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"Amyopathic" MDA5-positive dermatomyositis with severe lung involvement presenting with net myositic morphological features - insights from an autopsy study

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ABSTRACT

Anti-MDA5-positive dermatomyositis (MDA5-DM) often presents with extramuscular, especially pulmonary and skin manifestations, and apparent clinical signs of frank myositis can be missing (so called amyopathic DM). We hereby present two male patients who died from respiratory failure during the course of MDA5-DM. While overt signs of myositis or any skin involvement were absent at admission to hospital we noticed conspicuous inflammatory alterations in various skeletal muscles morphologically, showing different degrees of affection. Furthermore, pathological changes of the lungs compatible with rapid progressive interstitial lung disease and characteristic cutaneous vasculoocclusive features were identified at autopsy. This observation shows that muscles and skin are subclinically affected in a widespread fashion, hence subtle signs of muscle involvement should be sought after in anti-MDA5-positive patients with predominant lung affection to ensure adequate treatment.

1. Introduction

Dermatomyositis (DM) can be associated with antibodies against the helicase MDA5 (anti-melanoma differentiation-associated gene 5) [1]. The physiological role of the pattern recognition receptor MDA5 is the identification of viral RNA and subsequent induction of type I interferon signalling [2].

A salient feature of anti-MDA5 antibody positive dermatomyositis (MDA5-DM) is the relatively frequent association with interstitial lung disease (ILD), with a rapid progressive course (RP-ILD) [1,3,4] while muscle symptoms may be strikingly mild, hence the term clinically amyopathic DM (CADM) had been created [5]. By definition, patients suffering from CADM exhibit cutaneous alterations such as ischemic necrosis of digits, Gottron's papules, heliotrope rash, without or with minimal subclinical muscle pathology, but without overt muscle weakness [3]. In addition to the skin changes of "classical" DM, a unique skin phenotype consisting of tender palmar papules with fibrinoid vasculopathy and perivascular inflammation has been described in MDA5-DM as well as more severe vasculopathy in general, including cutaneous ulceration [6]. Affection of joints can be a feature of MDA5-DM [6,7]. A study identified three different subgroups in MDA5-DM: Patients with RP-ILD show the highest mortality rate, those with skin vasculopathy and clinical myositis exhibit an intermediate prognosis and sole dermato-rheumatologic symptoms were associated with the best outcome [4].

Histological hallmarks of "classic" DM include perifascicular muscle fibre atrophy (PFA) with diffuse MHC class I expression, accentuated in perifascicular atrophic fibres, and accompanied by perivascular and perimysial inflammatory infiltrates [5,8]. Sarcoplasmic expression of myxovirus resistance protein A (MxA) is a sensitive and specific marker for DM, even with absent PFA, although expression varies between different autoantibodies [9].

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Table 1
Antibodies used for immunohistochemistry in this study.

Antibody	Clone	Supplier
anti-CD3	Rabbit, polyclonal	Dako
anti-CD8	mouse, clone C8/144B	Dako
anti-CD31	mouse, clone JC70A	Dako
anti-CD45	mouse, clone UCHL1	Dako
anti-CD56	mouse, clone ERIC-1	Serotec
anti-CD68	mouse, clone EBM11	Dako
anti-C5b-9	mouse, clone aE11	Dako
anti-MHC class I	mouse, clone W6/32	Dako
anti-MHC class II	mouse, clone C3/43	Dako
anti-MyHC fast	mouse, clone WB-MHCf	Novocastra
anti-MyHC slow	mouse, clone WB-MHCs	Novocastra
anti-MxA	mouse, clone M143	Millipore
anti-HSP70	mouse, clone 6535	abcam
anti-SIGLEC-1	mouse, clone HSn7D2	Novus Biologicals

Histopathological alterations of ILD associated with CADM include idiopathic nonspecific or usual interstitial pneumonia and diffuse alveolar damage (DAI) [10].

The features of cutaneous lesions in DM comprise interface dermatitis with lymphocytic infiltration, dyskeratosis, mucin deposition, endothelial injury (with C5b-9 deposition), vascular ectasia and vascular fibrin deposition [11].

This study aimed to systematically analyse histopathological findings of different organ systems in the light of clinical findings in two deceased patients with MDA5-DM with fatal RP-ILD.

