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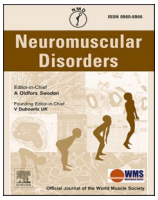

Case report

Sporadic late onset nemaline myopathy responsive to plasma exchanges discovered during a Graft-versus-host disease

Sarah Souvannanorath [a,1,e], Giovanni Umberto Borin [a,b,1], Rabah Redjoul [c], Dehbia Menouche [d], Elsa Poullot [e], Anissa Moktefi [e,f], Gianmarco Severa [f], Baptiste Periou [a,e], Sultan Bastu [f,g], François-Jerome Authier [a,e,f], Jean-Michel Goujon [g], Emmanuele Lechapt [e,f], Edoardo Malfatti [a,e,f,*]

[a] Reference Center for Neuromuscular Disorders, APHP Henri Mondor University Hospital, Créteil, France
[b] Department of Neurosciences, Biomedicine and Movement Science, Section of Clinical Neurology, University of Verona, Verona, Italy
[c] Clinical Hematology Unit, APHP Henri Mondor University Hospital, Créteil, France
[d] Apheresis unit, APHP Henri Mondor University Hospital, Créteil, France
[e] Department of Pathology, APHP Henri Mondor University Hospital, Créteil, France
[f] University Paris Est Créteil, Inserm, U955, IMRB, F-94010 Créteil, France
[g] Departement of Pathology, Poitiers University

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ABSTRACT

Sporadic late-onset nemaline myopathy (SLONM) is a rare adult-onset acquired myopathy characterized by the presence of clusters of nemaline bodies (rods) inside atrophic muscle fibers, with mild to no inflammation. Graft-versus-host disease (GVHD) is a systemic disorder occurring after allogenic hematopoietic stem cell transplant (allo-HSCT) variably associated with immune-mediated neuromuscular complications such as myositis, peripheral neuropathy, and myasthenic syndromes.

A 49-year-old woman with an acute myeloid leukemia with translocation (6;9), and transcript DEK-NUP, was treated with chemotherapy and allo-HSCT. One month later, she developed a skin and digestive GVHD followed by the development of subacute progressive proximal muscular weakness. Serum CK were normal, and there was no MGUS. Muscle MRI showed oedema of paravertebral, pelvic girdle, and lower limbs muscle. Corticosteroids, IVIg, immunosuppressive, and anti-JAK treatments ameliorated the GVHD, but were ineffective on muscle weakness. A *vastus lateralis* muscle biopsy revealed clusters of rods in the majority of fibers and mild MHC-I expression in keeping with a SLONM. Plasma exchange therapy (PLEX) led to complete recovery of the muscle strength in several months.

In conclusion we report a case of SLONM discovered during a chronic GVHD that responded to prolonged PLEX therapy.

1. Introduction

Sporadic late-onset nemaline myopathy (SLONM) is a rare, acquired myopathy, with an usual onset during the fifth decade of life [1]. Cluster of nemaline bodies (rods), often filling atrophic fibers are the pathological hallmark. SLONM can show inflammatory findings, such as major histocompatibility complex class I (MHC I) and muscle inflammatory cells infiltrates, mostly macrophages and cytotoxic T cells [1].

Graft-versus-host disease (GVHD) is a common complication of allogenic hematopoietic stem cell transplantation (allo-HSCT), occurring due to the presence of immunocompetent T lymphocytes in the graft attacking the immunodeficient recipient tissue due to histocompatibility differences, and causing tissue damage [2]. It involves primary bowel, skin, liver, and bone marrow [3]. Neuromuscular manifestations are rare, and include myositis (2.9 %), peripheral neuropathy (0.3 %) and myasthenia gravis (0.15 %) [4,5].

* Corresponding author at: Université Paris Est, U955 INSERM, IMRB, APHP, Centre de Référence de Pathologie Neuromusculaire Nord-Est-Ile-de-France, Henri Mondor Hospital, France.
E-mail address: edoardo.malfatti@aphp.fr (E. Malfatti).
[1] Co-first Authors.

