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CASE REPORT

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Sporadic late onset nemaline myopathy with concurrent dermatological symptoms responding to immunosuppressive treatment

Anirban Nandy¹, Hatice Tankisi², Anne Bruun Krøigård³, Maiken Glud Dalager⁴, Marie Skov Hvidbjerg⁵, Henrik Daa Schrøder³ and Izabella Obál^{1*}

Abstract

Background Sporadic late onset nemaline myopathy is a rare, progressive muscle disease, presenting in adulthood, mainly affecting proximal limb and bulbar muscles. Muscle biopsies show characteristic nemaline rods. The putative mechanism is considered immune-related. Other manifestations aside from neuromuscular symptoms have not been described previously.

Case presentation We present a case with atypical sporadic late onset nemaline myopathy (SLONM) of a non-HIV, non-MGUS subtype, where skin manifestations preceded neuromuscular symptoms, and a residual thymus with the histology of thymic follicular hyperplasia was detected during the diagnostic workup. Thorough dermatological investigations could not explain the skin presentations. Muscle biopsy revealed variation in fiber diameter, ragged-red and COX-negative fibers associated with discrete fibrosis. Electron microscopy detected atrophic muscle fibres with disorganization of the myofibrils, nemaline rods and abnormal mitochondria. Single-fiber EMG suggested signs of a neuromuscular transmission defect, EMG showed signs of myopathy. Analyses of antibodies associated with myasthenia gravis were negative. The patient showed improvement after intravenous immunoglobulin treatment regarding both the skin and the muscle symptoms.

Conclusions Our case highlights the heterogeneity of SLONM with its varied spectrum of presentation. A unique combination of dermatological symptoms and SLONM could be seen with skin lesions as primary presenting symptoms. An association can be considered between the different manifestations, presumably based on immune etiology, where immunosuppressive therapy has been beneficial.

Keywords Muscle disease, Nemaline, SLONM, Skin manifestations, Autoimmunity

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Background

Sporadic late onset nemaline myopathy is a rare, acquired muscle disease presenting in adulthood, predominantly characterized by proximal limb weakness with frequent bulbar, axial, limb muscle and respiratory involvement [1] [2] [3]. Muscle biopsies show pathological accumulation of nemaline rods in muscle fibers. SLONM is frequently associated with monoclonal gammopathy of unknown significance (MGUS) and HIV infection. [2] [3] [4]. The detection of MGUS and HIV positivity is important because the choice and effectiveness of treatment can be affected by the subtype of SLONM [2] [3]. The treatment regimen includes immunosuppressive therapy, whereas, especially in MGUS-SLONM, chemotherapy (melphalan) and autologous stem cell transplantation may be considered [2] [3] [4] [5].

Case Presentation

We describe the case of a 59-year-old woman, with previously known hypertension, osteoporosis and slight thrombocytopenia, who presented with recurrent rashes and blisters on the extremities and the trunk, approximately one year before developing neurological symptoms. Dermatological investigations have not revealed any other specific dermatosis, besides an episode of urticaria. The main causes of blistering diseases, including porphyria, have been excluded. Genetic examination for acute intermittent porphyria was negative. The patient was referred to our neuromuscular outpatient clinic because of progressive head drop, speech and swallowing difficulties, without clear daily variation. Neurological examination revealed a pronounced head drop with neck extension muscle strength of 4 on the MRC scale, bilateral ptosis, reduced facial mimic, mild dysarthria and dysphagia. Fatigability could not be observed. Sensorimotor examinations and reflexes were normal. Scapular winging or myotonia was not observed.

Aggravation of the symptoms could be seen during the follow up with a neck extension muscle strength of 3 on the MRC scale and more significant swallowing difficulties requiring adjustments in food intake. The skin lesions had been present in the year prior to the onset of muscle weakness but could also be detected continuously after.

An extensive workup focusing on a presumed myopathy, myasthenia, malignancy and associated paraneoplastic syndrome was carried out. Figure 1 A. Biochemical analysis showed a slightly increased creatine kinase, myoglobin and LDH level. Thoracal CT and PET CT scanning showed a residual thymus with FDG enhancement. Other results were normal.