2. Materials and methods

2.1. Patients and samples

We studied two patients who underwent clinical autopsy at Charité University Medicine, Berlin, Germany, due to death from severe RP-ILD with confirmed positivity for anti-MDA5 autoantibodies.

Tissue from various skeletal muscles, heart, lung and skin was harvested during autopsy. Brain autopsy was performed upon fixation of the whole brain for at least two weeks in 4 % paraformaldehyde. Informed consent was obtained from both patients' relatives and ethical approval was granted by the Charité ethics committee (EA2/163/17).

2.2. Histologic procedures

Fresh muscle tissue was immediately frozen in 2-Methylbutane cooled in liquid nitrogen. The following stains were performed on cryostat sections (7 µm) according to standard procedures: haematoxylin and eosin (H&E), modified Gömöri trichrome (Gö), Elastica-van-Gieson, periodic acid-Schiff, Oil-Red-O and Congo red. Enzyme histochemistry included non-specific esterase, acid phosphatase, nicotinamide adenine dinucleotide dehydrogenase-tetrazolium reductase (NADH-TR), succinate dehydrogenase (SDH), cytochrome c oxidase (COX), myophosphorylase, myoadenylate deaminase (MADA) and ATPase at pH 4.3, 4.6 and 9.4. Brain, skin and lung tissue was fixed in 4% paraformaldehyde, embedded in paraffin and stained with H&E. Immunohistochemistry was performed on an automated staining system (BenchMark XT, Ventana Medical Systems), see Table 1 for used antibodies. Histological slides were assessed independently (BE, MTH, WS). All stains were performed including appropriate positive and negative controls as a standard procedure.

2.3. Transmission electron microscopy

For ultrastructural analysis fresh tissue was fixed in 2.5 % glutaraldehyde (4 °C, 48 h), post-fixed in osmium tetroxide and embedded in araldite®. Ultrathin sections were stained with lead citrate and uranyl acetate, and transmission electron microscopy was performed on an EM 902 (Zeiss). A total of 100 capillaries were studied per case.

3. Results

3.1. Clinical and laboratory findings

Patient 1 (male, 42 years old) presented to the hospital with ILD of unknown origin. He reported fatigue, cough and painful swelling of his hands for weeks. No skin symptoms were noticed. Serum creatine kinase (CK) level was mildly elevated (432 U/l). Soluble IL2 receptor was markedly elevated (3588 U/l, normal value: <710 U/l). CD169 expression/monocytes (flow cytometry) were significantly elevated as a sign of active type I interferon activity [12]. A muscle biopsy previously performed in a different hospital (without further details of the biopsy site or performed immunohistochemical studies available) did not show signs of myositis, a first myositis autoantibody blot-test showed no positive results. Despite anti-inflammatory treatment with etoricoxib and prednisolone, the patient developed lung failure and required artificial ventilation. The respiratory situation improved under nitric oxide-ventilation and volume depletion. A pneumonia was treated antibiotically with meropenem and vancomycin. Because of a positive testing for anti-MDA5 autoantibodies in the repeated immunoserological diagnostic (EUROLINE Autoimmune Inflammatory Myopathies 16 Ag Profile; Euroimmune), an immunosuppressive therapy with cyclosporine, tofactinib and cyclophosphamide was initiated. Other autoantibodies were not detected by a line blot assay. The patient died from methicillin-resistant *Staphylococcus aureus* sepsis with multi organ failure. Clinical autopsy confirmed acute respiratory distress syndrome (ARDS) with respiratory insufficiency as primary cause of death.

Patient 2 (male, 30 years old) attended the emergency unit because of dyspnoea and thoracic pain and received antibiotic and later on antimycotic treatment due to pneumonia caused by *Aspergillus fumigatus*. No muscle biopsy was performed during admission. Intubation was required nine days after admittance to the hospital. A veno-venous ECMO-system was installed. Furthermore, a spontaneous pneumomediastinum occurred. CK was mildly elevated (432 U/l). A strongly positive test for anti-MDA5 antibodies (Euroimmune, see above) and the presence of Gottron's papules led to the diagnosis of MDA5-DM. Other autoantibodies were not detected by lineblot essay. CD169 expressing monocytes were significantly elevated (flow cytometry). An immunosuppressive therapy (prednisolone, intravenous immunoglobulin, cyclosporine, cyclophosphamide and tofactinib) was initiated. Eight and a half weeks after the initial presentation at the hospital, the patient developed diffuse pulmonary haemorrhage. The patient passed away in septic shock. Respiratory failure due to lung fibrosis was the assigned cause of death at autopsy. Bronchopneumonia was confirmed histologically.

