), AP (134 U/L, N: 35 - 105 U/L), soluble interleukin-2 receptor (1440 IU/ml, N: < 710 IU/ml), IgG4 (1.288 g/l, N: 0.052–1.250 g/l), and eosinophils (1.74 cells/nl, N: 0.02–0.50 cells/nl). Anti-nuclear antibodies as well as anti-citrullinated protein antibodies and rheumatoid factors were absent. Interestingly, anti-Mi-2 autoantibodies and PM-Scl75 antibodies were present at time of second biopsy (commercial lineblot; Myositis Profile IV; Euroimmune, Kiel, Germany). Further blood tests including electrolytes, C-reactive protein, creatine and blood count were within normal ranges. EMG-analysis revealed a myopathic pattern. MRI scans of the thigh muscles and the spine were performed using a 1.5 T imager (Magnetom Avanto; Siemens Healthineers; Erlangen, Germany) and a multichannel surface coil (Fig. 1).

Multifocal muscle oedema was depicted by short-tau inversion recovery (STIR) sequences, and signs of myositis were confirmed after intravenous application of contrast media (Dotarem; Guerbet LCC; New Jersey, USA). T1 and T2 weighted images showed severe fatty muscle replacement of the left vastus lateralis muscle, the biceps femoris and the lateral part of the erector spinae system bilaterally, corresponding to a grade 3 of the Goutallier classification.

2.1. Morphological analysis

Skeletal muscle of two biopsies (right vastus lateralis) from 2012 (age 48 years) and 2017 (age 53 years) was analysed. Routine stains were performed on 7-μm cryostat sections, according to standard procedures. Methods were applied as described previously [9]. In brief, 7 μm cryostat sections were stained by various routine preparations including H&E and Gömöri trichrome. Immunohistochemical staining of these sections was performed, using the *i*view-Ventana DAB (diaminobenzidine)-Detection Kit (Ventana, Tucson, Arizona, 85755 USA). Appropriate biotinylated secondary antibodies were used, and visualization of the reaction product was performed on a Benchmark XT immunostainer (Ventana). Omission of primary antibodies in control sections resulted in absence of any cellular labeling and demonstrated specificity of the primary antibody. In addition, appropriate positive and negative controls for the immunohistochemical reaction were used if necessary. In addition we employed normal muscle tissue as negative control (or physiological control e.g. staining of arterioles by MHC class I positivity of capillaries) for all reactions. The primary antibodies were mouse monoclonal MHC class I dilution 1:1.000; Dako clone w6/32, mouse monoclonal C5b-9, dilution 1:100; Dako clone aE11, mouse monoclonal CD68, dilution 1:100; Dako clone EBM11, rabbit monoclonal CD138, dilution 1:100; Epitomics clone EP201, mouse monoclonal MUM1 dilution 1:50; Dako clone MuM1P, and rabbit monoclonal IgG4 dilution 1:100; Epitomics clone EP138.

Both biopsies showed numerous leukocytes predominant in the endomysium, comprising macrophages and histiocytes, giant cells and eosinophils, hence a granulomatous chronic inflammatory tissue reaction yet without overt circumscribed granuloma-formation (Fig. 2A–C). Numerous $CD138^+$ and $Mum1^+$ plasma cells (Fig. 2D) were IgG4-positive (Fig. 2E; insert shows a high-power field (HPF) illustrating more than 100 $IgG4^+$ cells). MHC class I as well as terminal C5b-9 were sarcolemmaly expressed (Fig. 2F). Tissue of the second biopsy was identical but gradually less affected (under therapy) (Fig. 2G). In addition, obliterative phlebitis was overt (Fig. 2H). Although we observed increased endomysial fibrosis, it did not exhibit a storiform pattern.

