Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.0859-18
Intern Med 58: 277-282, 2019
http://internmed.jp

【 CASE REPORT 】

Extranodal NK/T-cell Lymphoma Mimicking Granulomatous Myositis

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Abstract:
Extranodal NK/T-cell lymphoma (ENKTL) is an aggressive non-Hodgkin lymphoma that typically develops in the upper aerodigestive tract. We encountered an ENKTL patient who presented with generalized muscle weakness with eyelid swelling, diplopia, and facial edema. A muscle biopsy revealed lymphocytic infiltration without significant atypia; some lymphocytes formed granuloma-like structures. Although the initial response to steroids was encouraging, an ulcerative eruption appeared in the thigh, and a skin biopsy revealed lymphocytes with atypia. A re-analysis of the muscle biopsy with additional immunohistochemistry revealed neoplastic NK/T lymphocytes in the granulomatous structures. Our case highlights the significance of re-evaluating muscle biopsy specimens in cases of atypical myositis.

Key words: extranodal NK/T-cell lymphoma (ENKTL), granulomatous myositis, eyelid swelling, muscle biopsy, immunohistochemistry

(Intern Med 58: 277-282, 2019)
(DOI: 10.2169/internalmedicine.0859-18)

Introduction

ENKTL is an aggressive non-Hodgkin lymphoma that most frequently occurs in East Asia and Latin America, with an increasing incidence in the United States (1). ENKTL usually arises in the nasal cavity, but extra-nasal sites are involved including skin, soft tissue, and gastrointestinal tract (2). The neoplastic cells are various in morphology from small or medium-to-large populations with reactive inflammatory cells. The clinical and pathological variability could mislead and delay the diagnosis. We report here a case of ENKTL who manifested generalized muscle weakness and mimicked granulomatous myositis.

Case Report

A 54-year-old previously healthy Japanese man presented with generalized muscle weakness in all 4 limbs. Three months later, he developed diplopia and was admitted to our department. He also presented with erythema around the eyes, facial edema, and a low-grade fever. A neurological examination revealed external limitation of the eye movement in the right eye, bilateral eyelid swelling, facial weakness, jaw claudication, dysarthria, dysphagia, and proximal-dominant muscle weakness in four limbs (Medical Research Council grade 4) with grasping pain. Laboratory investigations showed elevated muscle enzymes [creatine kinase (CK), 796 U/L; myoglobin, 1,021 ng/mL]. The serum lactate dehydrogenase (LDH) level was mildly elevated (529 U/L). Lysozyme and angiotensin-converting enzyme (ACE) values were within normal limits. Anti-signal recognition particle and anti-aminoacyl transfer RNA synthetase antibodies were negative. The serum soluble interleukin-2 receptor (sIL-2R) level was elevated (2,730 U/mL; normal range, <519 U/mL).

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Received: January 22, 2018; Accepted: April 28, 2018; Advance Publication by J-STAGE: August 24, 2018
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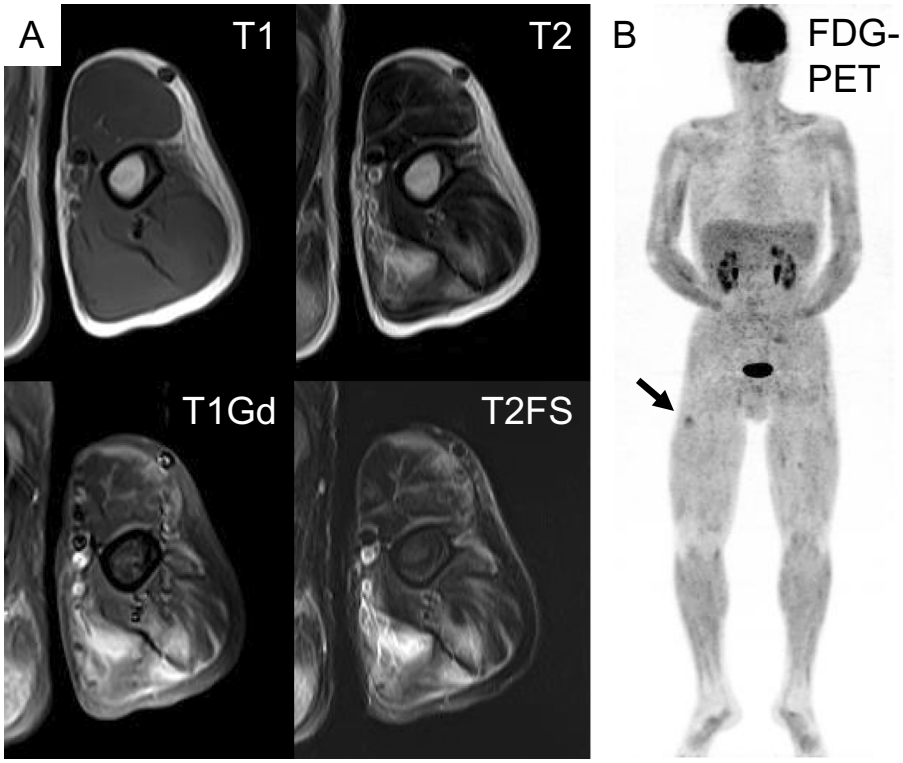