Noteworthy, the patient complained about arthralgia in his finger- and toe joints a year prior to his death. Approximately eight months antemortem, a skin rash of the face and joints, suspicious of psoriasis had occurred. Also, progressive dyspnoea assigned as post-infectious was noticed. Retrospectively, all these findings are highly suspicious as early signs of amyopathic MDA5-DM.

Table 2
Histological findings of various muscle biopsies of patient 2.

Muscle	PFA	MHC class I	C5b-9	MxA	Lymphocytes	Macrophages
Diaphragm	absent	occasional sarcolemmal	sarcolemmal	sl –Mp+	sparse	moderate
M. iliopsoas	focal	focal sarcolemmal and sarcoplasmic	sarcolemmal	sl –Mp+	sparse	moderate
M. gastrocnemius	focal	diffuse sarcoplasmic	sarcolemmal	sl –Mp+	sparse	moderate
M. deltoideus	yes	Sarcolemmal and sarcoplasmic, peri– to centrofascicular gradient	sarcolemmal	sl –Mp+	sparse	moderate
M. biceps brachii	yes	sarcoplasmic, peri– to centrofascicular gradient	sarcolemmal	sl –Mp+	very sparse	moderate
M. vastus lateralis	no, more diffuse atrophy	absent	sarcolemmal	sl –Mp+	sparse	moderate

PFA= perifascicular atrophy.
Sl= sarcolemma.
Mp= macrophages.

3.2. Histological findings

Skeletal muscle:

Patient 1: The muscle autopsy results (left deltoid and left vastus lateralis muscle) showed a very mild fibre size variability. In some fascicles few atrophic fibres were present in the perifascicular areas. Some fibres harboured internalized myonuclei. A sparse CD8+/CD45+ lymphocytic infiltrate occurred in the perimysium and perivascular regions, but no invasion of muscle fibres was present. CD68+ macrophages were found relatively sparsely in the peri– and to a lesser extent the endomysium. Some perifascicular fibres showed a COX-pallor, but no clear COX-negative and SDH-positive muscle fibres were found (not shown). Some fibres showed a sarcolemmal staining of MAC (C5b-9) with a perifascicular pattern gradient, as did endomysial capillaries. Major histocompatibility complex (MHC) class I expression was seen on the sarcolemma and sarcoplasm, with a perifascicular to centrofascicular gradient. MHC class II immunohistochemistry was negative on the sarcolemma and the sarcoplasm while physiologically positive on capillaries. Myofibres were MxA- and HSP70-negative, single macrophages were MxA-positive, while many macrophages with perifascicular predominance were SIGLEC-1 (Sialoadhesin, CD169)-positive.

Patient 2:

Skeletal muscles from various regions were analysed (Table 2). In addition to inflammatory changes, we found nuclear clumps in the gastrocnemius, deltoid and pectoralis muscle with signs of neurogenic muscle damage with fibre grouping in the M. gastrocnemius by MyHC fast and -slow immunohistochemistry, attributable to a neurogenic process by critical illness neuropathy. A sarcolemmal deposition of MAC was seen in perifascicular fibres of deltoid, gastrocnemius and iliopsoas muscles. MHC class II was exclusively expressed on capillaries, physiologically. MxA and HSP70 were not detectable on myofibres but were positive in dendritic cells and macrophages in the perifascicular region and epimysium. SIGLEC-1 was strongly expressed in peri– and endomysial macrophages and dendritic cells with perifascicular predominance (see Fig. 1)

In both patients, no vacuoles, overt endomysial fibrosis, congophilic deposits or sarcolemmal lipid accumulation in muscle fibres were present. Glycogen distribution was normal.

Myocardium (patient 1 and 2): Significant inflammatory alterations were absent, fibre diameter and structure of muscle cells were without pathological findings (not shown).