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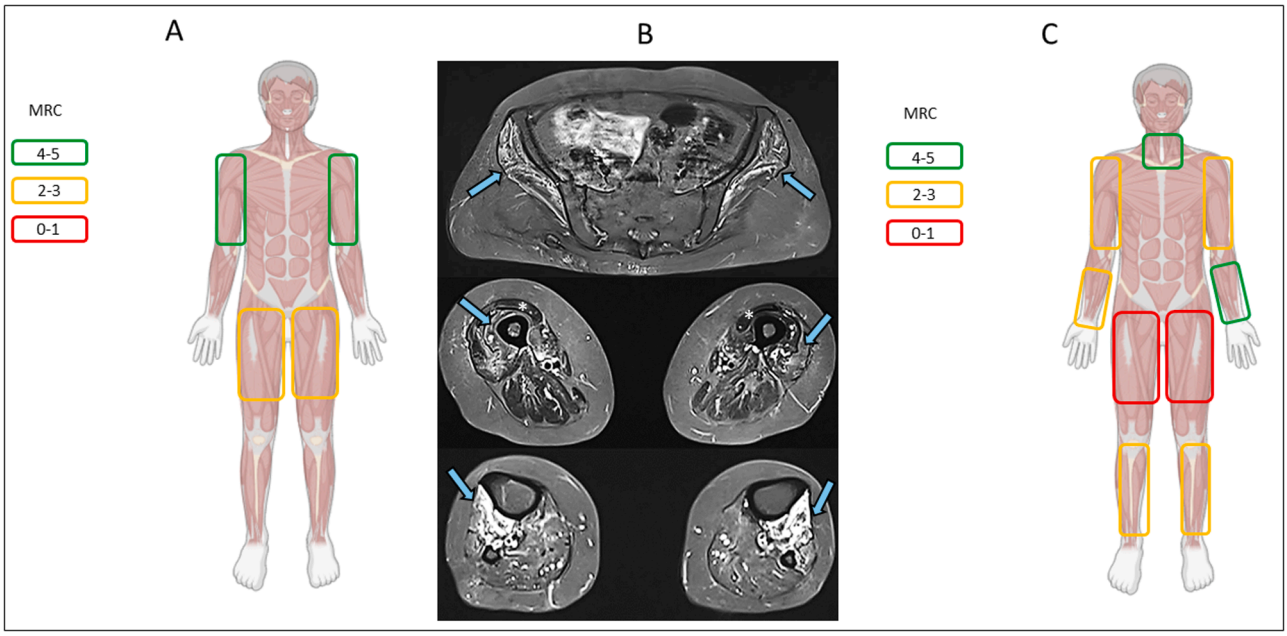

Fig. 1. Distribution of muscular weakness and lower limbs muscle MRI.
A Muscle weakness distribution at onset. Upper limbs: proximal weakness quoted 4 MRC. Lower limbs: proximal weakness quoted 3 MRC. **B.** Lower limbs muscle MRI, STIR images, showing multiple areas of bilateral and symmetrical hypersignal (blue arrows) involving *gluteus medius, gluteus minimus,* and *quadriceps*, with sparing of *rectus femoris* and *tibialis anterior*. **C.** Muscle weakness distribution after GVHD therapies. Upper limbs: mild proximo-distal involvement with asymmetric distal pattern. Axial: mild involvement of the neck-flexors. Lower limbs: severe and symmetrical involvement of proximal muscles, moderate symmetrical involvement of distal muscles.

Interestingly, SLONM can be variably associated with a gammopathy [6], and a recent proteomic study performed on SLONM muscles highlighted the upregulation of a light chains variable region (IGKV3-20) in both patients with and without MGUS, considered as a possible marker of non-specific immune activation [7].