Figure 1. **A: Axial muscle MRI of the left upper limb showed hyperintense lesions in T2-weighted, T2 fat-suppressed (T2FS) and T1 gadolinium-enhanced fat-suppressed (T1Gd) images. B: FDG-PET showed the diffuse accumulation in the muscles of all four extremities and the accumulation in the right thigh (arrow).**

Needle electromyography revealed low-amplitude, polyphasic motor unit potentials and early recruitments in both distal and proximal muscles and positive sharp waves in the vastus medialis. A nerve conduction study exhibited no abnormality. Muscle magnetic resonance imaging (MRI) showed high-signal-intensity areas on T2-weighted images in the proximal muscles of all four limbs with gadolinium enhancement in the left upper limb (Fig. 1A). Brain MRI findings were normal, including examinations of the orbits and cranial nerves. Whole-body computed tomography (CT) and gallium scintigraphy showed no abnormalities.

A muscle biopsy of left biceps brachii on frozen sections revealed massive infiltration of lymphocytes forming granuloma-like structures in the endomysium, preferentially at the center of muscle bundles and around the vessels in the perimysium (Fig. 2C). Necrotic myofibers were scattered around the granuloma-like structures. Epithelioid cells, giant cells, and caseous necrosis were not observed. Alkaline phosphatase staining showed intensely stained perimysial areas, but there was no staining in the granuloma-like structures (Fig. 2D). Immunostaining for HLA-class I, CD3, CD4, CD8, CD68, and CD20 revealed diffuse overexpression of HLA-class I on sarcolemma, predominantly CD4-positive lymphocytes and smaller numbers of CD8+ and CD20+ lymphocytes forming the granuloma-like structures. Increased numbers of CD68+ cells were found to be diffusely scattered in the endomysial and interstitial regions. Further immunohistochemical analyses with additional markers including CD34 staining revealed increased numbers of dilated capillaries among the granuloma-like structures (Fig. 2I). In addition, a skin biopsy of the facial erythema showed lymphocytic infiltrations without atypia prominently in the basal layers of the epidermis and mildly in the superficial layers. Massive lymphocytic infiltration was also observed around the vessels in the deep layers of the epidermis. Based on these findings, we diagnosed the case as atypical myositis with granuloma-like structures and decided to try immunotherapy.

After administering oral prednisolone (1 mg/kg/day), all of his symptoms disappeared within 2 weeks. The serum CK and LDH levels were normalized, and the serum sIL-2R level decreased to 538 U/mL. Subsequently, oral prednisolone was tapered to 30 mg/day over the next 2 months. However, three months after initiating prednisolone, generalized muscle weakness recurred followed by a high fever and weight loss. The serum CK and sIL-2R levels were elevated to 401 IU/L and 5,140 U/mL, respectively. The serum LDH level was also increased (564 U/L). Whole-body CT detected hepatosplenomegaly and pleural effusion without lymph node enlargement, and an ulcerative eruption developed on his right thigh. A skin biopsy of the lesion revealed massive cell infiltration with atypia in the dermis (Fig. 3). These cells were stained positive for CD3, CD56, Epstein-Barr Virus (EBV)-encoded small RNA (EBER) *in situ* hybridization (ISH), Granzyme B, and T-cell-restricted intracellular antigen-1, establishing the diagnosis of EBV-related