Lung (both patients): A massive interstitial and alveolar oedema, hyaline membranes and intraluminal fibrinoid deposits as signs of DAI and compatible with the histological picture of ARDS [13] were present in both patients (representatively shown in patient 2; Fig. 1A). Furthermore, we found an infiltration by macrophages and neutrophilic granulocytes in an abscess-like formation in patient 2.

Skin (patient 2): The skin showed fibrinoid deposits in dermal vessels representative of thrombogenic vasculopathy (Fig. 1B). A perivascular, sparse lymphocytic infiltrate (CD8+, CD45+) but no ulcerations or signs of fibrinoid necrosis / frank vasculitis was noted. There were no overt MAC deposits. SIGLEC-1 expression was present in subepidermal and singular epidermal mononuclear cells. Platelet endothelial cell adhesion molecule (PECAM1, CD31) was found on endothelial and some mononuclear cells (not shown).

Brain (both patients): A mild oedema attributable to blood congestion during the terminal phase but no signs of inflammation were detected.

3.3. Ultrastructural findings

Transmission electron microscopy showed absence of tubuloreticular inclusions in endothelial cells of both patients. Signs of critical illness myopathy (loss of myosin) were noted in the leg muscles of patient 1 and 2.

4. Discussion

Here we illustrate autopsy studies of two young men, who both died of catastrophic lung disease in the context of serological ‘MDA5-positivity’. Both patients did not show any overt muscle symptoms until hospitalisation, and skin symptoms were insignificant, apart from mild Gottron’s papules in one of them. However, our study reveals characteristic signs of muscle inflammation by histopathological analysis, occuring clinically ‘silent’ in the presence of signs of DAI, a typical pathology of ILD in MDA5-DM [10,14]. Similarly, and although prominent skin symptoms with ulcers or necrosis were not macroscopically present, patient 2 had cutaneous thromboocclusive pathological alterations with fibrinoid vascular deposits.

Clinically, anti-synthetase syndrome (ASyS) has to be considered as a differential diagnosis of anti-MDA5-DM with ILD and ulcerative lesions on hands and feet [7]. ASyS in contrast to MDA5-DM does not show MxA on muscle fibres [9,15,16]. Morphologically, ASyS is characterised by perifascicular myofibre necrosis [8]. Another valuable marker to distinguish between ASyS and classical DM is the strong myofibrillar, perifascicular expression of MHC class II present in ASyS, which is absent from myofibres in MDA5-DM [17].

Allenbach et al. [4] describe a combination with skin sclerosis in 9.6% in their cohort of anti MDA5-DM patients, with skin sclerosis particularly present in the vasculopathic cluster (22.7%). The histopathological diagnosis of myopathy in systemic sclerosis (SSc) is indeed difficult, given the heterogeneous histological picture and lack of specific diagnostic criteria [18,19]. Capillary deposition of MAC and sarcolemmal MHC class I expression can be found in SSc as well, however, most muscle biopsies in SSc display conspicuous endo- and perimysial fibrosis [18,19] absent in our