Quantitative electromyography (EMG) showed signs of myopathy in the sternocleidomastoid, brachial biceps, medial vastus and anterior tibial muscles. There were only fibrillations and positive sharp waves in the biceps

brachii. Repetitive nerve stimulation was normal both in proximal and distal muscles. Single fibre EMG (sfEMG) of the frontalis muscle suggested a neuromuscular transmission defect. Figure 1B, C. Motor and sensory nerve conduction studies were normal.

Muscle biopsies from the m. splenius capitis were taken with a 3-month difference. The age of the patient was 59 at the time of the biopsies. Light microscopy of the muscle biopsy revealed fibre diameter variations with the presence of round and angular atrophic fibres and vacuolisation. Figure 2 C-F. An increased amount of interstitial collagen was seen, and type I predominance could be observed. Atrophy was visible among both type 1 and type 2 fibres. No central nuclei, but regenerating fibre could be detected. No necrosis was visible. Gomori trichrome staining showed a few ragged red fibres. Figure 2D. A few COX-negative fibres were also detected in double staining for COX/succinate dehydrogenase. Figure 2 F. The presence of rods could not be excluded. Infiltration of T cells or other inflammatory features, such as upregulation of MHC I or MAC could not be detected. The cytoplasmatic lipid content was normal.

Electron microscopy revealed atrophic muscle fibre with disorganization of the myofibrils and aggregates of Z-disc material in the form of numerous nemaline rods, as well as abnormal mitochondria. The conclusion was nemaline rod myopathy. Figure 2 A, B.

As mitochondrial diseases can present with similar symptoms, we aimed to investigate the possibility of mitochondrial etiology. A metabolic examination of the biopsies was done, which showed normal respiratory chain enzyme activity. Moreover, a PCR analysis of the whole mitochondrial genome was carried out from muscle cell DNA, extracted from a part of the muscle biopsy sample. The analysis showed a normal result corresponding to the patient's age, mitochondrial gene mutations could not be found.

An NGS analysis of 256 genes associated with myopathies, including those responsible for congenital nemaline myopathy, showed a negative result. Table 1.

The skin lesions were present parallel with the patient's neuromuscular symptoms. Figure 3 A-F. Repeated biopsies of the skin lesions could not reveal any explanatory underlying dermatological condition. One biopsy showed changes consistent with urticaria, as expected; the rest showed ulceration, granulomatous reaction, and oedema of the papillary dermis with perivascular infiltration of lymphocytes. Examination for herpes virus infection was negative. An unspecific immune reaction with immunoglobulin A (IgA) and immunoglobulin M (IgM) deposit on the surface of the endothelium of the blood vessels was detected in one out of three biopsies.

Cardiological and pulmonary examinations were also carried out. Pulmonary function tests were normal. The

A

PARACLINICAL INVESTIGATIONS	Results	SEROLOGY	Results
CT-THORAX & ABDOMEN	Showed a residual thymus, without signs of malignancy	PARANEOPLASTIC ANTIBODY PANEL Anti-GAD65, -amphiphysin, -DRP5, -paraneoplastic TR, - HU, i-PNMA2, -recoverin, -NOVA1, -SOX1, -CDR2, -Zinc finger protein ZIC4	Negative
FDG-PET CT	Increased (fluorodeoxyglucose) FDG enhancement in the described thymus	VASCULITIS ANTIBODY PANEL ANCA, ANA, myeloperoxidase IgG, proteinase 3-IgG, phospholipid, -Beta 2 glycoprotein, -cardiolipin antibodies	Negative
LABORATORY WORKUP Hematology, electrolytes, kidney, liver parameters, thyroid function, thyroid antibodies, glucose, Hba1c, B-12, methylmalonate, M-component, immunoglobulins, erythrocyte sedimentation rate, coagulation parameters, hepatitis A-C, HIV 1+2, syphilis, borrelia burgdorferi antibodies, myoglobin, creatine kinase	Within normal range except slightly elevated LDH: 362 (Normal: 105-208 U/l), elevated creatine kinase max. 560 (Normal: 50-150 U/l)	MYASTHENIA GRAVIS /LEMS ANTIBODY PANEL Acetylcholine receptor, MUSK, LRP4, Titin, Calcium channel p/q antibodies	Negative
CEREBROSPINAL FLUID (CSF) Routine examination (Leucocytes, Protein, Glucose, IgG-index, Albumin) Intrathecal PCR for herpes simplex, Varicella Zoster and Borrelia	Within normal range	MYOSITIS ANTIBODY PANEL Histidin T-, RNA ligase (Jo1), -polymyositis Ku, -MDAS, -Chromodomain helicase-DNA binding protein 4, MI 2 alpha, MORC3, PL-12, -PL-7, -Glycyl tRNA synth., - Isoleucin tRNA synth, -EXOSC10, -EXOSC9, -52kDA-RO, -SAE1, -SRP, -TIF1 gamma antibodies	Negative
MR SCANNING OF BRAIN, SPINAL CORD	No abnormalities		