3. Discussion

We describe a patient with progressive refractory inflammatory myopathy that does not fulfil any diagnostic criteria for the known types of IIMs [8,10]. From a descriptive point of view, the patient suffers from a biopsy-proven chronic granulomatous myositis with numerous $IgG4^+$ plasma cells, giant cells and eosinophils. Clinically, the symptoms comprise severe muscle weakness affecting upper and lower extremities as well as lower trunk muscles leading to progressive immobilization, the latter being unusual for IIM. Whereas most IgG4RD affect multiple organs such as salivary glands, orbits, mediastinum, retro-peritoneum, lungs, aorta or kidney, our patient had pure muscle disease and did not feature any additional manifestations [5]. Since age 21, the patient had suffered from recurrent arthralgia and hence had been diagnosed with seronegative RA. Other than RA, there was no further relevant preceding condition. The patient was only treated intermittently (initially gold, later MTX) and showed no signs of erosive joint destruction over the years. Hence, we conclude that the diagnosis of RA is highly equivocal as the patient needed therapy only intermediately and over the course of more than 30 years, no detectable joint alterations had developed. In RA, elevation of IgG1 and IgG3 has been described, and myositis is usually not a common symptom though overlap-syndromes may occur occasionally [11]. Conversely, IgG4RD is usually not associated with joint inflammation. Surprisingly, our patient's disease progression was