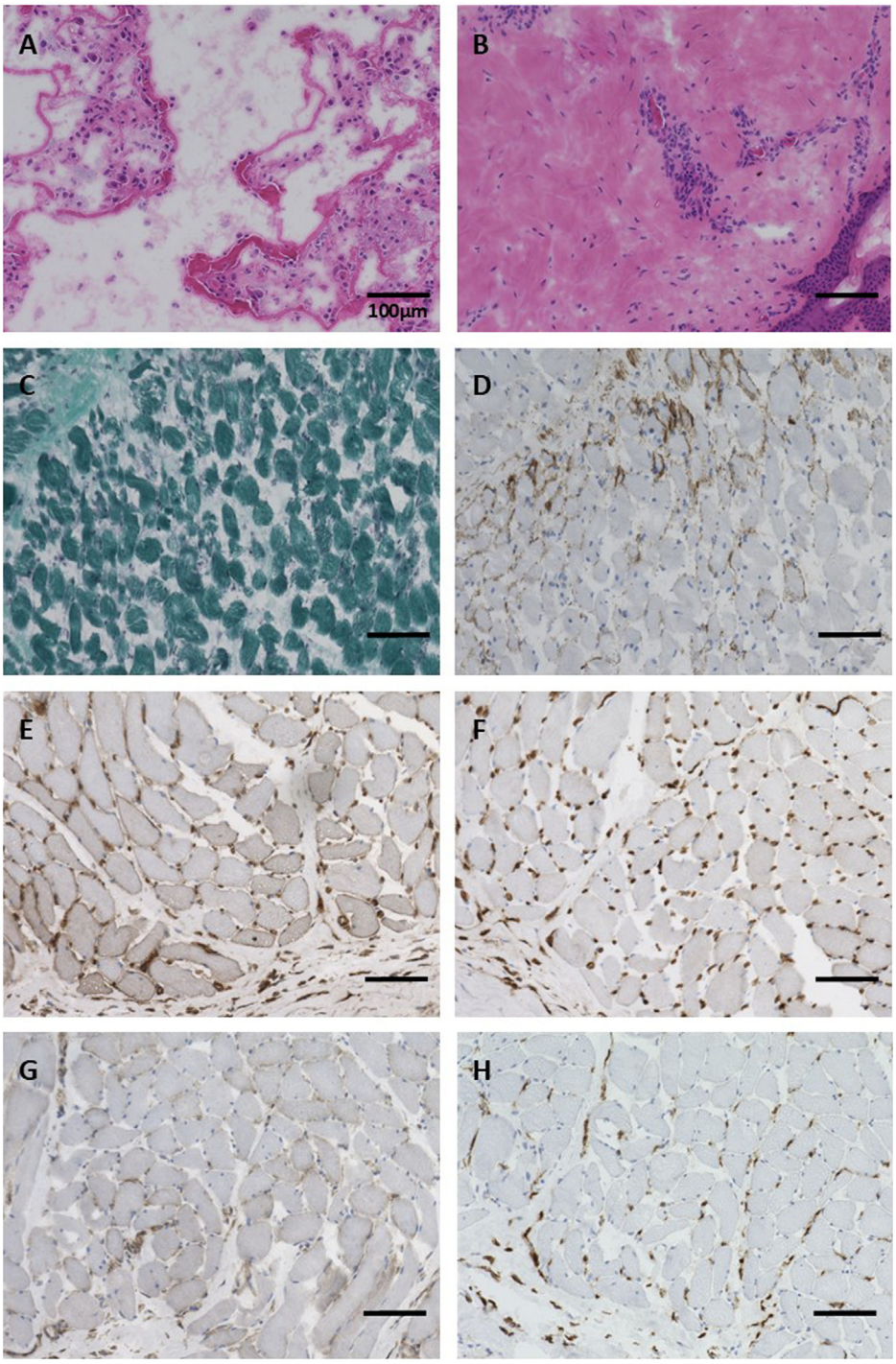

Fig. 1. Pulmonary, dermal and skeletal muscle pathology in MDA5-dermatomyositis
Representative photomicrographs of the histopathological findings of patient 2.
A: Pulmonary hyaline membranes in terminally altered interstitial lung disease (HE).
B: Occluded skin vessels (capillaries) representing vasculopathy (HE).
C: Severely altered and partially atrophic perifascicular fibres in skeletal muscle tissue (deltoid muscle) (modified Gömöri trichrome).
D: Sarcolemmal complement deposition predominantly detectable on perifascicular myofibres (C5b-9).
E: Sarcolemmal MHC class I staining on perifascicular myofibres (MHC I).
F: Absence of sarcolemmal MHC class II staining on myofibres (MHC II).
G: Presence of scarce MxA-positive macrophages predominantly detectable in the endomysium of perifascicular regions (MxA).
H: Presence of Siglec1-positive macrophages especially in the endomysium of perifascicular regions (Siglec1).
All slides showing original magnifications x200 (scale bar 100 μm).

samples. MxA staining is absent on sarcoplasm and on capillaries in scleromyositis with minimal inflammation [20]. Characteristic alterations of endomysial capillaries with basement membrane thickening in multiple layers as feature of SSc [18–20] were not visible in the muscle biopsies of the two cases presented herein.