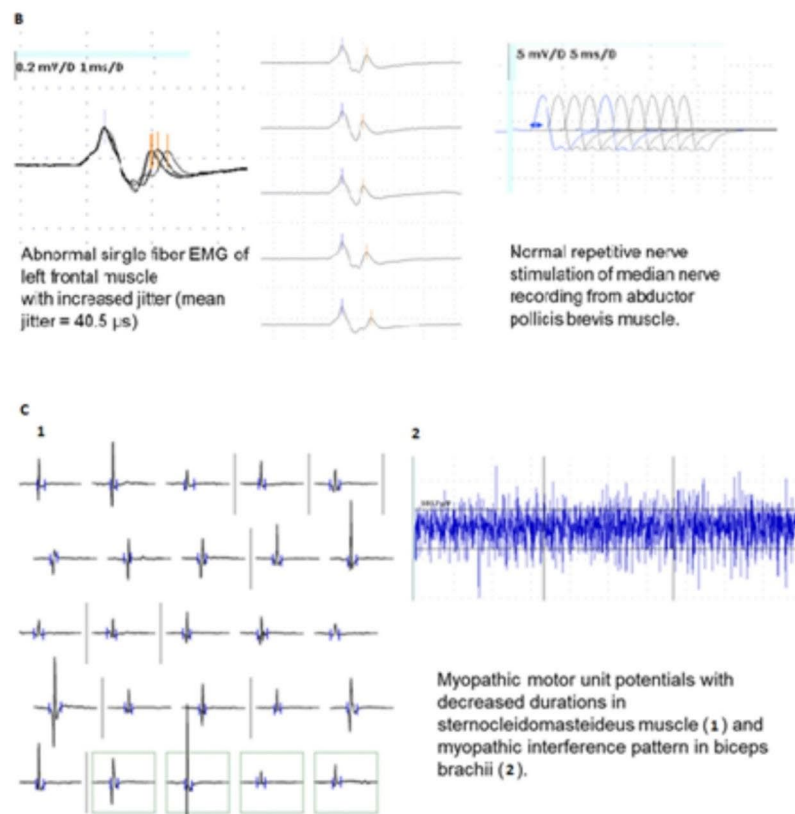


Fig. 1 Diagnostic workup. **A.** The list of all the paraclinical examinations. **B.** Single fiber EMG of the left frontal muscle with increased jitter (mean jitter: 40.5 μs (normal value: mean 20.6 ± 3.6 SD)). Repetitive nerve stimulation of the median nerve, recording from the abductor pollicis brevis muscle. **C.** Myopathic motor unit potentials with decreased durations from the m. sternocleidomastoideus and myopathic interference pattern in m. biceps brachii