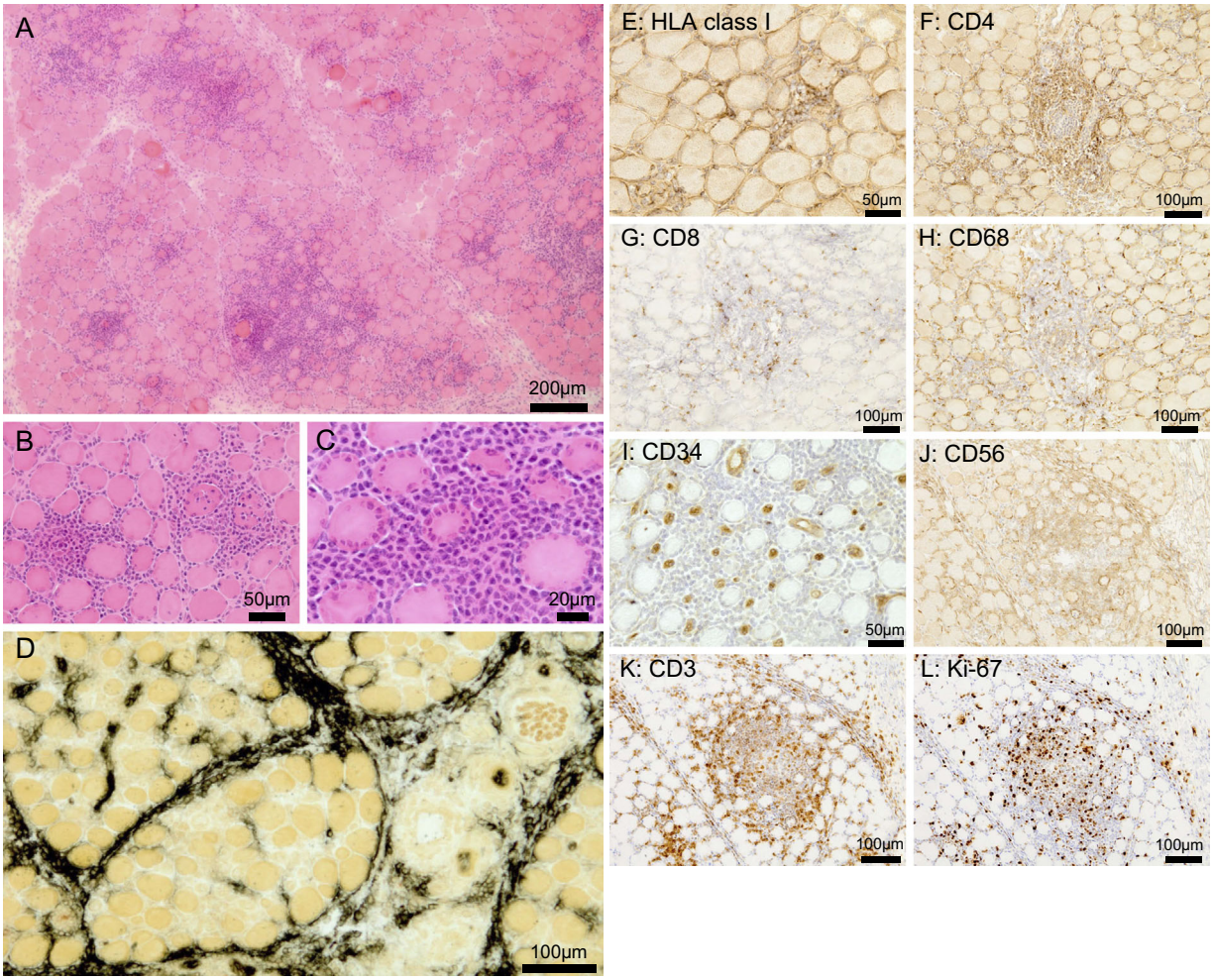

Figure 2. **A: A muscle biopsy of the left biceps brachii showing massive infiltration of lymphocytes in the endomysium [Hematoxylin and Eosin (H&E) staining, bar=200 μm]. B: Lymphocytes infiltrated into the myofibers and formed necrosis (H&E staining, bar=50 μm). C: High magnification of the granuloma-like structures revealed a high density of lymphocytes with a large nucleus. Neither epithelioid cells nor giant cells were observed (H&E staining, bar=20 μm). D: The perimysial area was intensely stained with alkaline phosphatase staining (bar=100 μm). E: Human leukocyte antigen class I (HLA-class I) was diffusely overexpressed on sarcolemma. The granuloma-like structures were composed of cells positive for CD4 (F), CD8 (G), CD68 (H), CD56 (J), and cytoplasmic CD3 (K). CD34-positive dilated capillaries were observed among the granuloma-like structures (I). Nearly 60% of dikaryotic lymphocytes were positive for Ki-67 (L). Bars=50 μm (E, I), 100 μm (F-H, J-L).**

ENKTL.