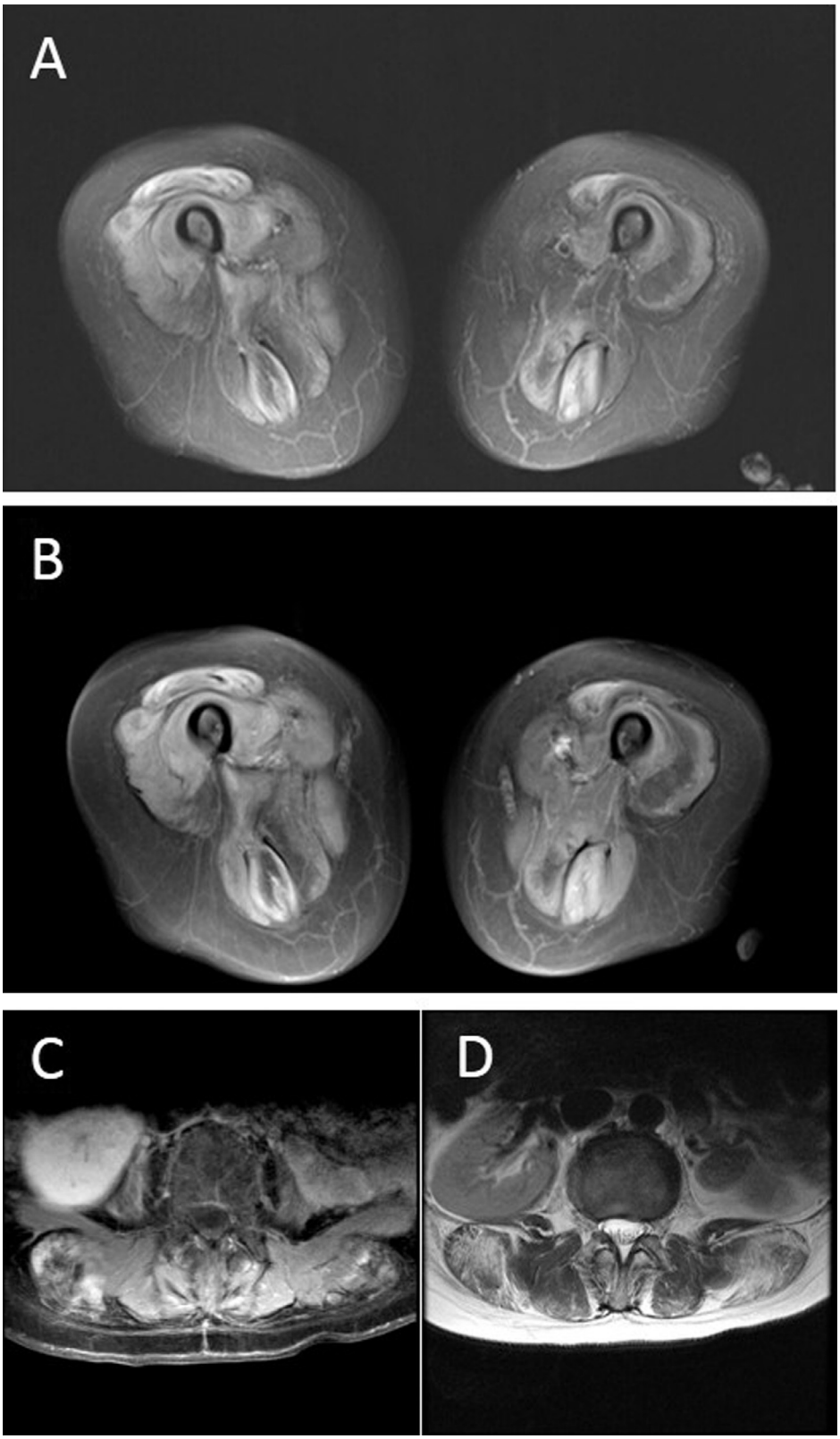

Fig. 1. (A, B) Magnetic resonance imaging of bilateral femoral quadriceps: (A) short tau inversion recovery (STIR)-weighted images and (B) T1-weighted fat suppressed images after administration of contrast agent (gadoteric acid) show high-intensity in terms of muscle oedema and inflammation; (C, D) Magnetic resonance imaging of the spine: (C) axial T1-fat suppressed images after intravenous contrast injection show patchy myositis; (D) axial T2-weighted images show high intensity of the muscle – in comparison with the fat-suppressed image (C) a combination of oedema and fatty degeneration (Goutallier III).

