Available online at www.sciencedirect.com
ScienceDirect
Pathology – Research and Practice 204 (2008) 609–623
PATHOLOGY RESEARCH AND PRACTICE
www.elsevier.de/prp

DIAGNOSTIC SEMINAR

Myopathology of non-infectious inflammatory myopathies – The current status

Ekkehard Hewer[a,*], Hans H. Goebel[a,b]

[a]*Institute of Neuropathology, University Hospital Zurich, Zurich, Switzerland*
[b]*Department of Neuropathology, Johannes Gutenberg University, Mainz, Germany*

Received 18 November 2007; accepted 4 March 2008

Abstract

Besides the classical inflammatory myopathies (IM), dermatomyositis (DM), polymyositis, and inclusion body myositis, the much larger spectrum of IM includes focal and nodular myositis, granulomatous myositis, macrophagic myofasciitis, graft vs. host myositis, eosinophilic myositis, and other immune-associated conditions, some of them only recently described. In addition, paraneoplastic, statin-induced and critical illness myopathies have been considered immune-associated IM. Infectious, i.e., bacterial, viral, and parasitic IM are much less frequent in the northern hemisphere. In IM, muscle biopsy is an essential diagnostic procedure to initiate therapy. The myopathological spectrum encompasses disease-specific histopathological features, such as perifascicular atrophy in DM, non-necrotizing granulomas in sarcoid myopathy, autophagic vacuoles with tubulofilamentous inclusions in inclusion body myositis, rarely electron microscopic criteria, such as undulating tubules in endothelial cells of DM specimens, and, foremost, immunohistochemical findings. These latter features concern inflammatory infiltrates, the muscle parenchyma, the interstitial compartment, and the vasculature with varying involvement of each component in the different IM. Differences in immunohistochemical parameters among the IM, such as major histocompatibility complexes I and II, cytokines, cell adhesion molecules, different types of inflammatory cells, metalloproteinases, and complement factors procure a large gamut of data, the individual patterns of which characterize the myopathology of individual IM.

Keywords: Inflammatory myopathies; Myopathology; Immunohistochemistry; Polymyositis; Dermatomyositis

Introduction

Inflammatory myopathies (IM) frequently require muscle biopsy as an essential diagnostic procedure to document inflammation as a general myopathological process or to reveal certain IM-specific additional features, such as lymphocytes within intact muscle fibers in polymyositis (PM) and inclusion body myositis (IBM), conspicuous PAS-positive macrophages in macrophagic myofasciitis, rimmed or autophagic vacuoles with tubulofilamentous inclusions and/or intracellular amyloid in IBM, a perifascicular pattern of lesions or undulating tubules in dermatomyositis (DM). IM as a generic group of diseases encompass the entire age spectrum, although with different emphasis of different IM at different ages, e.g. juvenile DM or late-onset IBM. Being grossly divided into infectious and non-infectious (immune-related) conditions, IM do

*Corresponding author. Tel.: +41 44 255 4905; fax: +41 44 255 4402.
E-mail address: ekkehard.hewer@usz.ch (E. Hewer).

0344-0338/$ - see front matter © 2008 Elsevier GmbH. All rights reserved.
doi:10.1016/j.prp.2008.03.006

occur worldwide, although infectious forms are more frequently seen in the developing world as distinct entities. However, infectious IM may certainly be encountered in "developed" countries, probably most often in conjunction with trauma and surgical procedures, but then, muscle biopsy is usually not a diagnostic procedure. Hence, the entire spectrum of myopathological diagnostic parameters and markers for IM yields different patterns during and for diagnostic workup of IM specimens. As it is true for the overwhelming majority of neuromuscular disorders in general, autopsy studies of IM, employing modern diagnostic myopathological techniques, have been and still are rarely performed and, therefore, have provided little information to the diagnostic myopathological regimen, to distributional patterns of individual IM, and have hardly ever been available to corroborate biopsy-based findings. Patients who die of IM may be few because of treatability and curability, whereas patients who die with IM may be many because still a sufficient number of IM are long-lasting chronic diseases. This autopsy-based potential of available muscle tissues has not yet successfully and gainfully been explored, which affords the opportunity for multiple, even abundant sampling of specimens from numerous different muscles to address the frequent diagnostic myopathological problem of focality in IM.

Predicated on the essentiality in the diagnostic regimen of IM of the muscle biopsy, only the armamentarium of modern techniques employed in myopathology may allow a thorough and, perhaps, complete myopathological investigation of the biopsied muscle. Different techniques, e.g. histology, enzyme histochemistry, electron microscopy, and immunohistochemistry have different diagnostic values in different forms of IM, but for each IM-suspected biopsied muscle tissue, adequate preparative conditions have to be provided for a panoply of investigations. This care for subsequent optimal diagnostic investigations of the biopsied muscle tissue commences with choosing the correct muscle for biopsy and continues in the operating room where, upon removal of the biopsied tissue, the proper techniques have immediately to be employed, i.e., freezing of muscle for light microscopic studies and adequate fixation of muscle for electron microscopy, and, perhaps, complementary light microscopic investigations.

While the individual histological, enzyme histochemical, and electron microscopic methods have not been expanded over the past 20 years, the introduction of immunohistochemistry into myopathology has revolutionarily augmented our diagnostic armamentarium and our myopathological knowledge concerning IM. Immunoglobulins, complement factors, cell adhesion molecules, cytokines, chemokines [15], metalloproteinases [20,31], and not the least, major histocompatibility complexes (MHC-) I and II [24] (Tables 1 and 2), subtyping of lymphocytic infiltrates, and recently of macrophage subpopulations (Tables 3–5) have yielded different results in different forms of IM and, thus, accorded different diagnostic connotations to individual IM. Therefore, the impact of immunohistochemistry on diagnostic myopathology in IM will be the major component in this review, whereas myopathologically relevant non-immunohistochemical techniques and findings will precede the subsequent canvassing of individual and groups of IM.

While non-inflammatory neuromuscular diseases largely affect the muscle parenchyma, i.e., the myofibers, sometimes connective tissue, and rarely vessels, IM are

Table 1. Immunohistochemical expression of MHC-I in muscle tissue

On the surface of *myofibers*
Diffusely across *regenerating myofibers*
In *inflammatory infiltrates*
In *vessel walls*

Table 2. Immunohistochemistry of MHC-I expression in neuromuscular diseases

Polymyositis
Dermatomyositis
Inclusion body myositis
Statin myopathy [37]
Duchenne muscular dystrophy [2,56]
Dysferlinopathy [13]
Limb girdle muscular dystrophy

Table 3. Markers of macrophages

CD68	General
KiMIP	General
MRP14, 27E10	Early
MRP8	Intermediate
25F9	Late
Metalloproteinases	

Table 4. Macrophages in myositis

Inflammatory myopathy with abundant macrophages (IMAM)
Macrophagic myofasciitis (MMF)
Granulomatous myositis (esp. sarcoid myopathy)
Whipple disease

Table 5. Different types of macrophages in inflammatory myopathies [5,44]

Type of antibody	PM	DM	IBM	GM	Controls[a]	Controls[b]
KiM1P *Dianova* Pan-type	+	+	+	+	+	+
27E10 *BMA biomedicals* Early/acute	17%[c] *Perimysial:* 35%[d] *Endomysial:* 47%[d]	37%[c] *Perimysial:* 13%[d] *Endomysial:* 25%[d]	24%[c]	6%[c]	+	<10%
MRP14 *BMA biomedicals* Early/acute	14%[c] *Perimysial:* 90%[d] *Endomysial:* 66%[d]	19%[c] *Perimysial:* 15%[d] *Endomysial:* 33%[d]	6%[c]	6%[c]	+	<10%
MRP8 *BMA biomedicals* Intermediate/subacute	21%[c]	26%[c]	31%[c]	15%[c]	Not evaluated	Not present
25F9 *BMA biomedicals* late/chronic	10%[c] *Perimysial:* 18%[d] *Endomysial:* 23%[d]	17%[c] *Perimysial:* 14%[d] *Endomysial:* 24%[d]	7%[c]	47%[c]	Not evaluated	50%

PM: polymyositis; DM: dermatomyositis; IBM: inclusion body myositis; GM: granulomatous myositis.
[a][5] – Neurogenic atrophy and "degenerative" myopathies.
[b][44] – Duchenne muscular dystrophy.
[c][5] – Paraffin sections.
[d][44] – Frozen sections.

marked by involvement of all skeletal muscle constituents, i.e., muscle fibers, vessels of different calibers, i.e., capillaries, arterioles, venules, connective tissue, and as an important additional component, by inflammatory infiltrates of heterogeneous nature. Each of these components may provide typical or atypical patterns of immunohistochemically expressed parameters in different IM. The abundance of applicable antibodies may demonstrate diagnostic overlap in different types of IM, sometimes showing the usefulness of semi-quantitative information [52], the application of "inflammatory scores" [51], or the proportion or ratio of, e.g. T4 to T8 lymphocytes in different IM [53] to better assess the diagnostic value of individual immunohistochemical parameters in the complex myopathology of IM on the diagnostic path to clearly identify the individual IM. Hence, in immunomyopathology of IM, not only expression of antigens and their demonstration by respective antibodies and immunohistochemical patterns in different IM are of importance, but also immunohistochemical profiles of all the individual muscle tissue constituents among the many different IM.