The most common manifestation of SLONM is progressive proximal muscular weakness, either symmetric or asymmetric, involving both upper and lower limbs. Axial muscles are affected in about 50 % of patients leading to drop head and bent spine. Distal weakness is found in approximately 50 % of patients, but a selective distal involvement is rare [1]. Bulbar involvement in form of dysphagia and dysarthria is described as well as the presence of ptosis and ophthalmoparesis [8]. Respiratory muscles involvement can be objectivated, and it could be life-threatening, while the cardiac muscle is usually spared [1]. Corticosteroids, immunosuppressants, intravenous immunoglobulins (IVIG), chemotherapy and allo-HSCT lead to a variable clinical response in about 30 % of patients [1]. PLEX is also proposed as an alternative therapeutic approach in rare cases [9].

Here we describe a 49-year-old woman with a SLONM discovered during a GVHD who responded dramatically to plasma exchange therapy (PLEX).

2. Case report

A 49-year-old French woman with a highly aggressive acute myeloid leukemia with (p23; q34) resulting in the fusion of the DEK gene on chromosome 6 with the NUP 214 (CAN) gene on chromosome 9 (translocation 6;9), was treated with chemotherapy and allo-HSCT [10]. Two days after the transplantation, she exhibited a diffuse maculopapular erythema covering more than 80 % of the body surface without itching or skin peeling, and gastrointestinal symptoms characterized by abdominal pain and profuse diarrhea (more than 1 liter/day). The research of pathogens including, PCR for HSV 1/2, EBV, CMV, HHV6, parvovirus B19 resulted negative; abdominal ultrasound was negative, the abdominopelvic CT showed appearance of jejuno-ileitis, and multiple colon and a rectal biopsies showed necrosis of isolated cells in the crypts with the presence of at least 6 apoptotic bodies confirming the diagnosis of an acute skin and digestive GVHD according to international guidelines [11]. A topic corticosteroid treatment with clobetasol allowed an initial disappearance of the maculopapular erythema, that reappeared successively on the photo-exposed areas. A treatment with corticosteroid 2mg/kg per day, was started and lead to a partial amelioration of the gastrointestinal symptoms, but a rebound with abdominal pain and profuse diarrhea (more than 1 liter daily) was observed. There was no respiratory involvement, and the cardiac workup was normal. From a neurologic standpoint, the patient started manifesting difficulties in walking and rising from a chair after twenty days from the GVHD. In addition to the steroid therapy at 2mg/kg, she received mycophenolate mofetil, cyclosporin and IVIg, and a second line GVHD treatment with anti-JAK (Ruxolitinib) that led to an amelioration of skin and digestive symptoms without effect on the muscular weakness quoting 3 MRC in lower limbs and 4 MRC in upper limbs (Fig. 1A). A medullary MRI excluded a medullary compression and was interpreted as normal. The patient underwent a cerebral MRI to look for infectious complications in the context of severe immunodepression, that was normal. Lumbar puncture was not in favor of infectious and do not find intrathecal Ig production. Serum creatine kinase was normal, and an antibody panel for antibodies-mediated myositis was negative. The patient underwent a routine search by serum protein electrophoresis, immunofixation, serum level of free kappa and free lambda chains: serum electrophoresis only showed low level of gamma globulins with 6.8 g/L (normal values: 8–13.5). The value of kappa light chains was 1.35 mg/L (normal values: 6.7–22.4) and the value of lambda light chains was 1.39 mg/L (normal values: 9.3–27). Kappa/lambda ratio was 0.97 (normal value: 0.31–1.56). Low level of lymphocytes (0.1 Giga/L) was noticed (normal values 1–4 Giga/L). The presence of MGUS was hence excluded.