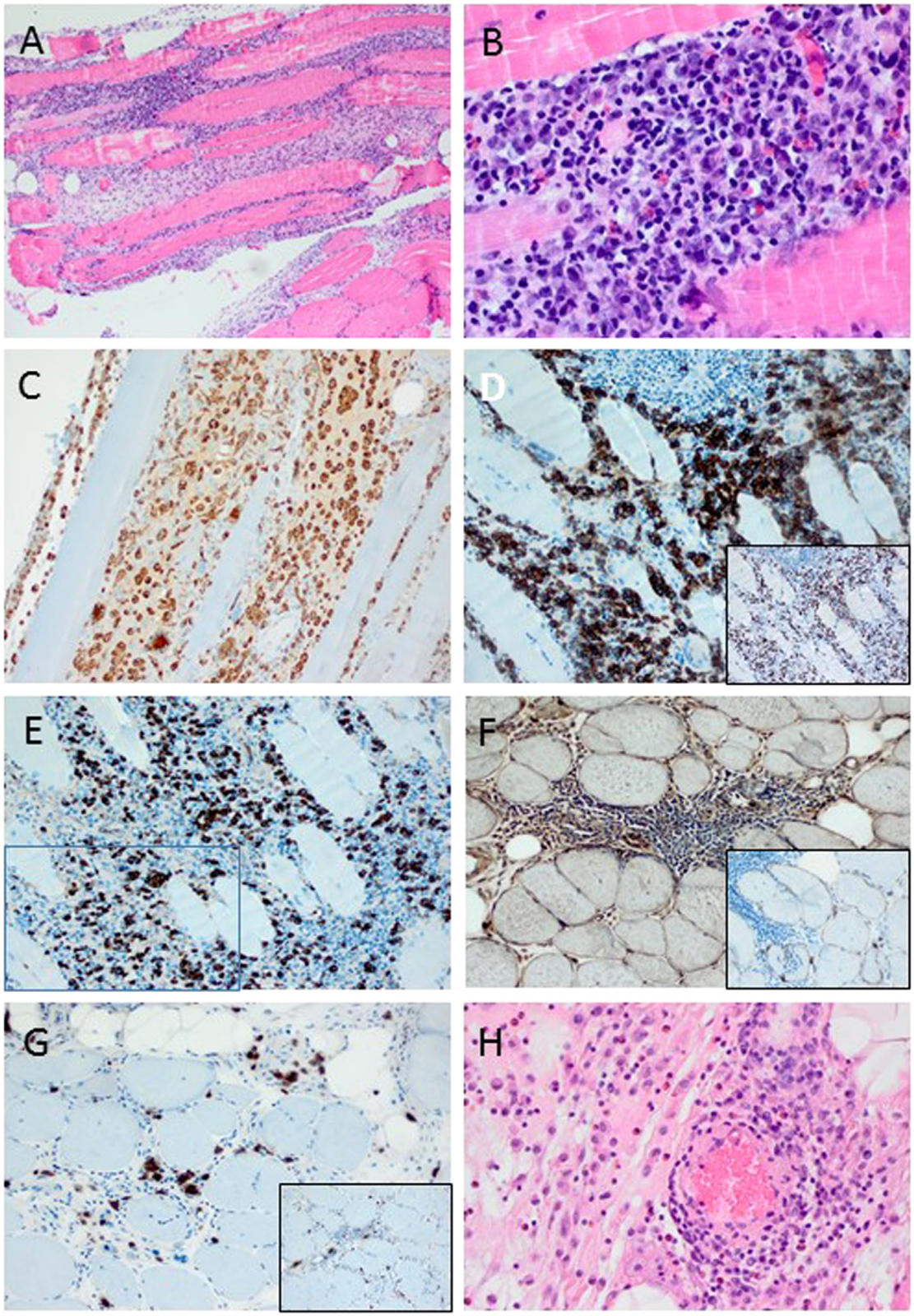

Fig. 2. An unusually dense endomysial infiltrate comprising plasma cells, lymphocytes, macrophages and eosinophils was identified (A–C). Single giant cells were stained by CD68 (C) and plasma cells were $CD138^{+}$ and showed nuclear MUM1 labeling (D and insert). >100 plasma cells/high power field were $IgG4^{+}$ (E) and the sarcolemma of myofibers was MHC class I-positive (F) and occasionally $C5b\text{-}9^{+}$ (F insert). The second biopsy was gradually less affected but still showed numerous $CD138^{+}$ plasma cells (G) and many of them were $IgG4^{+}$ (G insert showing a high power field). In addition, obliterative phlebitis was noticed (H).

rapid and refractory to highly effective medications such as glucocorticoids, methotrexate, cyclophosphamide, rituximab and intravenous immunoglobulins. Although relapses occur, IgG4RD typically responds well to glucocorticoids and especially to rituximab, hence, failure of the mentioned therapies is uncommon [12,13].

IgG4-related-disorders are diagnosed according to characteristic clinical presentation (organ involvement), elevated levels of IgG4 in peripheral blood, and most importantly, histopathological examination (so-called Comprehensive Diagnostic Criteria; CDC) [6]. Tissue of IgG4RD patients characteristically features lymphoplasmacytic and eosinophil infiltrates, storiform fibrosis and obliterative phlebitis, with the ratio of $IgG4^+$ to $IgG4^-$ plasma cells being above 40% [14]. Our patient's biopsies fulfilled three of these diagnostic criteria- although storiform fibrosis was not overt in the skeletal muscle. We hypothesize that the storiform pattern is more likely to develop in other tissues (e.g. like the retroperitoneum). We discussed other differential diagnosis like sarcoidosis due to histopathological signs of granulomatous tissue reaction in the muscles and elevation of soluble interleukin-2 receptor. Recently, a case of severe sarcoidosis-associated myositis with similar clinical presentation has been reported [15]. On the other hand, sarcoidosis usually involves the lung and exceptionally features myositis as a single organ affection [16]. CT scans of chest and abdomen showed no other organ manifestation in our patient. Besides, elevation of soluble interleukin-2 receptor is common in IgG4-RD [17]. In addition, there was no elevation of serum calcium, ACE, 25 hydroxy and 1,25 hydroxy vitamin D in our patient. To our knowledge, neither elevation of IgG4 antibodies nor $IgG4^+$ plasma cells in biopsies of patients with sarcoidosis have been described though elevated IgG4 levels may occur in other diseases and even in the normal population [18].

Interestingly, so called 'myositis-specific' Mi-2, and 'myositis-associated' PM-Scl75 antibodies were found in our patient's blood [19]. However, there were no signs of skin alteration or pulmonary fibrosis that can be present in classic IIM, and since the morphological picture did not fit diagnostic criteria for IIMs but featured abundance of $IgG4^+$ plasma cells and elevated levels of IgG4 were detected in our patient's peripheral blood, we evaluated Mi-2 and PM-Scl75 as false positive. Actually, after repeated autoantibody testing in a different laboratory, both autoantibodies were absent. In addition, it has been shown that lineblot assays are less sensitive than RNA immunoprecipitation tests or immunoblots [20]. In conclusion, we propose to include myositis with typical IgG4RD associated features into the group of IgG4RD, thereby enlarging their nosological spectrum and suggest recognition of a new entity, provided that other patients will be reported with similar clinical and morphological features as described here: IgG-4 related myositis.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2018.11.009.

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