

EDITORIAL

Recent data and developments in myositis

Myositis is an acquired group of diseases, largely encountered in adults and of autoimmune origin and thus amenable to an ample spectrum of variegated therapies. Therapeutic efforts and successes have sharpened the focus of different molecular aspects of myositides or idiopathic inflammatory myopathies. The once classical classification into dermatomyositis, polymyositis and inclusion body myositis as the major forms has now been refined by adding immune-mediated necrotizing myopathy, linked to single-recognition-particle (SRP) and Hydroxy-3-Methylglutaryl-Coenzyme A Reductase (HMGCoR) antibodies, and antisynthetase syndrome, but reducing the nosological significance of polymyositis (1). Largely through the now well ensconced serology of muscle-specific autoantibodies, which is considered part of a standard diagnostic workup of myositides (2) and their myopathological correlation, dermatomyositis appears as a group of disorders rather than a single entity.

The paper by Radke et al. (3) addresses this diversity with respect to the aspect of association with malignancies in two of these DM subgroups, namely, anti-Mi2 and -TIF1 γ -associated DM. Adult patients with TIF1 γ autoantibodies and complement deposition on capillaries have an exceedingly high risk of existing or developing cancer (4), while the association of cancer with Mi2 autoantibodies is still a matter of debate (5). While a recent French study showed an unexpected association with cancer, a study conducted in the Netherlands on 12x more patients did not identify this association as did a large Chinese study. Radke et al. use a novel technique (NANOSTRING®) that allows the identification of more than 800 genes involved in immunity and cancer and show that both groups are clearly distinguishable by their gene expression profile. Moreover, the technique identifies a comprehensive set of markers that are specifically upregulated in TIF-1 γ ⁺ and cases with cancer-associated myositis, indeed a prognostically relevant finding.

The rich diagnostic spectrum of imaging procedures—namely, the use of modern MRI techniques and their applications to the various inflammatory myopathies is the topic by Allenbach et al. (6) who also emphasize differences between information in images such as edema or fibrofatty replacement of muscle parenchyma and cellular

details by myopathology. The beauty of imaging techniques clearly lies in their applicability for therapeutic and prognostic as well as for diagnostic purposes over time, since imaging can be applied at multiple occasions during the disease development and offers great insights into the pattern and distribution of skeletal muscle involvement during disease. The authors detail out for which of the known entities this may follow a characteristic pattern such as in inclusion body myositis (IBM) and immune-mediated necrotizing myopathy (IMNM). They also mention the emerging usefulness of muscle ultrasound as a technique that is even transportable to the patients, but probably needs more widespread expertise for its routine applicability.

In another paper, Bolko et al. (7) investigate the different types and pathophysiological pathways of interferons in inflammatory myopathies and relate these to hereditary interferonopathies. This is a concept that is both fascinating and tempting. Genetic dysfunction of interferons leads to ultrarare but well delineated monogenetic diseases mostly affecting children and commonly grouped under the umbrella of so-called autoinflammatory syndromes. After a detailed introduction into the different types of interferons, the authors highlight overlapping clinical and pathophysiologic features between hereditary interferonopathies, and acquired interferon-related myositis such as dermatomyositis.

Moreover, they detail out, which types of interferons may be related to which type of myositis, based on pathogenetic concepts that have recently become overt.

Inclusion body myositis is still an enigmatic condition, which not only demonstrates inflammatory parameters and degenerative features in muscle fibers, but abnormal mitochondria as the third component. Carola Hedberg-Olfors and Anders Oldfors et al. (8) undertook a more profound—the group had studied this subject before—mitochondrial genetic analysis in IBM. Here, they undertook deep sequencing (whole-genome sequencing with a mean depth of mtDNA coverage of 46,000x) to study mtDNA variants in muscle samples from 21 IBM patients. They identified markedly increased levels of large deletions and duplications as well as increased somatic single nucleotide variants compared to age-matched controls. The fact that mtDNA defects were similar but

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much more pronounced in IBM compared to a “normal aging group,” and given the similarities with the pattern of PolyA-associated disease opens up the hypothesis that there is a defective mtDNA replication machinery in IBM muscle leading to an accelerated aging process in the context of chronic inflammation. Dr. Hedberg-Oldfors et al. (8) beautifully demonstrate the power of whole genome sequencing approaches to explore new pathophysiological hypotheses in diseases beyond monogenic ones (see 9).


SLONM (sporadic late onset nemaline myopathy) is now also considered an acquired disease—that occurs ultrararely at middle—advanced age. The disease owes its name to the intriguing fact that nemaline bodies (rods) occur within the skeletal muscle. In about 50% of cases, the SLONM is associated with MGUS (monoclonal gammopathy of unknown significance), but it can—even more sporadically—occur in HIV infection, lupus erythematosus, Hodgkin disease and others. Of note, MGUS association *per se* and if not treated has a bad prognosis. Conversely, if patients with MGUS-associated SLONM are treated aggressively by melphalan and stem cell transplantation the long-term prognosis is quite good (10). Recent reports also indicate that less invasive treatment for SLONM patients, that is, with immunoglobulins may also be highly effective even in patients harboring M protein. The reports on good or less convincing therapy effects always lack convincing statistical power, which is an inherent problem of ultrarare diseases. However, the intriguing question of whether SLONM with or without MGUS may exhibit differences at the level of morphology, with respect to immune features detectable by simple analysis under the microscope was the starting point of a joint research project between Tokyo and Berlin: Hence, the myopathology in SLONM of the group with and the one without MGUS (n = 49 patients overall) is discussed by Tanboon and Uruha et al. in much detail. The authors find out that inflammatory features are present in both subgroups but without differences detectable. Of note, also clinical features between both groups did not differ significantly. They conclude that SLONM is, indeed, an inflammatory disease supporting the approach to treat this disease by immunotherapy regardless of the M-protein status.

Finally, as a reminder, that infections of skeletal muscle do exist and may be severe, the paper by Gayathri and Nandeesh summarizes several forms of infective myositides, which, in global times, might not be confined to certain regions of the world. The authors comprehensively sum up the pathogens and their interference with skeletal muscle spanning from acute and chronic bacterial infections, via viral ones, to fungal infections parasitic as well as helminthic ones. The authors also discuss diagnostic tools and difficulties. Many of the specific pathomechanisms leading to certain tissue reactions are still unclear and may be better understood in the future as modern techniques for studying the pathogenesis of these diseases become more widely available.

We are sincerely grateful to all contributors to this minisymposium and we are also very proud that this series of papers mirrors the up-to-date level of research in myositis. It also gives a perspective on how broadly the field has developed recently and still is developing further.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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