When diagnosing IM by myopathology, three general aspects are of concern: IM with inflammatory infiltrates, IM without inflammatory infiltrates, and non-IM though with inflammatory infiltrates, such as certain muscular dystrophies.

Immune-mediated inflammatory myopathies

Dermatomyositis

The myopathological hallmark of DM (Fig. 1) is the perifascicular pattern of lesions. In a severely affected specimen, the perifascicular pattern may be replaced by a panfascicular pattern, although it may not necessarily be present in each fascicle of the biopsied muscle tissue. Inflammatory infiltrates may be most pronounced in the perimysium extending into the individual muscle fascicles along the endomysium. Peripherally located muscle fibers in the fascicles may undergo necrosis and degeneration, regeneration, or atrophy. Employing more than histological stains, this perifascicular pattern may be recognized by activated acid phosphatase, both in interstitial cells and muscle fibers, by the presence of enzyme histochemically partially or non-reacting "ghost" muscle fibers, and by additional immunohistochemical labeling of infiltrating cells or upregulation of proteins. This pattern implies a vascular background which renders DM a multi-organ disease, not only affecting skeletal muscle and, often, skin but, occasionally, also the gastrointestinal tract and the lungs [14]. However, at the ultrastructural level, damage to endothelial cells of capillaries, their necrosis and subsequent regeneration amounting first to depletion in capillaries, evidenced by numerous vascular markers,

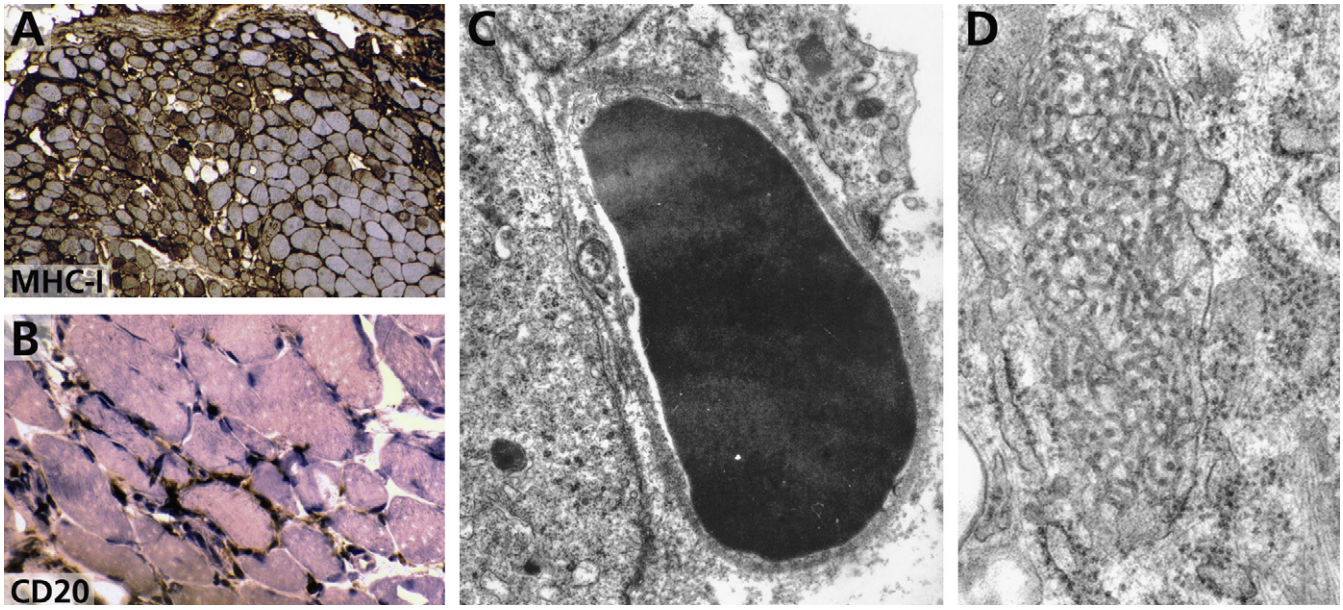

Fig. 1. Dermatomyositis: (A) Perifascicular involvement is marked by infiltration of the endomysium and by regenerating muscle fibers, in contrast to the more centrally located part of the muscle fascicle, with only variation in fiber diameters and sarcolemmal upregulation of MHC-I. (B) B-lymphocytes among muscle fibers of various sizes. (C) Ultrastructurally, a red blood cell is only surrounded by a vascular basement membrane after degeneration of endothelial cells. (D) By electron microscopy, tubuloreticular profiles/undulating tubules may be present in endothelial cells.

then increased angiogenesis [37], is conspicuously encountered by electron microscopy. Another hallmark of DM are tubuloreticular profiles or undulating tubules not only within endothelial cells but also within circulating blood lymphocytes, thus emphasizing the systemic nature of this condition. These undulating tubules may actually precede clinical and major histopathological features [19]. Undulating tubules may also occur in systemic lupus erythematosus, Sjögren syndrome, and human immunodeficiency virus (HIV) infection. Another ultrastructural feature in endothelial and lymphocytic cells of DM is cylindrical confronting cisternae [26]. While capillaries are evenly spread across normal muscle fascicles with approximately one capillary per muscle fiber, the perifascicular lesional pattern cannot exclusively be explained by capillaropathy primarily causing DM.

Apart from labeling mural cells of vessels, foremost endothelial cells and, thereby, recognizing DM on the ground of capillary depletion and renewal, abnormal presence of the chemokine monocyte chemo-attractant protein 1 (MCP1) [15] and the C5b9 complement or membrane attack complex (MAC) in capillary walls denote DM as a microvasculopathy. The density of capillaries within muscle fascicles may immunohistochemically be documented by endothelial markers or vessel-related extracellular matrix proteins, such as laminins or MHC-I, the latter also normally being expressed in vessel walls. Infiltrating lymphocytes largely consist of B-cells and fewer CD4 helper T-lymphocytes. Among subtypes of macrophages, late or mature macrophages marked by the late-activation marker 25F9 seem to prevail [44]. The MHC-I is sarcolemmally expressed, most markedly in the perifascicular area, but may also be encountered across the entire muscle parenchyma. Likewise, MHC-II is upregulated in DM even when inflammatory infiltrates may not be present [24]. Of cytokines interleukin-2, tumor necrosis factors alpha and interferon gamma may be expressed in interstitial cells, especially interleukin 4 [52]. Matrix metalloproteinases (MMP) [42] or metalloproteinases-disintegrins (ADAMS) may variedly be upregulated in inflammatory cells and muscle fibers, i.e., MMP 2, 7, and 9 in the sarcolemma of atrophic fibers [47] and regenerating myofibers [12] or diffusely in small fibers [43].

A DM-like inflammatory myopathy is inflammatory myopathy with abundant macrophages (IMAM). Subtle immunohistochemical differences between DM and IMAM have been outlined [8,9] in that MAC is present in capillaries of DM but absent from IMAM, while macrophages in IMAM express the early inflammation marker MRP-14. Similarities concerning infiltrating cells in both conditions are found in the expression of CD4 and CD8 T-cells and CD20 B-lymphocytes, as well as interleukin-10.

Necrotizing myopathy, associated with serum antibodies against the signal recognition particle (SRP), is also marked by prominent capillary pathology, although in a more uniformly scattered fashion than the more

patchy and perifascicular type in DM [36]. Those conditions show deposition of the MAC/terminal component C5b9 of the complement cascade, which is also seen in another type of necrotizing myopathy marked by so-called "pipestem capillaries" [23]. However, the anti-SRP myopathy hardly, if ever, shows inflammatory infiltrates and a weak, incomplete, and varying pattern of MHC-I expression on muscle fibers [36].

