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Scientific Correspondence

Morphological characteristics of the transition from juvenile to adult dermatomyositis

We report a 44-year-old male patient suffering from a 40-year course of relapsing dermatomyositis (DM) with onset in infancy. DM is an inflammatory disorder of the skeletal muscle and skin, with occasional involvement of joints and lung that occurs in adults and children. In most juvenile patients, their disease does not persist into adulthood. Patients with DM typically present with subacute, symmetric proximal weakness [1]. Skin manifestations, such as Gottron's papules, facial and periungual erythema and heliotrope rash are common [1]. More rarely, DM can occur before the age of 16 years, then termed juvenile dermatomyositis (jDM) [2]. Nonetheless, DM is the prevailing form of inflammatory myopathies in children [3]. Whereas muscle-related symptoms of jDM are similar to those of adult (a)DM, association with malignancy (especially in association with anti-TIF-1γ antibodies) is limited to anecdotal reports in jDM [2,4,5]. Conversely, some symptoms are considered more typical for jDM, such as calcinosis and intestinal involvement [2], both of which are related to the presumed pathophysiological paradigm of a microangiopathy. The 'hypoxic' pattern is a consequence of the presumed vasculopathy, which goes along with severe muscle weakness, symptoms affecting the gastrointestinal tract (e.g. bleeding) and a poorer prognosis necessitating aggressive treatment [6-10]. In addition to hypoxia-related pathomechanisms, we have highlighted the relevance of type I interferon-related gene expression in aDM and jDM showing that there are indeed clear differences between both age groups [11]. Despite distinct, yet overlapping clinical and morphological features, DM is a heterogeneous disease [4]. Thus, determination of different myositis-specific antibodies should be performed when classifying DM [4].

DM harbours a relatively high disease-related mortality (>10%), mostly due to associated malignancy and interstitial lung disease [12]. In a longitudinal study, long-term follow-up after at least 2 years revealed that one quarter of patients with DM showed severe muscle weakness or were significantly disabled [12]. Whereas the course of aDM is mostly continuous or polycyclic, and patients with jDM are more likely to exhibit a monocyclic course of disease [12]. Most children with jDM showed complete remission or exhibited only minimal physical impairment after a long period of follow-up (up to 29 years) [3]. Nevertheless, the transition of adolescents with jDM and their long-term course into adulthood has not been well described [3], especially as to how this relates to the histopathological features.

The patient initially developed muscle weakness and skin symptoms at 4 years of age at a different centre. He was successfully treated with corticosteroids for an unknown period and remained free of symptoms and any medication until adulthood. His first relapse occurred at the age of 25 years with proximal muscle weakness in both upper and lower extremities, followed by a flare of his skin changes, and responded well to corticosteroids. His condition worsened after the age of 30 years, but no medical advice was sought. At age 44, the patient was admitted to a local hospital due to progressive dysphagia, proximal and distal muscle weakness and elevated creatine kinase (CK) levels (499 U/L), and a relapse of DM was considered. He had suffered a substantial involuntary weight loss of 30 kg in 10 years and this was thought to be linked to progression of disease, as alternative causes were excluded. Treatment with corticosteroids and azathioprine was partially effective for his dysphagia. His symptoms progressed with gait difficulties, head drop, cutaneous ulcerations, pain, swelling and erythema of his lower legs and photosensitivity. Clinical examination revealed Gottron's papules, severe digital ulceration and subcutaneous calcification of the gluteal and tibial region (Figure S1). There was mild muscle weakness of his upper arms, intrinsic finger muscles (but not long finger flexors), hip flexors and extensors (Figure S1).

Neither monoclonal gammopathy nor any myositis-specific autoantibodies (EUROLINE autoimmune inflammatory myopathies 16 Ag; (Euroimmun, Lübeck, Germany) were detectable. Muscle biopsy showed markedly increased variability in fibre diameter with