A re-evaluation of the muscle biopsy specimen revealed that most lymphocytes in the granuloma-like structures had mild atypia with a Ki-67 index of up to 60% and were positive for CD56, CD3, and focally CD5 (Fig. 2L). Positron emission tomography (PET)-CT showed the accumulation of ^{18}F-fluorodeoxyglucose (FDG) in the ulcerative eruption on his right thigh (SUV maximum of 3.5) and generalized FDG accumulation in the skeletal muscles (SUV maximum of 3.6) (Fig. 1B). EBV DNA was elevated in the blood (6,000 copies/μg DNA), and rearrangements in T-cell receptor genes were not observed. The ultimate diagnosis was ENKTL invasion in the muscles with chronic active EBV disease. Therapeutically, combination chemotherapy with steroids, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE regimen) and hematopoietic stem cell transplantation were attempted. However, his general condition deteriorated, and he died due to sepsis. An autopsy was not performed.

Discussion

ENKTL usually arises in the nasal cavity or surrounding structures, such as the sinuses or palate. Only seven cases of ENKTL that manifested myopathic symptoms have been reported, and they were all initially diagnosed as myositis (Table) (3-9). Clinically, all of the cases except our own exhibited localized lesions as the initial symptom. However, these lesions did not show a tendency to be located in the proximal regions of the four limbs. Only our case showed gener-

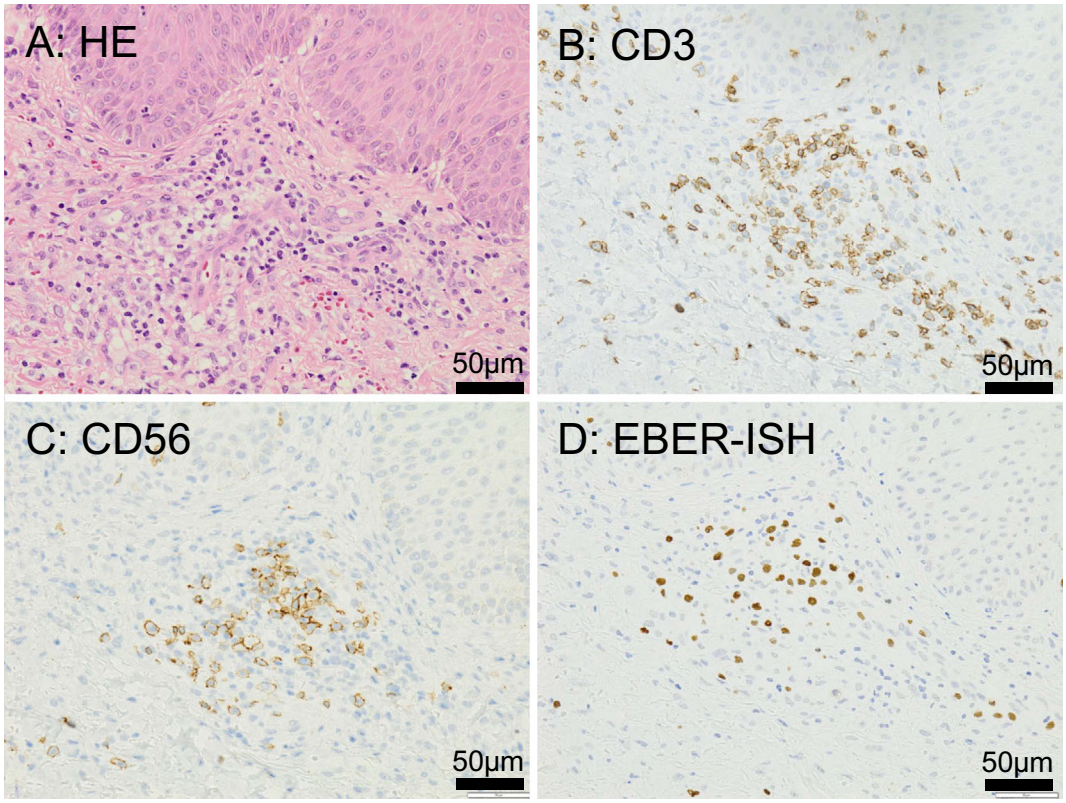

Figure 3. **A skin biopsy from ulcerative eruption on the right thigh showed the infiltration of neoplastic lymphoid cells positive for CD3 (B), CD56 (C), and EBER-ISH (D) in the dermis. [Hematoxylin and Eosin staining (A), bar=50 μm].**