Polymyositis

PM (Fig. 2) is an immune-mediated, often subacute inflammatory myopathy supposedly caused by autoaggressive inflammatory cells which, as a myopathological hallmark, enter and destroy apparently normal muscle fibers. The cause why intact myofibers are attacked is still unknown. Upregulation of MHC-I may even precede infiltration by inflammatory cells to attract cytotoxic T8 lymphocytes and allow their entry into normal-looking muscle fibers. Such upregulation of MHC-I may occur both in clinically affected and non-affected muscles [22], and the same appears to be true for upregulation of MHC-II [22], apparently a prerequisite to bind CD4 helper T-lymphocytes. Inflammatory cells, particularly lymphocytes, among which CD8 lymphocytes are more numerous than CD4 cells, are distributed across the muscle fascicles often surrounding individual muscle fibers of normal appearance, from where their entry into these intact muscle fibers originates. As part of the attack of CD8 lymphocytes to intact muscle fibers, the cytolytic proteins granulysin and perforin are encountered in these cytotoxic lymphocytes [30] as well as MPC-1 [15]. B-lymphocytes are few or absent. Necrosis and regeneration of myofibers associated with variability in size, together with endomysial fibrosis, add to the myopathological pattern of PM, then resulting in a chronic myopathy with or without inflammation which may disappear after successful treatment, while upregulation of MHC-I and II may persist. Among macrophages, early-activation subtypes 27E10 and MRP-14 predominate [44].

In addition, cell adhesion molecules are upregulated in inflammatory and mural cells of vessels, such as intercellular cell adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1) alpha and beta [51]. Of the metalloproteinase-disintegrins (ADAMs), ADAMs 17 and 19 are expressed in T-lymphocytes, both of the helper and cytotoxic subtypes, while ADAM 8 is associated with macrophages [20]. MMP 2, 7, and 9 are expressed in non-necrotic MHC-I-positive muscle fibers, regenerating muscle fibers, atrophic fibers [43,47], and endothelial cells [12], or MMP9 in inflammatory cells [31].

Inclusion body myositis

IBM (Fig. 3) is marked by the combination of two tissue patterns, firstly the inflammatory component largely mimicking the tissue pattern in PM, which includes upregulation of MHC-I and II, predominantly CD8 cytotoxic T-cells within the infiltrates as well as inside non-necrotic muscle fibers and the upregulation of respective ADAMs proteins and, secondly, myopathic features, such as variation in fiber diameters, necrosis, and regeneration of muscle fibers. Moreover, there seem to be no differences in the expression of certain ADAMs and subtypes of macrophages between IBM and PM. This high similarity in immune-related components between PM and IBM may often render an exact distinction of the two conditions difficult. Even ragged red fibers and, more often, myofibers devoid of cytochrome-C oxidase (COX) activity, representing a mitochondrial component, and partial COX deficiency, frequently encountered in IBM, may be a rare feature in PM [6]. Furthermore, IBM may be considered a degenerative myopathy defined by autophagic/rimmed vacuoles and aggregation of proteins. Rimmed vacuoles, a prominent feature in a diverse number of neuromuscular disorders, including IBM, distal myopathies, late-onset type-II glycogenosis, neurogenic processes, myofibrillar myopathies (MFMs), oculopharyngeal muscular dystrophy, and others show activation of the lysosomal marker enzyme acid phosphatase. Inclusion bodies may be seen within nuclei as loosely arranged aggregates of tubulofilaments, which actually consist of tau-containing paired helical filaments and, more frequently, similar and more densely packed aggregates of tubulofilaments within the sarcoplasm, often in the vicinity of autophagic vacuoles. However, aggregation of proteins is not confined to tubulofilamentous aggregates, which themselves may be encountered in a large variety of neuromuscular disorders (Table 6). The most prominent protein accumulating in muscle fibers in IBM is beta-amyloid, recognizable as small haphazardly deposited filaments which, when forming aggregates, display congophilia enhanced by Texas red-type fluorescence microscopy when using the Congo red stain, but also stain with crystal violet and Thioflavin S. Many more proteins of very diverse nature aggregate in IBM muscle fibers, too (Table 7). IBM shares the myopathological features of autophagy and protein aggregation with genetically different and sporadic forms of MFM, the latter also displaying many different proteins [1,17], many of which are encountered in both IBM and MFM. Similarly, proteins of the ubiquitin proteasome pathway of extralysosomal protein degradation are also upregulated [25].

Finally, small angulated fibers are often encountered in IBM muscle specimens, suggesting a subtle

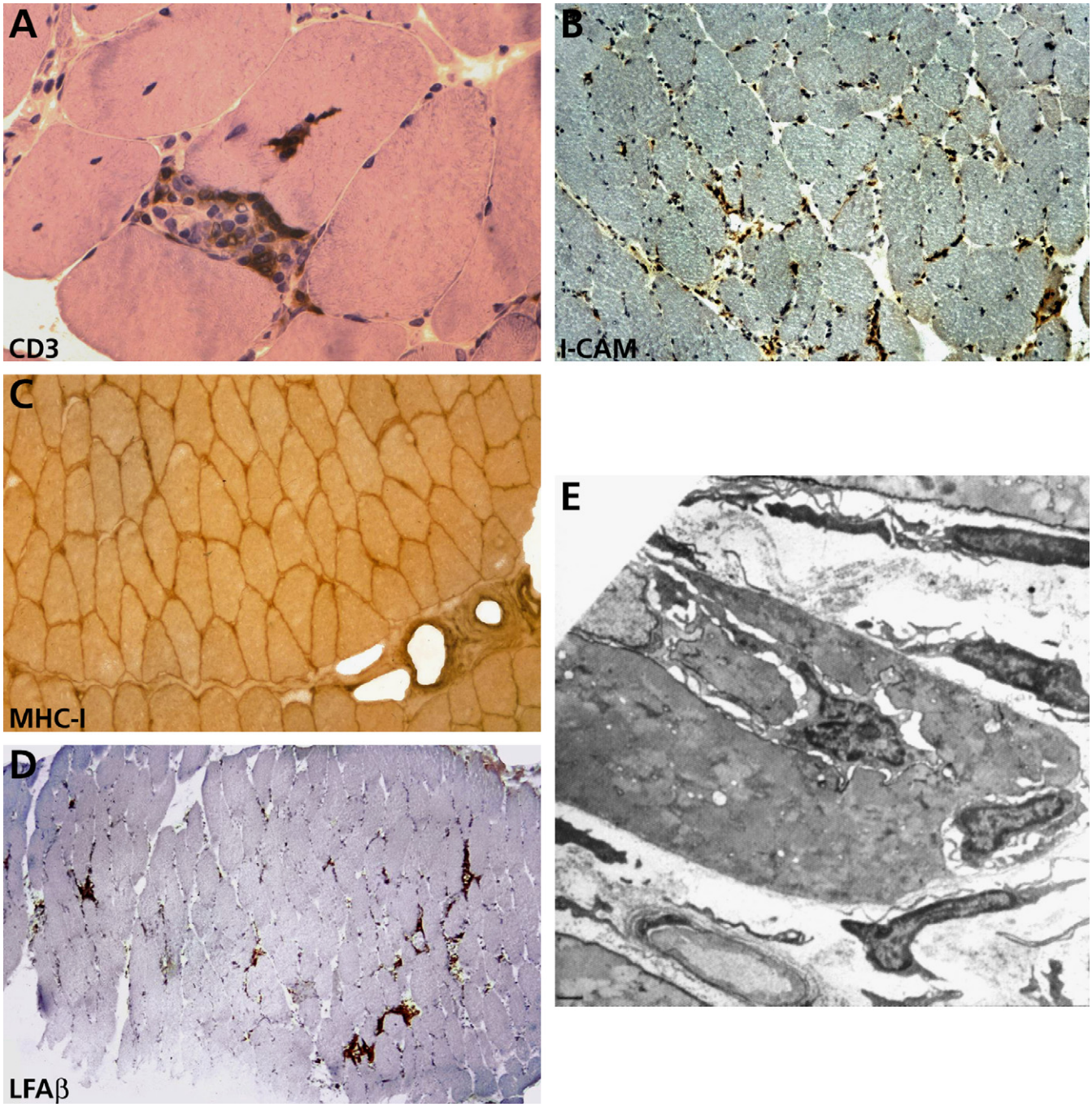

Fig. 2. Polymyositis: (A) T-lymphocytes not only appear between muscle fibers but also within an intact muscle fiber. (B) I-CAM (interstitial cell adhesion molecule) is upregulated in the interstitium among muscle fibers. (C) In spite of little myopathology, MHC-I is upregulated in the sarcolemma of each muscle fiber. (D) Multifocal upregulation of the lymphocyte function antigen beta (LFAβ) is apparent among muscle fibers. (E) At the ultrastructural level, a lymphocyte is situated within an intact muscle fiber, the electron microscopic equivalent to T-lymphocytes in intact muscle fibers at the light microscopic level, as seen in Fig. 2a.

neurogenic component of denervation, while large-group atrophy and fiber type grouping following reinnervation are absent. Such angulated atrophic muscle fibers display increased histochemical activities of acid phosphatase and non-specific esterase as well as of the oxidative enzymes NADH and MAG, in the latter two preparations often without the normal reciprocity of fiber types.