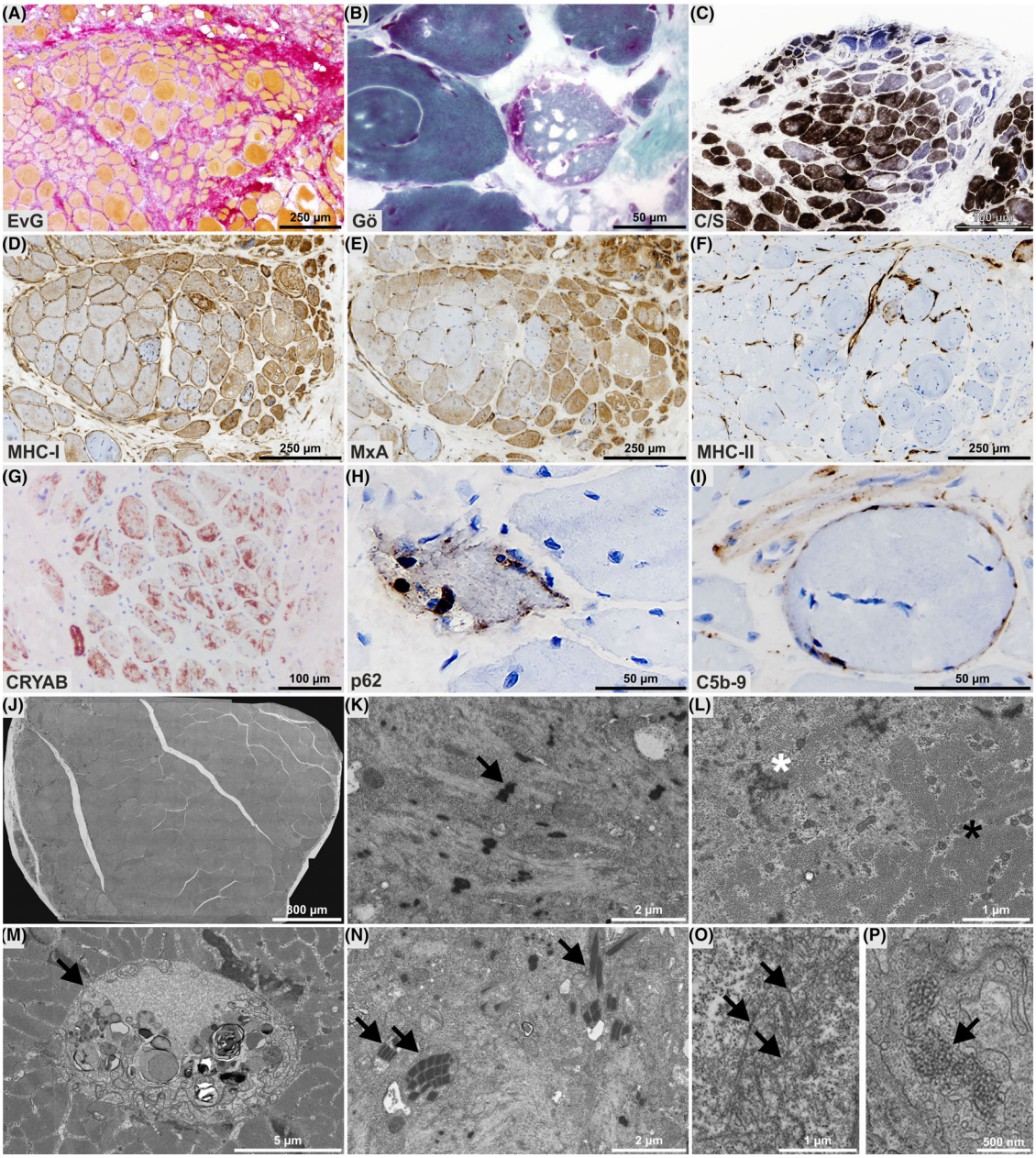

Figure 1. Histopathological (A-I) and ultrastructural (J-P) features observed in the muscle biopsy of our patient. (A) Abundant endomysial and perimysial fibrosis as shown in the Elastic-van-Gieson (EvG) stain; note the perifascicular atrophy. Ragged red fibre in the Gömöri trichrome (Gö) stain (B) and multiple COX-negative/SDH-positive (C/S) fibres – mostly in perifascicular areas (C) indicating mitochondrial damage. Immunohistochemistry showed sarcolemmal and sarcoplasmic staining of major histocompatibility complex (MHC) class I (D) and myxovirus resistance protein A (MxA; E) with perifascicular enhancement, but no sarcolemmal staining of MHC class II (F). Irregular sarcoplasmic staining of alpha-B-crystallin (CRYAB; G). Individual fibres show p62-positive squiggly accumulations (H). Focal C5b-9 complement deposition on the sarcolemma as well as a mild deposit on capillaries (I). An entire ultrathin section (J) was imaged by large-scale digitization (nanotomy) using a field-emission scanning electron microscope, equipped with a scanning transmission electron microscopy detector [21] at a pixel size of 7.3 nm. This technique provided an unbiased, complete and reproducible analysis. The data set (with dimensions of about 220.000 x 160.000 pixels) for internet browser-based pan & zoom can be freely accessed via (http://www.nanotomy.org/OA/index.html). K-P; detail views of the same data set (digitally magnified) as in J, showing alterations of muscle filaments such as I-Z-I bands (K; arrow), regular (black asterisk) and disrupted (white asterisk) sarcomeric structures (L), vacuoles containing debris (M; arrow), enlarged mitochondria with paracrystalline inclusions (N; arrows), sarcoplasmic tubulofilaments (O; arrows) and tubuloreticular inclusions in endothelial cells (P; arrow)