alized muscle weakness with proximal-dominance. The diagnoses based on muscle biopsies were not homogeneous in the previous cases (Table). One case was considered to be sarcoid myositis because of the presence of granulomatous structures (4). Three cases were diagnosed as polymyositis (5, 6, 8). Another case was clinically suspected of being dermatomyositis since the patient had skin lesions (3). These previous findings along with our own suggest that ENKTL can present various clinicopathological patterns and should be considered as a differential diagnosis in patients with atypical myopathic symptoms.

The systemic symptoms, including eyelid swelling and facial edema, may have been caused by direct invasion of the tumorous cells and paraneoplastic mechanism. Previous reports have shown that the eyelid and facial swellings were caused by the direct invasion of lymphocytes into the muscles (10, 11). Furthermore, some cases of ENKTL with myopathic symptoms were reported to exhibit bilateral eyelid swellings (8, 9). Thus, symptoms such as eyelid swelling and facial edema can occur along with muscle weakness in ENKTL. Therapeutically, the initial response to steroid was outstanding in our case. Previous cases of ENKTL with myopathic symptoms showed a temporary encouraging response at the early phase but became refractory later (Table). The possibility of malignancy should therefore be considered when such a therapeutic response is recognized.

Granulomatous myositis is characterized by non-necrotizing granuloma and is frequently associated with sarcoidosis (12, 13). Initially, we diagnosed this case as atypical granulomatous myositis for the following reasons: 1) clinically symmetric generalized muscle weakness was evident as an initial manifestation; 2) systemic organ involvements were observed, including eyelid swelling, diplopia, dysarthria, and dysphagia; and 3) the muscular histological findings of the granuloma-like structures composed of CD4+ lymphocytes and CD68+ cells surrounded by CD8+ lymphocytes resembled sarcoid myositis (14). However, several features were not typical of sarcoidosis, such as the normal serum ACE level, lack of hilar lymph node enlargement, and the granuloma-like structures not containing epithelioid cells, giant cells, or clusters of CD68-positive cells which mimic but are not actual granulomas. Although our case exhibited heliotrope rash-like lesion and an alkaline phosphatase positive perimysial area, which is characteristic of antisynthetase syndrome (15), the muscle pathology was not entirely consistent with dermatomyositis. The case was therefore initially diagnosed as atypical myositis associated with unknown etiology.

However, additional immunostaining of a muscle biopsy specimen ultimately revealed that the granuloma-like structures predominantly contained CD56-positive NK/T cells and relatively few CD4-positive T cells. This cellular composition can be interpreted as the invasion of NK/T lymphomas into the skeletal muscles and subsequent inflammatory aggregation of CD4-positive T cells. Such admixed inflammatory infiltration is a characteristic feature of ENKTL re-

Table. Comparisons with the Previous Cases of ENKTL That Manifested Myopathic Symptoms.