MMP 2, 7, and 9 were seen in muscle fibers, inflammatory cells, and vessel walls [47], MMP 9 in inflammatory cells [31] and MHC-I-positive non-necrotic muscle fibers [12].

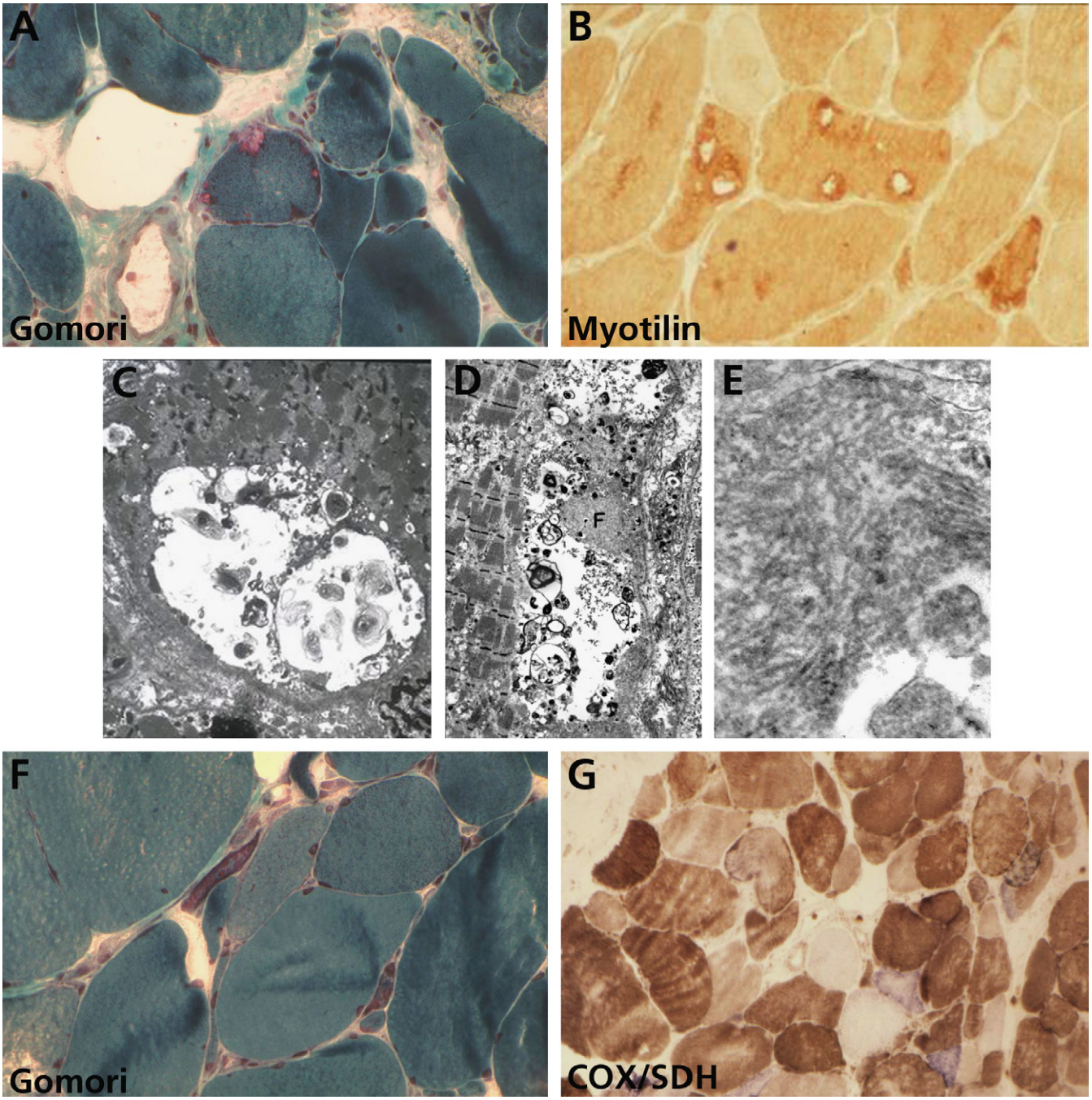

Fig. 3. Inclusion body myositis: (A) A rimmed/autophagic vacuole is present in the periphery of the central small muscle fiber, modified Gomori trichrome stain. (B) Around vacuoles and beyond, accumulation of myotilin, a sarcomeric protein which indicates protein aggregation often seen in inclusion body myositis. (C) The electron micrograph of a rimmed/autophagic vacuole with lamellar debris in the subsarcolemmal region of a muscle fiber, equivalent to the rimmed/autophagic vacuole in Fig. 3a. (D) Aggregates of filaments [F] are often seen in association with rimmed/autophagic vacuoles. (E) Higher magnification shows the ultrastructure of these tubulofilaments. (F) Variation in fiber size, here, is also marked by several small highly atrophic muscle fibers, one of them being a ragged red fiber, suggesting mitochondrial abnormalities, modified Gomori trichrome stain. (G) There are at least two small COX-negative, SDH-positive (blue) muscle fibers apparent, while necrotic fibers are devoid of any enzyme activity, combined cytochrome-C oxidate (COX)-succinic dehydrogenase (SDH) preparation.

Macrophagic myofasciitis

The inflammatory myopathy macrophagic myofasciitis (MMF) (Fig. 4) indicates a recently identified condition which develops focally after injection of aluminum-containing vaccines, even more than 10 years prior to biopsy [45], largely in the deltoid muscle, most often on the left side in adults or in the quadriceps

muscle in children, and is marked by aggregates of large macrophages together with inflammatory lymphocytes in fascia and vicinal skeletal muscle fascicles. The conspicuous macrophages have a PAS-intense cytoplasm – the PAS stainability being resistant to diastase digestion – which displays increased histochemical activities of acid phosphatase and non-specific esterase as evidence of lysosomal upregulation. These lysosomes contain aluminum-typical spicules, the aluminum nature of which can be further documented by laser microprobe mass analysis (LAMMA) [21].

Lymphocytes are largely of the T-cell type. Macrophages which react with the common antibodies CD68 and KI 1P appear, when tested for subtypes, as long-standing 25F9-type, while early-onset 27E10 macrophages are rare or absent [48]. MHC-I is often expressed close to the inflammatory macrophage infiltrates but is scarce in or absent from infiltrate-distant myofibers.

Muscle parenchyma may be scarcely affected in MMF, quite unlike that seen in PM, DM, and IBM, while the spectacular macrophage infiltrates may distract attention from the underlying neuromuscular disorder, which has led to the respective muscle biopsy revealing the clinically almost always unsuspected MMF.

The myopathological differential diagnosis of MMF encompasses Whipple disease, affecting skeletal muscle. However, by electron microscopy, the Whipple-typical organisms may be documented in conjunction with this systemic infection, while MMF is a localized process, at least myopathologically, even in view of claims that it may elicit immune-related generalized responses clinically and serologically [27]. Furthermore, MMF has to be distinguished from IMAM often seen with DM-type myopathology, and from cytophagic histiocytic panniculitis [4]. MMF, described without preceding vaccination [11,40] may represent IMAM rather than MMF.

Table 6. Tubulofilamentous aggregates in neuromuscular disorders

Inclusion body myositis/inclusion body myopathy
Welander distal myopathy
Familial myopathy and periventricular leukoencephalopathy
Nonaka Japanese familial distal myopathy *with rimmed vacuoles*
Dystrophic myotonia
Polyneuropathy
Sarcoidosis
Familial oculopharyngeal muscular dystrophy *with distal myopathy*
Rigid spine syndrome
Acid maltase deficiency
Amyloid neuropathy
Rimmed-vacuole myopathy *sparing the quadriceps*
Adult-onset autosomal-dominant limb girdle muscular dystrophy
Postpolio syndrome
Sporadic distal myopathy
Amyotrophic lateral sclerosis
Myofibrillar myopathy

Table 7. Comparative immunocytochemical results of protein aggregates in MM/IBM

Proteins	MM	IBM	Proteins	MM	IBM
Transsarcolemmal proteins			*Chaperone proteins*		
Dystrophin 1	+	–	Ubiquitin	++	+
Dystrophin 2	+		α-B Crystallin	++	+
Dystrophin 3	+	–	Heat shock protein 72/73	+	+
Utrophin (DRP2)	+/–	–/+	*Cytoskeletal proteins*		
α-Sarcoglycan	–/+	–	Desmin	++	++
β-Sarcoglycan	–/+	–	Vimentin	+	+
γ-Sarcoglycan	–/+	–	Plectin	+	+
δ-Sarcoglycan	+	+/–	*Sarcomeric proteins*		
Dysferlin	+	+	Actin	+	+
Merosin 80	+/–	–	α-Actinin	+	+
Merosin 300	+/–	–	Myotilin	+	+
nNOS	+	+	*Nuclear proteins*		
β-Laminin	+/–	–	Emerin	–	–
γ-Laminin	+/–	–	Lamin A/C	–	–
Collagen 6	+/–	–	*Others*		
Caveolin	+	+	Prion protein	–	–
α-Dystroglycan	+	–			
β-Dystroglycan	+/–	–			

MM: myofibrillar myopathy; IBM: inclusion body myositis; nNOS: neuronal nitric oxide synthase (by courtesy of Dr. Alexandra Vrabie).