The absence of hypoxic-necrotic muscle fibres in our samples supports the theory that PFA is at least not fully attributable to hypoxia, but to some extent due to disturbed type I interferon levels [21], which we identified in our muscle biopsies, despite 'myopathy' not being clinically overt. We additionally highlighted the presence of numerous SIGLEC1+ macrophages in the perifascicular areas and in the perimysium as well as in the epimysium, where the macrophages were also MxA-positive, a characteristic signature of increased interferon I activity in active DM [12]. We found MAC deposition on the sarcolemma but not prominently on endomysial capillaries. Combined with the MxA positivity on capillaries we underscore relevance of type I interferon-induced vasculopathy in our patients who had died of catastrophic ILD with MDA5-positivity. Allenbach and co-workers [4] have identified that 1/3 of their anti-MDA5+ cohort had this pattern of severe, clinically leading lung disease. The clinical course of the two patients described above with RP-ILD requiring intensive care treatment and early mortality relates to their first ("RP-ILD") cluster [4]. However, they describe a combination with certain skin symptoms, which we had not seen in patient 1. Patient 2 showed Gottron's papules on clinical examination and reported a skin rash approximately eight month antemortem, other common skin manifestations as reported by Allenbach [4] such as mechanic's hands, skin ulcers or necrosis were not noticed. Proximal muscle weakness was not apparent in both patients, with only mildly elevated CK levels. Increased CK levels were found in 2/3 of RP-ILD cluster patients in the study by Allenbach [4]. Of note, medical history taking and clinical examination might have been impaired by the patient's frailty. Dyspnoea and RP-ILD as present in our patients occurred in 100% of the patients in the first cluster [4]. Arthritis or arthralgia were described by Allenbach [4] in 26.7% of cluster one patients. Patient 1 initially presented with swollen hands, patient 2 had reported arthralgia in his finger and toe joints, about one year prior to death.

Uruha et al. [9] showed MxA expression in 50% of muscle biopsies from anti-MDA5 positive patients, compared to 83% in non MDA5-DM. A scattered pattern of MxA distribution was noted exclusively in muscle biopsies of MDA5-DM (30% of patients), whereas a perifascicular pattern was absent. However, the antibodies used by Uruha et al. differ between their study and the one presented here, thus we cannot exclude that the absent sarcolemmal MxA expression might, at least partially be due to these differences.

The absence of tubuloreticular inclusions at ultrastructural level does not contradict the diagnosis of MDA5-DM, since these are only present in around 50% of MDA5-DM cases [5].

The histological evaluation of the lung of both patients showed alterations compatible with the acute/exsudative phase of DAI [13]. In addition, acute inflammatory infiltrates were present in one patient.

We did not find any structural or inflammatory changes in the myocardium.

Interestingly, patient 2 presented initially with suspected psoriasis. Psoriatic lesions may resemble Gottron signs and therefore, especially in absence of muscular symptoms, may be misdiagnosed [22]. The initial arthralgia and later described dyspnoea combined with psoriatic-like lesions should draw attention to the differential diagnosis of MDA5-DM with ILD. Furthermore, before definitive diagnosis of MDA5-DM, patient 2 suffered from spontaneous pneumomediastinum, a rare but prognostically unfavourable complication of MDA5-DM [23].

5. Conclusion

Given the histological myositis pattern in two patients with a fatal course of MDA5-DM who, at the time of admission to the hospital, did not present with overt muscle weakness and none or subtle skin changes, we want to highlight the fact that inflammatory myopathy can antecede or occur independently of clinically apparent muscle weakness as well as that dermal vasculopathy can occur without apparent necrosis or ulceration. Even in these inflammatory, clinically not affected muscles, interferon type I seems to play an important role. Those findings may be of relevance for potential Jak-STAT inhibition.

Declaration of competing interest

Benjamin Englert does not disclose any conflict of interest
Carsten Dittmayer does not disclose any conflict of interest
Hans-Hilmar Goebel does not disclose any conflict of interest
Udo Schneider does not disclose any conflict of interest
Marie-Therese Holzer does not disclose any conflict of interest
Akinori Uruha does not disclose any conflict of interest
Werner Stenzel does not disclose any conflict of interest

CRediT authorship contribution statement

Benjamin Englert: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Carsten Dittmayer:** Conceptualization, Investigation, Visualization. **Hans-Hilmar Goebel:** Conceptualization, Investigation, Supervision, Writing – original draft. **Udo Schneider:** Investigation. **Marie-Therese Holzer:** Investigation, Visualization, Writing – original draft. **Akinori Uruha:** Conceptualization, Investigation, Supervision, Writing – original draft. **Werner Stenzel:** Conceptualization, Investigation, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing.

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