EMG showed a diffuse myogenic pattern without fibrillation potential or neuromuscular junction impairment. A lower limbs muscle MRI revealed slight fatty involution of all lower limb muscles and

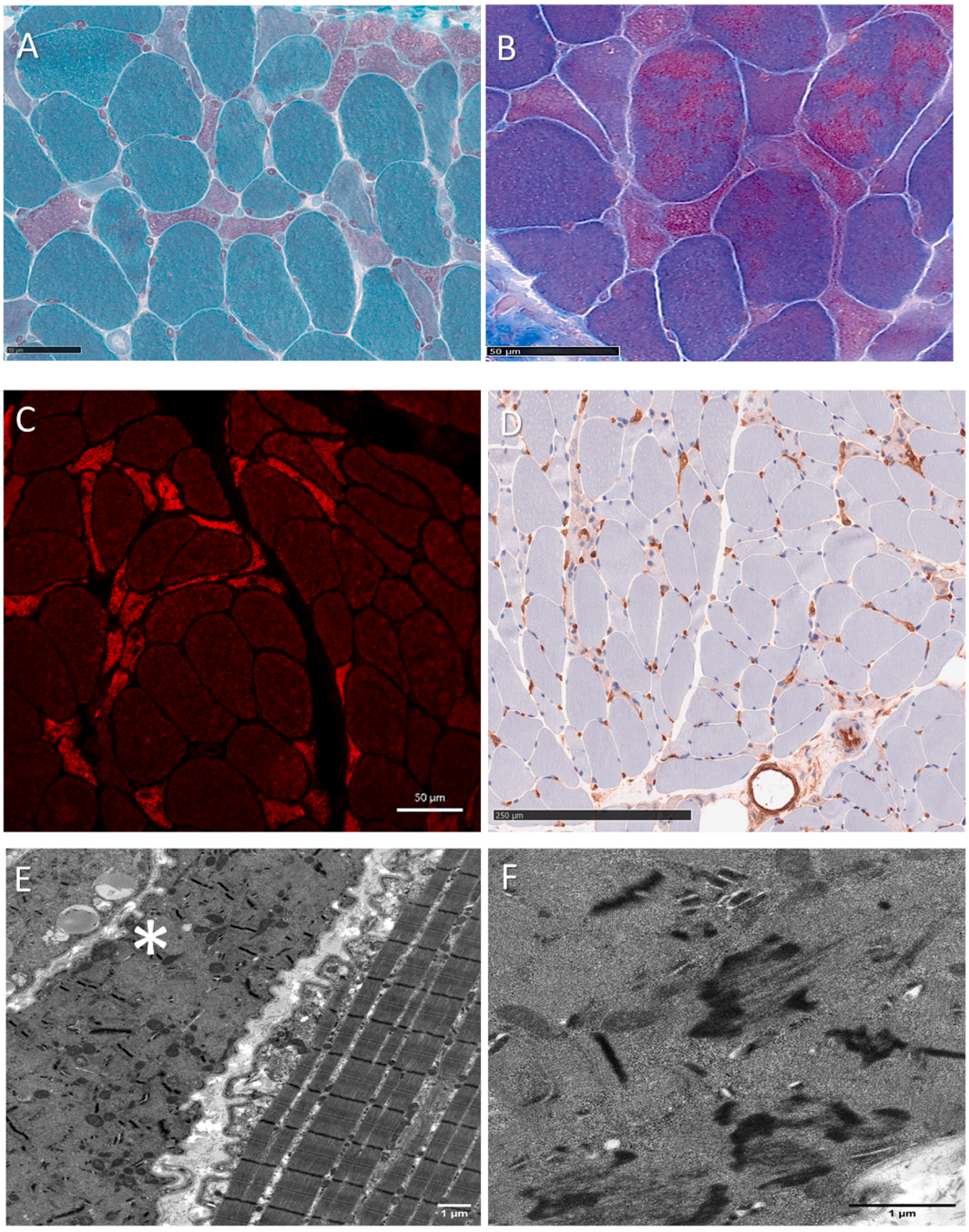

Fig. 2. Muscle morphological analyses.
A, Modified Gömöri trichrome staining showing the presence of granular fuchsinophilic material inside the atrophic fibers. **B.** Masson trichrome staining. The fuchsinophilic material is present in the cytoplasm of both atrophic and normally sized fibers. **C.** Immunohistochemistry for alpha-actinin 2 showed granular immunoreactivity corresponding to the rods. **D.** MHC-1 immunostaining shows the presence of abnormal expression in the cytoplasm of atrophic fibers. **E.** Transmission electron microscopy ultrastructural analysis showed the presence of one fiber (indicated by an asterisk) containing a completely disarrayed sarcomeric structure with enlarged fragments of Z-line next to a fiber with conserved sarcomeres. **F.** Higher magnification of a disarrayed fibers showing the presence of rods with variable shape constituted by dense osmiophilic material.