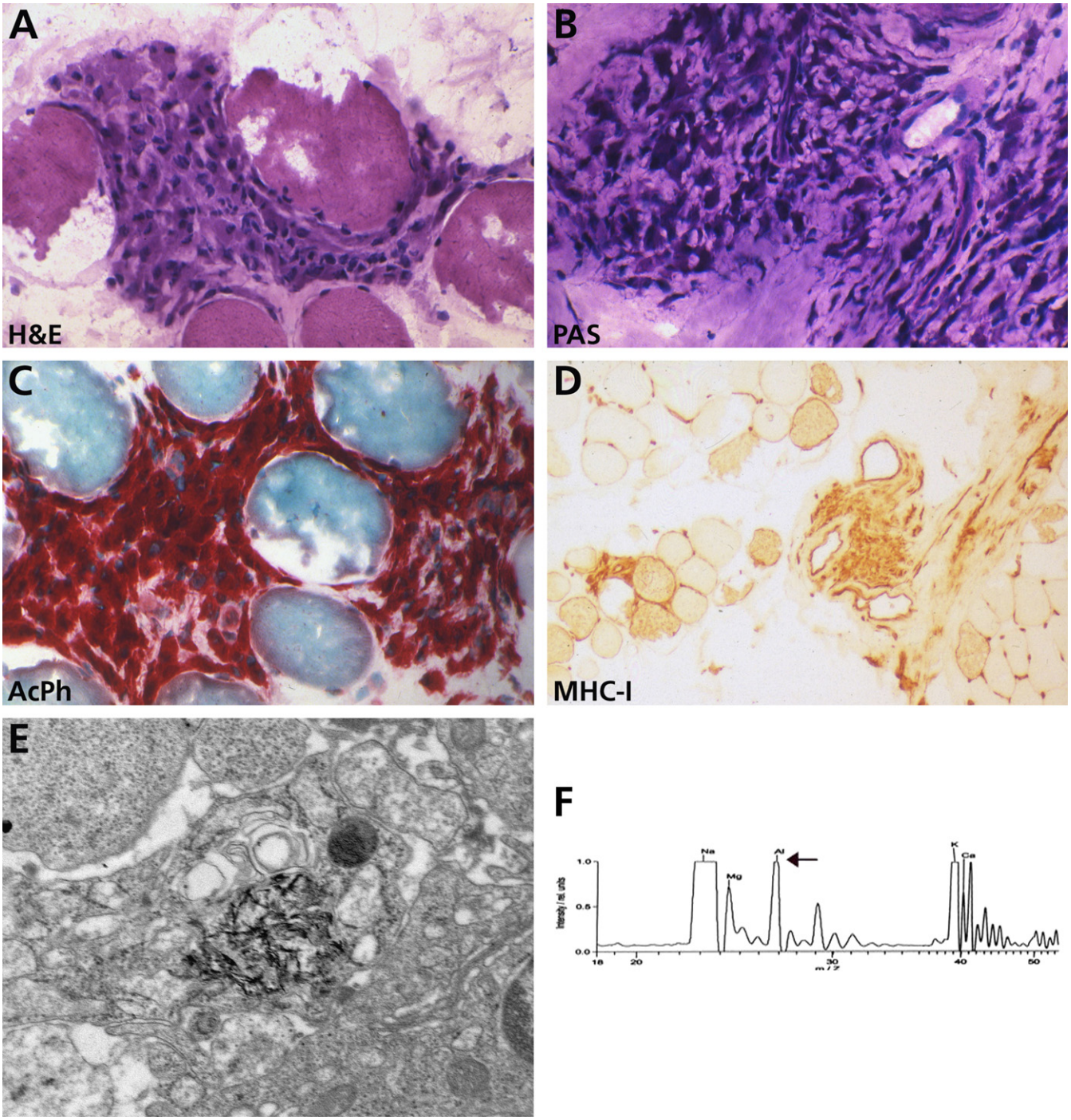

Fig. 4. Macrophagic myofasciits: (A) Large bluish macrophages among muscle fibers, hematoxylin–eosin. (B) Macrophages are strongly PAS-positive. (C) Macrophages express enhanced enzyme histochemical activity of the lysosomal marker enzyme acid phosphatase. (D) MHC-I is only upregulated in the sarcolemma of few myofibers located close to macrophage infiltrates next to three vessels. (E) Ultrastructurally, macrophages contain typical aluminum spicules. (F) The LAMMA technique applied to semithin sections, containing macrophage infiltrates, identifies an aluminium peak (arrow).

Granulomatous and eosinophilic myositis

Granulomas, i.e., focal aggregates of epithelioid histiocytic cells, macrophages, inflammatory lymphocytes, and occasional giant cells of the Langerhans type within muscle parenchyma, constitute granulomatous myositis (Fig. 5), which may be part of immune-mediated systemic disorders, such as collagenoses, sarcoidosis, in association with inflammatory bowel disease, myasthenia gravis, or infectious diseases.

Granulomas themselves show a similar expression of immunological parameters in muscle and other tissues, such as T4- and T8-lymphocytes, and, to a lesser extent, B-lymphocytes, the former also expressing interleukin-2 for MHC-II [54]. Extragranulomatous inflammatory infiltrates may also exist, while MHC-I was not demonstrated in muscle fibers in a series of six patients [54]. An acute necrotizing granulomatous myositis has recently been described in a patient with graft vs. host disease [32].

The presence of eosinophils among inflammatory cells may constitute an eosinophilic myositis (Fig. 6) or few additional neuromuscular conditions (Table 8).

Focal myositis

The three classical immune-mediated IM, PM, DM, and IBM, may have a focal or multifocal aspect, at least obvious from the biopsy of a single muscle, i.e., a focal biopsy, and are recognized as part of a more generalized disorder only by additional clinical or serological and myoimaging parameters and, sometimes, demonstrated by two-site biopsies with different myopathological pictures. IBM was found in paraspinal muscle but not in limb muscle of the same patient [29]. Thus, focal myositis (FM) may also be defined by exclusion of more generalized forms.

Although PM may have a focal start [28], more frequent examples of FM are considered a separate

Table 8. Eosinophils in myositis

Churg-Strauss disease
Esosinophilic polymyositis
Diffuse fasciitis with eosinophilia (Shulman syndrome)
Eosinophilia-myalgia (L-tryptophan) and toxic oil syndromes
Calpainopathy

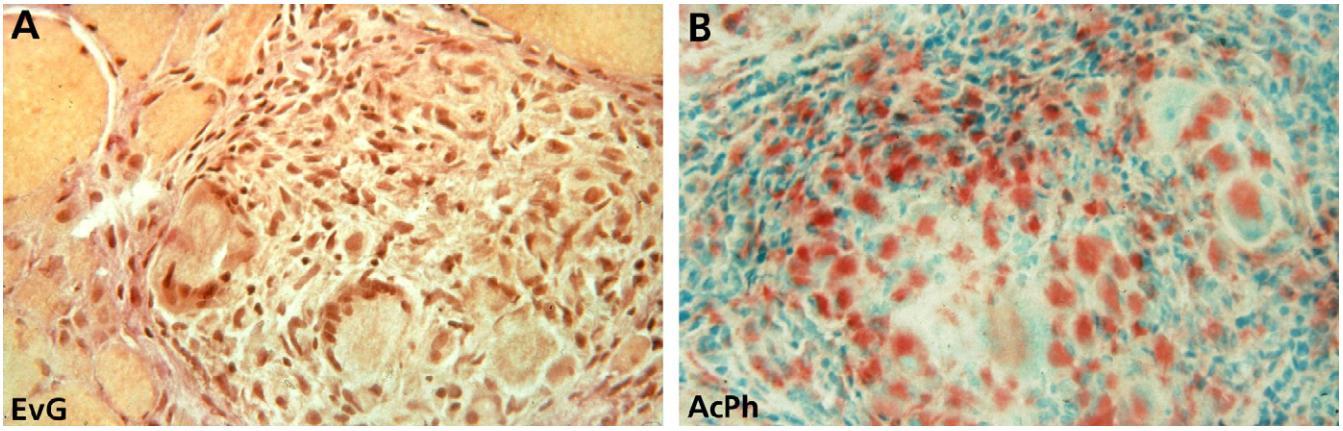

Fig. 5. Granulomatous myositis or sarcoid myopathy: (A) In the non-necrotizing granuloma, two giant cells are apparent, Elastica van Gieson. (B) Numerous macrophages, including giant cells, marked by histochemically upregulated acid phosphatase activity, are components of the granuloma.