perifascicular atrophy, abundant endomysial fibrosis, internalized myonuclei and numerous cytoplasmatic bodies (Figure 1). Violaceous fibres in perifascicular regions and some ragged red fibres were present on Gömöri staining. NADH-TR reaction revealed sarcoplasmic irregularities and whorled fibres, and there was bluish hue of pale perifascicular fibres in COX-SDH stains. Immunohistochemistry showed upregulation of major histocompatibility complex (MHC) class I and myxovirus resistance protein A (MxA), with a typical increasing gradient towards the perifascicular region, and capillary deposition of membrane attack complex. Lymphocytes and macrophages were sparse and seen mostly in perimysial or perivascular areas. The lymphocytes were PD-1-positive but did not stain for CD57 and KLRG1 antigens (Figure S2). Single fibres harboured p62-positive coarse sarcoplasmic inclusions, and some fibres showed abnormal accumulation of alpha-B-crystallin.

Electron microscopy demonstrated numerous sarcoplasmic abnormalities, such as vacuoles with debris, enlarged mitochondria with paracrystalline inclusions, rod-like Z-band material, tubulofilaments and endothelial tubuloreticular inclusions (Figure 1; and http://www.nanotomy.org/OA/index.html).

Hence, the biopsy showed typical features of DM, such as perifascicular atrophy with intense MHC class I and MxA immunostaining, capillary dropout, perifascicular bluish hue/pale fibres in COX/SDH reactions and endothelial tubuloreticular inclusions. However, unusual features, such as coarse p62-positive inclusions, X-fibres, that is inconspicuous muscle fibres containing alpha-B-crystallin, tubulofilaments and rimmed vacuoles (pathognomonic features of inclusion body myositis (IBM)), were also present, which are not characteristic of DM [13,14]. Of note, several other conditions featuring inclusions and vacuoles may be important to consider in general and therefore, we also considered a hereditary or a toxic cause, such as chloroquine treatment, certain protein aggregate myopathies or distal myopathies. We did not find any immunosenescent $CD57^+$ or $KLRG1^+$ lymphocytes, which would have been typical in IBM [15]. Clinically, the differential diagnosis of IBM was discussed, as the patient had weakness of intrinsic finger muscles and severe dysphagia, but was discarded due to typical clinical signs of DM and the initial onset of disease in his youth [1]. Corticosteroid treatment improved swallowing. Azathioprine was continued, and intravenous immunoglobulin (IVIG; 2 g/kg) was added. Unfortunately, we do not know whether IVIG infusions were repeated nor whether the patient had any benefit from this treatment.

Three previous patients with jDM have been described who developed clinical and pathological features of IBM after years without progression [16]. Adult patients suffering from DM and showing morphological features of IBM have exceptionally been reported [17,18]. The characteristic morphological features in both aDM and jDM skeletal muscle include perifascicular atrophy with positive MHC class I and MxA immunostaining, showing a perifascicular to centrofascicular gradient, capillary dropout and presence of tubuloreticular inclusions in capillary endothelial cells, as seen by electron microscopy [4,19,20]. Furthermore, endo- and perimysial or perivascular infiltration by mononuclear cells and sometimes, punched-out vacuoles within muscle fibres can be detected [4,13].

Here, we present a patient who had unequivocal jDM in his youth with a protracted course, relapses during adulthood, and who now presents clinical as well as morphological signs of DM and IBM. This course and its features raise the question of the specificity of certain features, such as sarcomeric disintegration with rod-like structures and tubulofilaments, mitochondrial abnormalities and rimmed vacuoles at advanced stages of myositis, which are usually considered degenerative processes in IBM. Our knowledge about the morphology at advanced stages of myositis is very limited, due to the general habit of taking skeletal muscle biopsies early in diagnostic workup of (sub-)acute forms of myositis. Indeed, there is also a lack of knowledge regarding the presence and relevance of autoantibodies, and it may well be that there is a currently undetermined myositis-specific autoantibody, associated with transition of a juvenile form of DM into adulthood.

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Author contributions

CD designed the study, performed experiments and drafted the manuscript. BE and AU designed the study and drafted the manuscript. WS and H-HG designed the study, read the samples and drafted the manuscript. MK and US performed clinical workup and drafted the manuscript.

Ethics statement

The study was approved by the institutional ethics review board of the Charité (EA2/107/14) and was undertaken in accordance with the declaration of Helsinki.

Conflict of interest

The authors in this article have no conflict of interest to disclose. The Editors of Neuropathology and Applied Neurobiology are committed to peer-review integrity and upholding the highest standards of review. As such, this article was peer-reviewed by independent, anonymous expert referees and the authors (including WS) had no role in either the editorial decision or the handling of the paper.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Clinical features of the patient. A) Ulcers and erythema at the fingertips and atrophy of the thenar and hypothenar muscles. B) Severe erythema of the lower legs and swelling of the forefoot.
Figure S2. Lymphocytes expressing PD-1 (A) labelling these cells as antigen experienced, while they are not immunosenescent being negative for KLRG1 (B) and CD57 (C).

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