Table 1
Detailed quantification of patient's myopathologic findings.

	Patient
Atrophic fibers	35–40 %
% Fibers with rods	35–45 %
Atrophic fibers with rods	85–90 %
Non-atrophic fibers with rods	10–15 %
Regenerative fibers	<1 %/neg
CD3 positive elements	0
MHC-I positive fibers	25 %
MHC-II expression in fibers	negative
MAC Sarcolemmal depositions	negative
MxA	negative

significative oedema of paravertebral muscles, the pelvic girdle, anterior compartment of thighs and legs (Fig. 1B). The patient's muscular weakness worsened with axial muscle weakness in neck flexors (4 MRC), proximal upper limbs weakness (2 MRC), distal weakness in finger extensors (4 MRC), right *interossei* muscles (3 MRC), and profound proximal lower limbs and *tibialis anterior* muscular weakness that led to gait loss (Fig.1C). Whole-body muscle MRI showed bilateral and symmetric STIR hypersignal of the *gluteus minimus* and the *gluteus medius* at pelvic level and *quadriceps* involvement with relative sparing of *rectus femoris*. The *vastus lateralis* muscle biopsy showed important fibers size variation with atrophic angulated fibers filled with finely granular fuchsinophilic material (Fig. 2A), corresponding to nemaline bodies (rods). Clusters of cytoplasmic rods were also evident in fewer, non-atrophic muscle fibers (Fig. 2B). A detailed quantification of myopathologic findings is reported in Table 1. Immunohistochemistry for alpha-actinin 2 showed granular immunoreactivity corresponding to the rods (Fig. 2C). There was a sarcolemmal and cytoplasmic expression of MHC-I in some atrophic fibers (Fig. 2D), and MHC-II and MAC immunostainings were negative (not shown). Transmission electron microscopy revealed the presence of atrophic fibers with a completely disorganized sarcomeric structure containing segments of Z-lines (Fig. 2E), and variably shaped and sized rods, thus confirming the diagnosis of SLONM (Fig. 2F). Immunofluorescence studies using an antibody against κ-light chain was negative (Fig. 3A) while there was multiple positive λ-chains immunoreactive material in both atrophic and non-atrophic fibers (Fig. 3B).

We therefore decided to start PLEX therapy at a regimen of 4 exchanges/week. Muscle evaluation after two weeks showed a rapid and sustained amelioration of the proximal muscle weakness with gait recovery. An intense physical therapy program was started and PLEX continued. After one year and 43 PLEX the manual muscle testing was completely normal. Since then, the patient has been considered in a state of hematological and neurological clinical remission. At the last follow up, one and a half years after the last PLEX, she did not show muscular weakness.