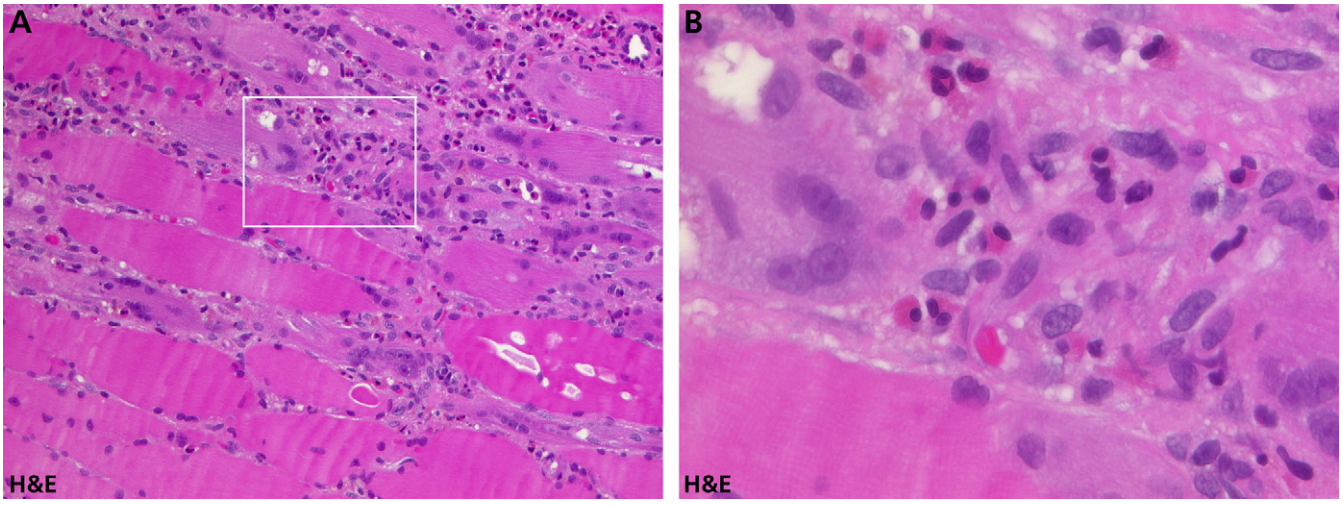

Fig. 6. Eosinophilic myositis: (A) several infiltrates containing esoinophils in the muscle parenchyma, hematoxylin–eosin; (B) at higher magnification, eosinophilic leukocytes are more apparent, hematoxylin–eosin.

entity, largely marked by a circumscribed mass, tender and located in limbs, most often affecting calves but also the trunk and even the temporal muscle of the face [38]. The progressive swelling, with or without pain, often suggesting a tumor, such as sarcoma, may be assured and cured by surgical excision. Histopathologically, necrosis and degeneration of muscle fibers, often occurring in lobules [50], may be encountered as well as inflammatory infiltrates which mostly consist of CD4 T-lymphocytes [10] and considerable amounts of B-lymphocytes [50]. MHC-I expression was not detectable on muscle fibers in a single patient [10], not checked in other patients [10,50], but present in a third group of patients, similar in frequency to that of CD8 lymphocytes [43]. In a series of four patients with painful FM in the calf region, upregulation of MHC-I on muscle fibers was observed in one patient's biopsy specimen but was not recorded in those of the other three patients [49]. Again, after steroid treatment, the myositic process receded without surgical intervention and did not proceed to generalized PM. Whether presence or absence of MHC-I may serve as distinguishing feature between FM and PM thus awaits further studies. Eosinophils have been encountered among inflammatory cells [10]. MMP9 was upregulated in atrophic fibers [43].

The term and condition "nodular myositis" sometimes appears to be interchangeable with FM, while proliferative myositis is marked by intensive regeneration of muscle fibers. Inflammatory infiltrates and other immuno-associated parameters, such as cytokines, cell adhesion molecules, and MHCs, have not been very well characterized in these conditions so far. Thus, since FM is still a controversial condition and because of non-specific inflammatory myopathic changes as well as absence or presence of MHC-I on muscle fibers, its lesions cannot be distinguished histopathologically from biopsied PM, although T8-lymphocytes within intact muscle fibers, which are characteristic features of PM and IBM, have not been reported in FM but, perhaps, may simply not have been explored. FM can only safely be diagnosed as a disease in conjunction with non-morphological, i.e., clinical and serological features.

Paraneoplastic involvement of skeletal muscle

Both DM and PM have been found associated with tumors, either simultaneously or in temporal intervals. Another subtype may be necrotizing myopathy which, apparently described only once, is associated with an adenocarcinoma and serologically abnormal titer against SRP [55], whereas SRP antibodies are often found together with necrotizing myopathy [36]. Necrotic muscle fibers in paraneoplastic myopathy may contain the C5b9 complex/MAC [34], not seen in anti-SRP myopathy [36].

Paraneoplastic myopathies may be associated with a number of serologically identifiable antibodies which, however, have not convincingly been documented by immunohistochemistry in respective biopsied or autopsied muscles.

Statin-induced myopathies

The pattern of muscle involvement induced by statin therapy appears similar to that of paraneoplastic muscle involvement in that both, DM and PM, as well as necrotizing myopathy have been noted, the latter in conjunction with upregulation of MHC-I, with or without inflammatory infiltrates [39], thus suggesting a continuous spectrum among these three conditions. MHC-I upregulation in muscle fibers and necrotizing myopathy have particularly been associated with statin therapy following its discontinuation, which indicates a possible autoimmune process and, thus, amenability to therapy.

Necrotizing myopathy

While necrotic muscle fibers occur in diverse types of neuromuscular diseases, such as metabolic myopathies, muscular dystrophies, and occasional denervation disorders, it may not infrequently be a feature in DM, PM, and IBM. In addition, ample necrosis of muscle fibers making up a necrotizing myopathy has also been observed in relationship to other immune-associated conditions. In paraneoplastic necrotizing myopathy, the terminal component of the complement cascade C5b9 may be encountered in necrotic muscle fibers, while increased activity of alkaline phosphatase enzyme may histochemically occur in connective tissue [34,46] and may be associated with so-called "pipestem" capillaries, these being marked by deposition of C5b9 or MAC [23], or associated with cutaneous lesions of the DM type and MHC-I upregulation on degenerating myofibers [3]. On the other hand, upregulation of MHC-I on muscle fibers has been found in skeletal muscle as a component of necrotizing myopathy following a discontinuation of statin therapy [39].

Inflammatory myopathy features in muscular dystrophies

There are certain muscular dystrophies or individual muscle specimens with muscular dystrophy marked by inflammatory infiltrates (Table 9). This may be particularly apparent in facio-scapulo-humeral muscular dystrophy, as well as in affected children [57]. Other such muscular dystrophies are dysferlinopathy associated

Table 9. Inflammation in muscular dystrophies

Dystrophinopathy
Dysferlinopathy
Caveolinopathy
Calpainopathy
Merosinopathy

with an upregulation of MHC-I on muscle fibers [13], merosin deficiency [41], or, rarely, Duchenne and limb-girdle muscular dystrophies, also marked by upregulation of MHC-I on muscle fibers [2,53,56]. On the contrary, among 200 muscle biopsy specimens of various conditions, sarcolemmal MHC-I expression was absent in all specimens with metabolic myopathies, congenital myopathies, neurogenic disorders, and healthy controls [56]. A peculiar feature is the appearance of eosinophilic myositis (Fig. 6) (Table 8) in children with mutational calpainopathy, occasionally associated with focal expression of MHC-I [33]. Another immune-associated feature in dysferlinopathies may be deposition of MAC in otherwise normal-appearing muscle fibers [8,9].