	Our case	Ref 5	Ref 3	Ref 8	Ref 2	Ref 4	Ref 6	Ref 7
Age/sex	54/Male	53/Male	34/Female	50/Female	68/Female	38/Male	52/Female	57/Female
Muscle involvement	generalized muscle, face, jaw, pharynx	Rt LL	Rt forearm	Both ULs, Lt thigh, Rt rectus	Rt forearm, face	Both LLs	Both LLs, buttock, Rt forearm, face	cardiac muscle
Other organs involved	eyelids, face, oral cavity, skin, liver, spleen	nasal cavity, skin	liver	eyelids, oral cavity, Lt thigh, Lt breast	lung and oropharynx	palate, inguinal LN, skin	lung	eyelids, lung, liver, spleen
Prognosis	death	death	death	death	death	death	death	death
Survival from initial onset	19 months	8 months	not available	72 months	1.5 months	8 months	26 months	36months
Initial symptom	generalized muscle weakness including face and mouth, eyelid erythema, facial edema, fever	localized muscle swelling in Rt LL	Rt forearm swelling, fever	muscle weakness of ULs, swelling of eyelids and lip	Rt forearm swelling, facial edema	mucocutaneous ulcer in LLs	swelling and pain in LLs	eyelid swelling, fever
Muscle pathology	massive infilration of lymphocyte among muscle bundles, epitheloid or giant cell(-)	infiltration of mononuclear inflammatory cells with massive destruction of muscle fibers, scattered granulomas	patchy infiltration of the perimysium and endomysium with medium-sized lymphoid cells	mild infiltration of small lymphocytes among mucle fiber bundles, regeneration and degeneration of muscle fibers	a multifocal, chronic inflammatory infiltrate of small lymphocytes without atypia, scattered muscle fiber necrosis	diffuse necrosis and massive destruction of the muscle fibers, many aggregating large atypical lyphoid cells with angiocentricity	Eosinophilic infiltration with lymphocytes showing mild atypia. A few vague granulomas(+)	a dense perivascular and intermuscular lymphoid infilatration consisting of atypical cells
IHC on muscle specimen	lymphocytes positive for CD56, CD3, focally CD5	scattered lymphoid cells positive for CD56 and CD30	lymphocytes positive for CD3ε, CD8, CD45RO, CD56 and EBER	lymphocytes positive for CD3ε, CD8, TIA-1 and EBER-1	not performed	cytoplasmic CD3(+), CD56(+), Granzyme B(+), CD30(+), EBER(+)	admixed CD3(+) cells and CD20(+) cells	EBER(+)
Initial diagnosis after muscle biopsy	GM, atypical	GM, atypical	PM	PM	PM (Burkitt lymphoma was already treated)	not conclusive (DM was clinically suspected)	Kimura disease	CAEBV-associated lymphoma
Response to initial steroid treatment	rapid resolution of all the symptoms	not available	resolution of the symptoms	transient response	not responsive	not responsive to chemotherapy	resolution of symptoms	transient response

UL: upper limb, LL: lower limb, LN: lymph nodes, Rt: right, Lt: left, GM: granulomatous myositis, PM: polymyositis, DM: dermatomyositis, CAEBV: chronic active Epstein-Barr virus infection

ported in other tissues (16), which may lead to the misdiagnosis of granulomatous myositis in cases with limited immunostaining findings. Furthermore, we were unable to detect mild lymphocyte atypia initially because it is challenging to discriminate mild atypia on frozen sections (5). Immunohistochemical evaluations on both frozen and paraffin-embedded sections along with an assessment of nuclear atypia might have helped us diagnose the present case earlier. These findings therefore suggest that evaluating the biopsy specimen on paraffin-embedded sections with extensive immunohistochemistry is necessary for the precise diagnosis of atypical myositis.

The primary lesion of the malignant lymphoma was not identified in our case. PET-CT showed the uniform accumulation in systemic muscles, suggesting a primary occult lesion and possible hematogenous metastasis to and proliferation in the skeletal muscles. Furthermore, a muscle biopsy revealed that lymphoma cells were predominantly distributed in the middle of each muscle bundle with increased and dilated capillaries. This pattern may reflect an angiocentric tendency of ENKTL cells (16).

In summary, we herein report a case of ENKTL mimicking granulomatous myositis. It is difficult to appropriately diagnose such an atypical myositis based on a muscle biopsy with limited immunohistochemical markers. Combined approaches of (1) careful clinical evaluations (3), repeated

biopsies, and (4) a review of the previous biopsy specimen with a broad panel of immunohistochemical markers, are imperative for the precise characterization of atypical myositis.

Author's disclosure of potential Conflicts of Interest (COI).
Ichiro Nakashima: Research funding, LSI Medience Corporation; Funding for a trip and speaks, Mitsubishi Tanabe Pharma and Novartis Pharma.

Financial Support

Naoki Suzuki has received an Intramural Research Grant (29-4) for Neurological and Psychiatric Disorders of NCNP. Masashi Aoki has received research grants for Research on Nervous and Mental disorders, Research on rare and intractable diseases, Research on Psychiatric and Neurological Diseases and Mental Health from the Japanese Ministry of Health Labor and Welfare, Grants-in-Aids for Scientific Research, an Intramural Research Grant for Neurological Psychiatric Disorders from NCNP, Grants-in-Aids for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT), and Practical Research Project for Rare/Intractable Diseases from the Japan Agency for Medical Research and Development (AMED).

Acknowledgement

The authors are grateful to Maya Narisawa for her excellent technical assistance.

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