3. Discussion

Here we describe a patient presenting a SLONM discovered during a GVHD. GVHD occurs after allo-HSCT due to the presence of immunocompetent T lymphocytes in the graft attacking the immunodeficient recipient histocompatibility divergent tissue, causing tissue damage [2]. Our patient developed a typical GVHD skin rash, and gastrointestinal symptoms classified as chronic GVHD according to the international guidelines [10]. The patient received high-dose corticosteroids, mycophenolate mofetil, ciclosporin and IVIG, that was partially effective on the GVHD. Upon the appearance of muscular weakness, we firstly considered as differential diagnosis a medullary compression, and a GVHD myositis, that is usually characterized by non-specific inflammatory myopathy with muscle fiber necrosis or polymyositis-like and dermatomyositis-like features with interferon type I activation and expression of MHC-II [12] reflecting an inflammatory process affecting both muscle and fascia [4,5]. We therefore started a second line GVHD therapy with Ruxolitinib [11] that contributed to the amelioration of skin and digestive symptoms, but did not ameliorated the muscular weakness that continued to worsen. A muscle MRI showed bilateral and symmetric STIR hypersignals of *gluteus minimus* and *gluteus medius* at pelvic level and quadriceps involvement with relative sparing of *rectus femoris*, suggesting a SLONM [13,14], and a *vastus lateralis* muscle biopsy revealed the presence of nemaline bodies (rods) in atrophic fibers by both light and electron microscopy (Fig. 2). The muscle biopsy disclosed the presence of inflammatory finding with MHC-I without MHC-II or complement deposition as previously described [1]. Very intriguingly, by immunofluorescence we identified the presence of λ-light chains immunoreactive material (Fig. 3), that was not paralleled by the presence of an MGUS that was actively searched with serum protein electrophoresis, immunofixation, serum level of free κ and free λ-chain. Unfortunately, urinary levels of free kappa and free lambda were not dosed. One hypothesis could be that strong immunosuppressive treatment led to a non-detectable gammopathy in circulating blood. Another possibility to consider is that clone B appeared after allogenic SCT and could be present in the donor. Indeed, our patient has a 100% donor chimerism, and no analysis was performed on the donor. Interestingly, the paradoxical identification of monotypic deposits in the absence of an underlying monoclonal gammopathy is a recognized clinico-pathological phenomenon in renal pathology. In a rare renal-limited disease called proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMIDs), immunofluorescence and ultrastructural analysis reveal granular electron dense monotypic deposits (mostly IgG3 Kappa) restricted to the glomeruli, but the detection rate of a circulating nephrotoxic monoclonal Ig is only 30 %. This entity highlights immunofluorescence as the cornerstone of diagnosis with major therapeutic impact by clone-directed approach, even in patients without detectable clones [15].

As the standard recommended treatments for SLONM [1] including corticosteroids, immunosuppressants, intravenous immunoglobulins (IVIG), chemotherapy and HSCT were already used without any success on muscular weakness in our patient, we decided to start PLEX [9]. This treatment was effective, leading to a clinical improvement over months, with a complete recovery of muscular weakness in one year. PLEX therapy was stopped in fall 2022. Since then, the patient is considered to be in a state of hematological and neurological clinical remission. We continue regular follow up, and no further immune-modulating therapy is planned, unless there is a reappearance of muscular weakness.

In conclusion, we describe a case of SLONM discovered during a chronic GVHD that responded dramatically to PLEX therapy. A muscle biopsy should be proposed systematically to patients who suffered from GVHD with muscular weakness.

CRediT authorship contribution statement

Sarah Souvannanorath: Writing – original draft, Resources, Formal analysis, Data curation. **Giovanni Umberto Borin:** Writing – review & editing, Writing – original draft, Resources, Data curation. **Rabah Redjoul:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Dehbia Menouche:** Writing – review & editing, Data curation. **Elsa Poullot:** Writing – review & editing, Formal analysis, Data curation. **Anissa Moktefi:** Writing – review & editing, Data curation, Conceptualization. **Gianmarco Severa:** Writing – review & editing, Resources, Methodology, Data curation. **Baptiste Periou:** Methodology, Formal analysis, Data curation. **Sultan Bastu:** Resources, Formal analysis, Data curation. **François-Jerome Authier:** Writing – review & editing, Methodology, Data curation. **Jean-Michel Goujon:** Validation, Methodology, Investigation. **Emmanuele Lechapt:** Writing – review & editing, Visualization, Validation, Supervision, Data curation. **Edoardo Malfatti:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