Skeletal muscle involvement in collagen vascular diseases

Among autoimmune connective tissue or collagen vascular diseases, there are some considered ''overlap syndromes'', indicating not only such an autoimmune collagen vascular disease but also an additional myositis, either of the PM or DM type (Table 10). Then, the myopathology is rather that of myositis than that of collagen vascular disease. Without such an overlap, myopathology in pure collagen vascular diseases is usually non-specific and mild, consisting of small inflammatory infiltrates and some muscle fiber atrophy. This latter finding may be pronounced, e.g. type-II muscle fiber atrophy in polymyalgia rheumatica. In systemic lupus erythematosus, undulating tubules similar to those seen in endothelial cells of DM, may be encountered. Vasculitis may be another mild pathological feature in individual muscle specimens with collagen vascular diseases. It has been claimed [7] that muscle pathology in early rheumatoid arthritis is associated with type-II muscle fiber atrophy, while a later stage, apparently when joint fixation and stiffness have advanced, is marked by type-I fiber atrophy. In juvenile idiopathic arthritis, few patients had upregulation of MHC-II, while upregulation of MHC-I and MAC C5b9 did not differ from controls [35]. In general, immunohistochemical parameters regarding skeletal muscle, such as MHC-I and II, cytokines, cell adhesion molecules and metalloproteinases, subtypes of macrophages or others, have – to our knowledge – not yet sufficiently and systematically been investigated in collagen vascular diseases without overlap.

Table 10. Collagen vascular diseases

Mixed connective tissue disease
Polymyalgia rheumatica
Rheumatoid arthritis
Sjögren syndrome
System lupus erythematosus
Systemic sclerosis

Future perspectives

As already outlined in the preceding sections of this review, immunohistochemistry with the ever-increasing abundance and availability of antibodies has greatly expanded our diagnostic myopathologial armamentarium of IM like, for instance, subtyping of macrophages or introduction of metalloproteinases. Transfer of these investigative findings from research projects to daily practice will increase in the future, depending on the diagnostic significance of individual antibodies in individual IM. Such diagnostic significance and diagnostic certitude will require comparative ''horizontal'' studies, i.e., immunohistochemical application of different antibodies in the same IM. A recently recommended myopathological algorithm for myositis already attests to the application of diverse groups of antibodies in the diagnostic workup of biopsied muscle [53].

While distribution of IM-affected muscles has earlier rested upon clinical and electromyographic findings, because muscle biopsy is usually restricted to a single muscle or, perhaps, two distantly located muscles at the most, (myo-)imaging techniques have recently successfully been employed to elucidate the lesional distribution of individual IM across limb and trunk muscles, and have added a further invaluable parameter to the prebioptic diagnostic regimen, the often convincing distinction between inflammatory and non-inflammatory lesions, the former associated with muscle edema. Here, comparative myoimaging-myopathological investigations are further needed, as edema is seldom equally apparent in biopsied muscle tissue, often only indirectly surmised from separation of muscle fascicles and muscle fibers and some loosening of the connective tissue, while the interstitial fluid is usually not recognized, because it is not stained. Immunohistochemical testing for the presence of albumin in the extracellular space of the biopsied muscle as evidence of extravasation may not necessarily distinguish between disease-related and surgery-related extravasation.

A further field of future research to be urgently incorporated in the diagnostic myopathological spectrum of

IM is immunohistochemical investigation of those numerous IM which do not form the core of immune-related IM, i.e., DM, PM, and IBM. Here, overlap syndromes, rheumatological diseases and beyond, i.e., infectious IM, hover as important targets. In these diseases, expansion of autopsy studies will be prospectively fruitful and should be studied aggressively when becoming available at the autopsy table to amplify both the diagnostic myopathological spectrum as well as the nosography of the respective IM conditions.

An immunological study of glucocorticoid receptors alpha and beta, which may variously be demonstrated in endothelial cells, infiltrating lymphocytes, sarcoplasm, or nuclei of muscle fibers in order to assess their validity in therapeutic prognostication did not reveal any differences among biopsied muscle specimens of the three major IM, i.e., DM, PM, and IBM – especially between PM and IBM – as well as control muscles, suggesting that immunohistochemical application of respective anti-glucocorticoid receptor antibodies in daily myopathological routine investigations of these IM will not be helpful [16].

Receptors for the β-chemokines (CCR1–CCR5) may differentially be expressed in inflammatory infiltrates, especially macrophages and T-lymphocytes, not B-lymphocytes, as well as in endothelial cells in IM, while, at lower levels, in endothelial cells of controls. However, apart from CCR4 upregulated in myonuclei of regenerating muscle fibers, CCR are not expressed within or on myofibers [18].

Acknowledgments

This *Diagnostic Seminar* originated from a Continuing Medical Education Conference on "Inflammatory Myopathies" at the Department of Rheumatology, University Hospital Zurich, Switzerland, February 1, 2007. Support by Profs. Renate and Steffen Gay and Dr. Haiko Sprott, as well as photographic aid by Walther Wagner and editorial assistance by Astrid Wöber are gratefully appreciated. Dr. P.F. Schmidt (Münster/Germany) kindly provided the LAMMA illustration.

References

[1] A.A. Amato, K. Kagan-Hallet, C.E. Jackson, et al., The wide spectrum of myofibrillar myopathy suggests a multifactorial etiology and pathogenesis, Neurology 51 (1998) 1646–1655.

[2] S.T. Appleyard, M.J. Dunn, V. Dubowitz, et al., Increased expression of HLA ABC class I antigens by muscle fibres in Duchenne muscular dystrophy, inflammatory myopathy, and other neuromuscular disorders, Lancet 1 (1985) 361–363.

[3] F.J. Authier, H. Kondo, R.T. Ghnassia, et al., Necrotizing myopathy with pipestem capillaries and minimal cellular infiltration: a case associated with cutaneous signs of dermatomyositis, Neurology 46 (1996) 1448–1451.

[4] G. Bassez, F.J. Authier, E. Lechapt-Zalcman, et al., Inflammatory myopathy with abundant macrophages (IMAM): a condition sharing similarities with cytophagic histiocytic panniculitis and distinct from macrophagic myofasciitis, J. Neuropathol. Exp. Neurol. 62 (2003) 464–474.

[5] M. Bergmann, S. Klingebiel, R. Rohkamm, et al., Activation pattern of macrophages in inflammatory myopathies, Acta Neuropathol. 112 (2006) 371–372 (abstract P1027).

[6] G. Blume, A. Pestronk, B. Frank, et al., Polymyositis with cytochrome oxidase negative muscle fibres. Early quadriceps weakness and poor response to immunosuppressive therapy, Brain 120 (1997) 39–45.

[7] M.H. Brooke, H. Kaplan, Muscle pathology in rheumatoid arthritis, polymyalgia rheumatica, and polymyositis: a histochemical study, Arch. Pathol. 94 (1972) 101–118.

[8] A. Brunn, A comparison between the "inflammatory myopathy with abundant macrophages" and dermatomyositis. 18. Kongress des Wissenschaftlichen Beirats der Deutschen Gesellschaft für Muskelkranke e.V.,Freiburg, 28.2.-3.3., Wecom Gesellschaft für Kommunikation mbH & Co. KG, 83 (abstract).

[9] A. Brunn, R. Schroder, M. Deckert, The inflammatory reaction pattern distinguishes primary dysferlinopathies from idiopathic inflammatory myopathies: an important role for the membrane attack complex, Acta Neuropathol. (Berl.) 112 (2006) 325–332.

[10] C.J. Caldwell, M. Swash, J.D. Van der Walt, et al., Focal myositis: a clinicopathological study, Neuromuscul. Disord. 5 (1995) 317–321.

[11] E.-S. Cho, A. Baisre, M.A. Cruz, et al., Extensive macrophagic myositis in deltoid and trabecular myopathy in quadriceps in a patient without antecedent vaccination (abstract 86), J. Neuropathol. Exp. Neurol. 64 (2005) 452.

[12] Y.C. Choi, M.C. Dalakas, Expression of matrix metalloproteinases in the muscle of patients with inflammatory myopathies, Neurology 54 (2000) 65–71.

[13] P. Confalonieri, L. Oliva, F. Andreetta, et al., Muscle inflammation and MHC class I up-regulation in muscular dystrophy with lack of dysferlin: an immunopathological study, J. Neuroimmunol. 142 (2003) 130–136.

[14] M.C. Dalakas, R. Hohlfeld, Polymyositis and dermatomyositis, Lancet 362 (2003) 971–982.

[15] J.L. De Bleecker, B. De Paepe, I.E. Vanwalleghem, et al., Differential expression of chemokines in inflammatory myopathies, Neurology 58 (2002) 1779–1785.

[16] J.L. De Bleecker, B. De Paepe, V.L. Vervaet, et al., Distribution of glucocorticoid receptor alpha and beta subtypes in the idiopathic inflammatory myopathies, Neuromuscul. Disord. 17 (2007) 186–193.