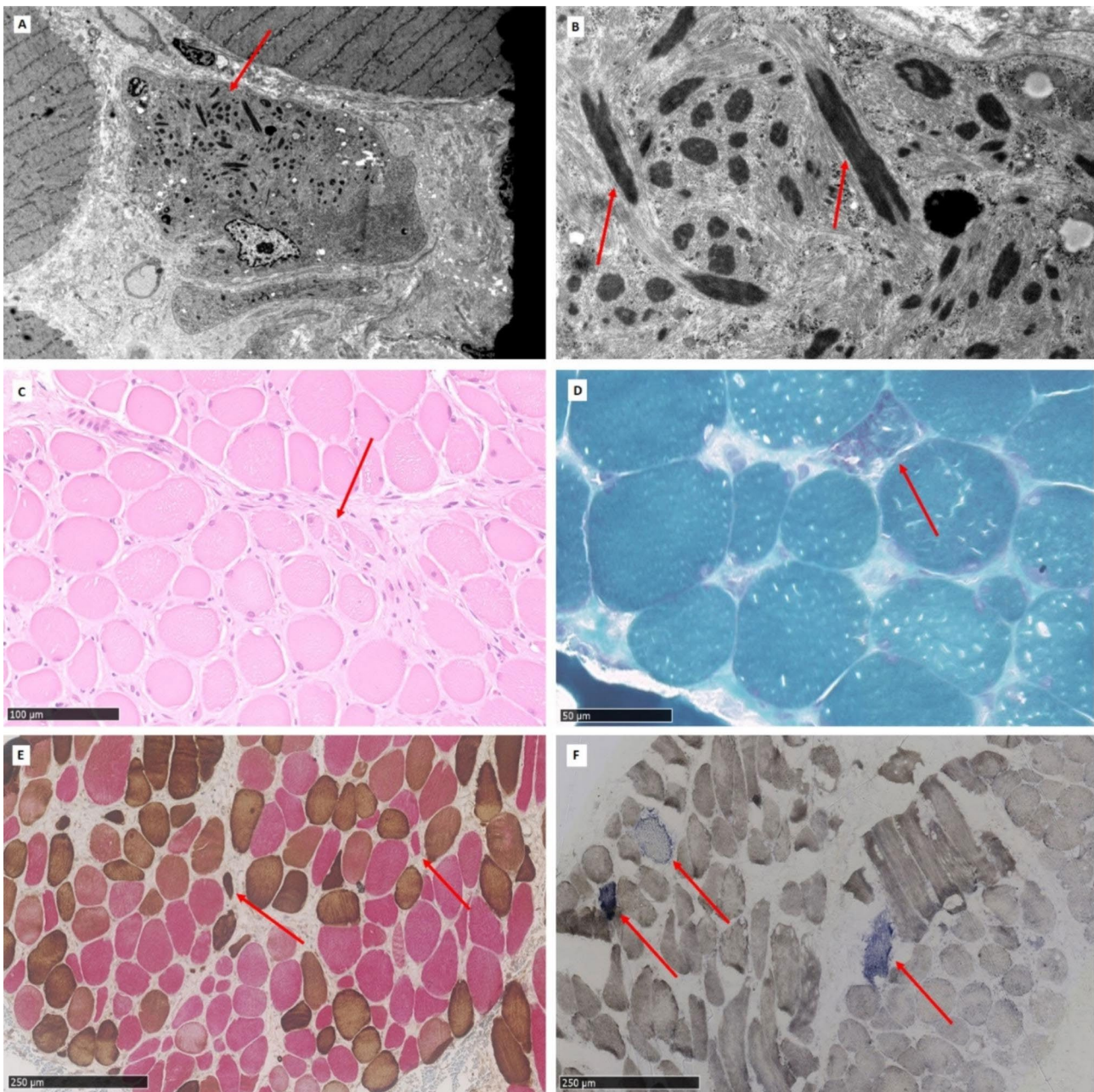


Fig. 2 Muscle biopsy. **A.** Electron micrograph of skeletal muscle fibers. In the center an atrophic fiber with activated nucleus is seen. The abnormal myofibrillar structure with aggregates of Z-disc material, i.e. the nemaline rods can be seen as “dark material” (arrows). **B.** Electron micrograph of a skeletal muscle fiber revealing disorganization of the myofibrils. Nemaline rods consisting of aggregates of Z-disc material are seen (arrows). No cores were identified. No infiltrates of lymphocytes or plasma cells were detected. **C.** Hematoxylin and eosin staining, revealing the presence of round and angular atrophic fibers (arrow) as well as increased amount of interstitial collagen **(D)** Gomori trichrome staining revealing a single ragged red fibre (arrow). **(E)** Double staining for slow (red) and fast (brown) myosin reveals predominance of type 1 fibres. Atrophy can be observed among both type 1 (red) and type 2 (brown) fibres (arrows). **(F)** Staining for COX/succinate dehydrogenase shows a few COX negative fibres (arrows)

cardiac workup was without pathology aside from slight left ventricular hypertrophy related to the patient’s hypertension. Ejection fraction was 60%, no signs of cardiomyopathy were observed.