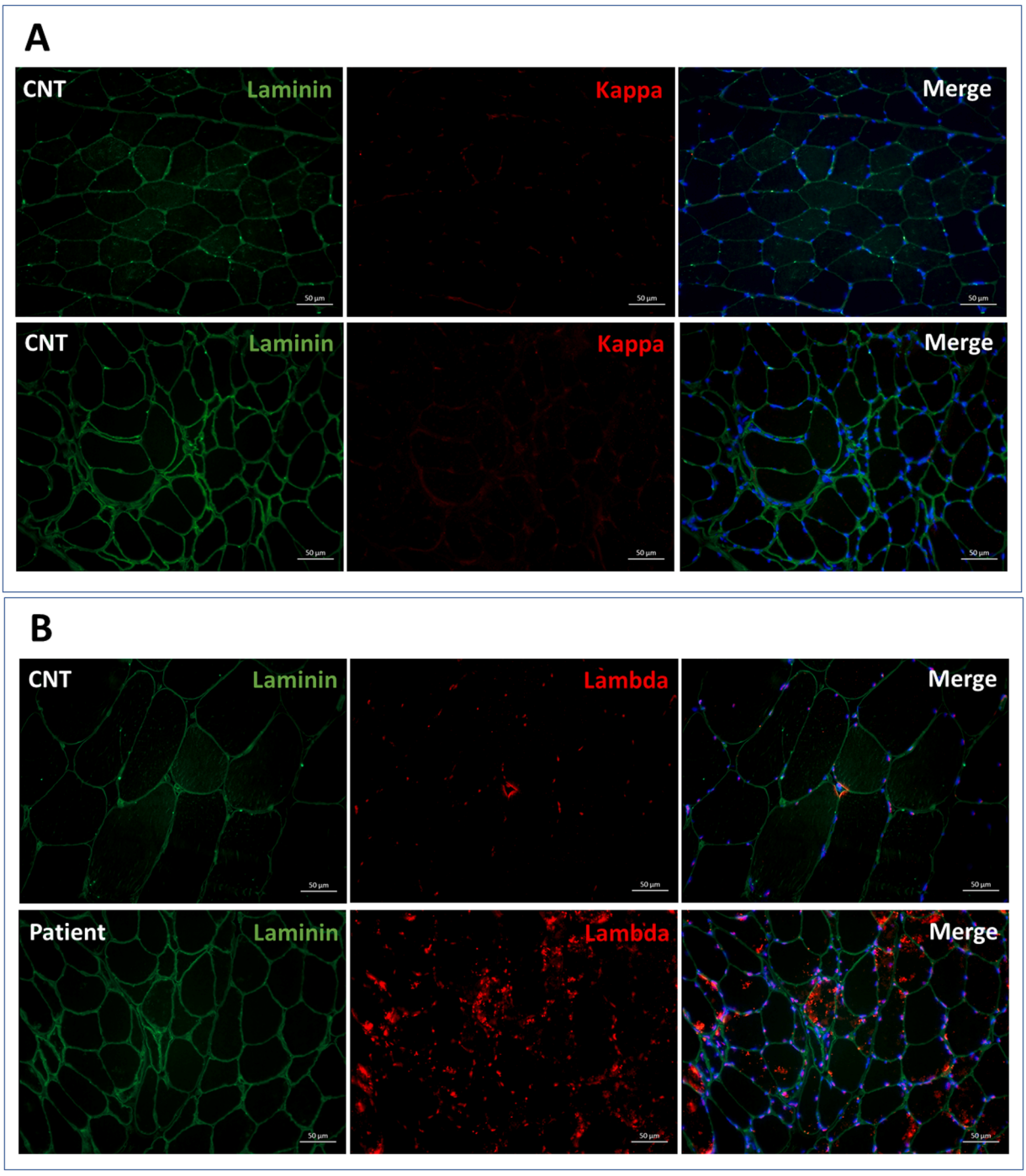

Fig. 3. Immunofluorescence with κ- (A) and λ-light chain (B) antibody in a histologically normal control (CNT) and the patient. **A.** Absence of κ-light chain material in both control and patient muscle. **B.** Presence of immunoreactive material corresponding to λ-light chains deposition in the patient's muscle fibers. Antibodies used: DB Biontech, DB039-0.5.

Declaration of competing interest

None.

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