[17] J.L. De Bleecker, A.G. Engel, B.B. Ertl, Myofibrillar myopathy with abnormal foci of desmin positivity. II. Immunocytochemical analysis reveals accumulation of multiple other proteins, J. Neuropathol. Exp. Neurol. 55 (1996) 563–577.

[18] B. De Paepe, J.L. De Bleecker, Beta-chemokine receptor expression in idiopathic inflammatory myopathies, Muscle Nerve 31 (2005) 621–627.
[19] M. De Visser, A.M. Emslie-Smith, A.G. Engel, Early ultrastructural alterations in adult dermatomyositis. Capillary abnormalities precede other structural changes in muscle, J. Neurol. Sci. 94 (1989) 181–192.
[20] T. Dehmel, A. Janke, H.P. Hartung, et al., The cell-specific expression of metalloproteinase-disintegrins (ADAMs) in inflammatory myopathies, Neurobiol. Dis. 25 (2007) 665–674.
[21] S. Doostkam, J. Bohl, P.F. Schmidt, et al., Macrophagic myofasciitis, Acta Neuropathol. (2005) 324 (abstract).
[22] C. Dorph, P. Englund, I. Nennesmo, et al., Signs of inflammation in both symptomatic and asymptomatic muscles from patients with polymyositis and dermatomyositis, Ann. Rheum. Dis. 65 (2006) 1565–1571.
[23] A.M. Emslie-Smith, A.G. Engel, Necrotizing myopathy with pipestem capillaries, microvascular deposition of the complement membrane attack complex (MAC), and minimal cellular infiltration, Neurology 41 (1991) 936–939.
[24] P. Englund, E. Lindroos, I. Nennesmo, et al., Skeletal muscle fibers express major histocompatibility complex class II antigens independently of inflammatory infiltrates in inflammatory myopathies, Am. J. Pathol. 159 (2001) 1263–1273.
[25] I. Ferrer, B. Martín, J.G. Castaño, et al., Proteasomal expression, induction of immunoproteasome subunits, and local MHC class I presentation in myofibrillar myopathy and inclusion body myositis, J. Neuropathol. Exp. Neurol. 63 (2004) 484–498.
[26] A. Fidzianska, H.H. Goebel, Tubuloreticular structures (TRS) and cylindric confronting cisternae (CCC) in childhood dermatomyositis, Acta Neuropathol. (Berl.) 79 (1989) 310–316.
[27] R.K. Gherardi, F.J. Authier, Aluminum inclusion macrophagic myofasciitis: a recently identified condition, Immunol. Allergy Clin. North Am. 23 (2003) 699–712.
[28] R.R. Heffner Jr, S.A. Barron, Polymyositis beginning as a focal process, Arch Neurol. 38 (1981) 439–442.
[29] E. Hund, R. Heckl, H.H. Goebel, et al., Inclusion body myositis presenting with isoloated erector spinae paresis, Neurology 45 (1995) 993–994.
[30] K. Ikezoe, S. Oshima, M. Osoegawa, et al., Granulysin expression in polymyositis and inclusion body myositis [abstract M-P-6.04],, Neuromuscul. Disord. 16 (2006) S87.
[31] B.C. Kieseier, C. Schneider, J.M. Clements, et al., Expression of specific matrix metalloproteinases in inflammatory myopathies, Brain 124 (2001) 341–351.
[32] S. Koeppen, E. Neuen-Jacob, M. Koldehoff, et al., Acute granulomatous myositis and fasciitis in GVHD, Clin. Neuropathol. 26 (2007) 134 (abstract).
[33] M. Krahn, A. Lopez de Munain, N. Streichenberger, et al., CAPN3 mutations in patients with idiopathic eosinophilic myositis, Ann. Neurol. 59 (2006) 905–911.
[34] M.I. Levin, T. Mozaffar, M.T. Al-Lozi, et al., Paraneoplastic necrotizing myopathy: clinical and pathological features, Neurology 50 (1998) 764–767.
[35] H. Lindehammar, B. Lindvall, Muscle involvement in juvenile idiopathic arthritis, Rheumatology (Oxford) 43 (2004) 1546–1554.
[36] T. Miller, M.T. Al-Lozi, G. Lopate, et al., Myopathy with antibodies to the signal recognition particle: clinical and pathological features, J. Neurol. Neurosurg. Psychiatry 73 (2002) 420–428.
[37] K. Nagaraju, L.G. Rider, C. Fan, et al., Endothelial cell activation and neovascularization are prominent in dermatomyositis, J. Autoimmune Dis. 3 (2006) 2.
[38] M. Naumann, K.V. Toyka, H.H. Goebel, et al., Focal myositis of the temporal muscle, Muscle Nerve 16 (1993) 1374–1376.
[39] M. Needham, V. Fabian, W. Knezevic, et al., Progressive myopathy with up-regulation of MHC-I associated with statin therapy, Neuromuscul. Disord. 17 (2007) 194–200.
[40] J.H. Park, K.S. Na, Y.W. Park, et al., Macrophagic myofasciitis unrelated to vaccination, Scand J. Rheumatol. 34 (2005) 65–67.
[41] E. Pegoraro, P. Mancias, S.H. Swerdlow, et al., Congenital muscular dystrophy with primary laminin alpha2 (merosin) deficiency presenting as inflammatory myopathy, Ann. Neurol. 40 (1996) 782–791.
[42] S. Renaud, D. Leppert, Matrix metalloproteinases in neuromuscular disease, Muscle Nerve 36 (2007) 1–13.
[43] C. Rodolico, A. Mazzeo, A. Toscano, et al., Specific matrix metalloproteinase expression in focal myositis: an immunopathological study, Acta Neurol. Scand. 112 (2005) 173–177.
[44] K.M. Rostasy, M. Piepkorn, H.H. Goebel, et al., Monocyte/macrophage differentiation in dermatomyositis and polymyositis, Muscle Nerve 30 (2004) 225–230.
[45] A.M. Ryan, N. Bermingham, H.J. Harrington, et al., Atypical presentation of macrophagic myofasciitis 10 years post vaccination, Neuromuscul. Disord. 16 (2006) 867–869.
[46] J.B. Sampson, S.M. Smith, A.G. Smith, et al., Paraneoplastic myopathy: response to intravenous immunoglobulin, Neuromuscul. Disord. 17 (2007) 404–408.
[47] B.G. Schoser, D. Blottner, H.J. Stuerenburg, Matrix metalloproteinases in inflammatory myopathies: enhanced immunoreactivity near atrophic myofibers, Acta Neurol. Scand. 105 (2002) 309–313.
[48] W.J. Schulz-Schaeffer, H.D. Müller, P.F. Schmidt, et al., Macrophagic myofasciitis in adults and children, Neuropathol Appl. Neurobiol. 33 (2007) 270–271 (abstract).
[49] K. Sekiguchi, F. Kanda, K. Oishi, et al., HLA typing in focal myositis, J. Neurol. Sci. 227 (2004) 21–25.
[50] A.G. Smith, S. Urbanits, M. Blaivas, et al., Clinical and pathologic features of focal myositis, Muscle Nerve 23 (2000) 1569–1575.
[51] D.S. Tews, H.H. Goebel, Expression of cell adhesion molecules in inflammatory myopathies, J. Neuroimmunol. 59 (1995) 185–194.
[52] D.S. Tews, H.H. Goebel, Cytokine expression profile in idiopathic inflammatory myopathies, J. Neuropathol. Exp. Neurol. 55 (1996) 342–347.
[53] D.S. Tews, H.H. Goebel, Diagnostic immunohistochemistry in neuromuscular disorders, Histopathology 46 (2005) 1–23.

[54] D.S. Tews, D.E. Pongratz, Immunohistological analysis of sarcoid myopathy, J. Neurol., Neurosurg. Psychiatry 59 (1995) 322–325.

[55] K. Traufeller, M. Deschauer, N. Siafarikas, et al., Paraneoplastische nekrotisierende Myopathie mit SRP-Antikörpern. 18. Kongress des Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke e.V., Freiburg, 28.2.–3.3.Wecom Gesellschaft für Kommunikation mbH & Co. KG, 2007, 81 (abstract).

[56] J. van der Pas, G.J. Hengstman, H.J. ter Laak, et al., Diagnostic value of MHC class I staining in idiopathic inflammatory myopathies, J. Neurol. Neurosurg. Psychiatry 75 (2004) 136–139.

[57] T. Voit, A. Lamprecht, H.G. Lenard, et al., Hearing loss in facioscapulohumeral dystrophy, Eur. J. Pediatr. 145 (1986) 280–285.