Treatment

Pyridostigmine treatment was introduced early during the workup because of the neuromuscular transmission defect seen on single fiber EMG and the residual thymus detected with the CT scans. The dose was titrated slowly up to 360 mg daily (6×60 mg), without a significant



Fig. 3 Skin manifestations. **A-F.** Skin manifestations with rashes and blisters on the trunk, proximal and distal extremities

treatment can be excluded. Various reports on SLONM patients without histological signs of inflammation have described different responses to immunosuppressive therapy. MGUS SLONM patients without signs of inflammation benefitted from over a 24 months-treatment with IVIG [4] [5] [10], while stabilization could be achieved in a patient non-MGUS SLONM [4] [7]. In fact, our patient also responded to immunosuppressive therapy with a significant improvement in neck-extensor muscle strength and dysphagia. The initial part of the treatment regime were steroids, but these had to be discontinued, because

the patient developed psychosis as a side effect. Therefore, treatment was changed to continuous IVIG therapy.

The presentation of myopathic symptoms related to SLONM preceded by blistering skin manifestations is a new constellation. The presence of two different disorders cannot be excluded, however a connection between the muscle and the skin presentations can also be considered. The positive effect of the immunosuppressive treatment regarding both manifestations can essentially be explained by a possible, common, immunogenic cause. Dermatological symptoms have been described in other



Fig. 4 Pictures of the patient showing the head drop. **A.** Before treatment **B.** After treatment

neuromuscular diseases and in SLONM as well [11]. However, the cases described in relation to SLONM have been observed in the context of another autoimmune comorbidity, for example SLE [12], or Sjögren [13] syndrome. In these cases, characteristic clinical symptoms and biochemical data supported the above-mentioned conditions. In connection with our patient, investigations regarding a specific underlying autoimmune disease did not yield positive results. Nevertheless, skin biopsies showed subtle immune reactions, suggesting an autoimmune component in the pathology. Furthermore, the patient's dermatological symptoms improved after immunotherapy.

The presentation of myasthenia gravis (MG) with SLONM has been documented before [14] [15]. However, in our case, characteristic serological signs of MG could not be found, and the clinical presentation was atypical, without daily variation of symptoms and fatigability. There was also a lack of effect of pyridostigmine administration. The relevance of the residual thymus with the histology of thymic follicular hyperplasia is difficult to determine. The additional findings of signs of neuromuscular transmission defect seen with the sfEMG can, however, raise the possibility of a comorbidity with seronegative myasthenia gravis. Nevertheless, it is also

feasible, that the described sfEMG changes are secondary to myopathy, which has been documented before.

Our case describes an unusual presentation of SLONM in a non-HIV, non-MGUS subtype with concurrent dermatological symptoms, where immunosuppressive therapy was effective for both muscle and skin manifestations. Thus, our data can provide further support for an immune pathogenesis in sporadic late onset nemaline myopathy.

Abbreviations

SLONM	Sporadic late onset nemaline myopathy
MGUS	monoclonal gammopathy of unknown significance
HIV	human immunodeficiency virus
MRC	Medical Research Council
LDH	lactate dehydrogenase
EMG	electromyography
sfEMG	single fiber electromyography
COX	cytochrome c oxidase
NGS	next generation sequencing
IgA	immunoglobulin A
IgM	immunoglobulin M
MG	myasthenia gravis
IVIg	intravenous immunoglobulin
MHC	class I human major histocompatibility complex

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Authors' contributions

IO and AN examined, diagnosed and treated the patient, collected data and were responsible for the drafting of the article. HT carried out the neurophysiological investigations and contributed to writing the manuscript. AK and HDS performed the histological examination of the muscle biopsy, analyzed the results and contributed to writing the manuscript. MGD performed the dermatological examinations and contributed to writing the manuscript. MSH was responsible for the genetic analysis and contributed to writing the manuscript. All authors read and approved the final version of the article.

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Data availability

All data generated or analyzed during this study are included in this published article.

Declarations**Ethics approval and consent to participate**

not applicable.

Ethical publication

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Consent for publication

Written informed consent was obtained from the patient regarding publication of data and pictures.

Competing interests

The authors declare no competing interests.

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