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【 CASE REPORT 】

Dropped Head Syndrome and the Presence of Rimmed Vacuoles in a Muscle Biopsy in Scleroderma-polymyositis Overlap Syndrome Associated with Anti-Ku Antibody

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Abstract:
A 66-year-old woman with a history of interstitial lung disease presented with a 3-month history of dropped head syndrome (DHS), followed by camptocormia and extremity weakness. A clinical examination revealed Raynaud phenomenon, arthralgia, distal skin sclerosis, and microbleeds in the nailfold capillaries. An anti-Ku antibody test was positive. A muscle biopsy revealed inflammatory myopathy with rimmed vacuoles (RVs). The diagnosis of scleroderma-polymyositis (SSc-PM) overlap syndrome was made. RVs on a muscle biopsy in a patient with inflammatory myositis involving axial muscles may be seen either in inclusion body myositis or SSc-PM overlap syndrome. The examination of the skin and autoantibody testing help determine the diagnosis and treatment strategy.

Key words: anti-Ku antibody, scleroderma-polymyositis overlap syndrome, dropped head syndrome, rimmed vacuole

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Introduction

Dropped head syndrome (DHS) is an uncommon condition in which patients present with a disabling inability to lift their head. It may arise in many neurological conditions and can be further divided into two categories: increased tone of the neck flexors (neck dystonia) or weakness of neck extensors associated with inflammatory myopathies (IMs) (1) including polymyositis or inclusion body myositis (IBM) (2). A histopathological hallmark of IBM is the presence of rimmed vacuoles (RVs) reflecting an impaired autophagy process. RVs can also be found in other muscle disorders, and recent data have shown that a few cases of IMs associated with anti-Ku antibody had IBM pathologic criteria (3). We encountered a case of scleroderma-polymyositis (SSc-PM) overlap syndrome with positive anti-Ku antibody in a patient who presented with DHS and RVs on a muscle biopsy. A careful examination of skin manifestations and the distribution of weakness as well as autoantibody testing helped correct the differentiation of SSc-PM overlap syndrome from IBM.

Case Report

A 66-year-old woman was referred for DHS and an elevated creatine kinase level. She had been diagnosed with interstitial lung disease (ILD) two years earlier and had been on a low dose of prednisolone. She had been asymptomatic until three months before her presentation, when she noted weakness in her neck and difficulty lifting her head. The symptoms gradually worsened, and she noticed that her back bent forward when she stood up and walked. She developed dysarthria, weakness of the extremities, and difficulty walking and maintaining her usual daily activities. She reported a 10-kg weight loss over the past 6 months, arthralgia in both hands and fingers, and Raynaud phenomenon. Ptosis, diplopia, dysphagia, and prominent weakness of the distal muscles, including finger flexors, was not present.

Her medical history was significant for hypertension, mild

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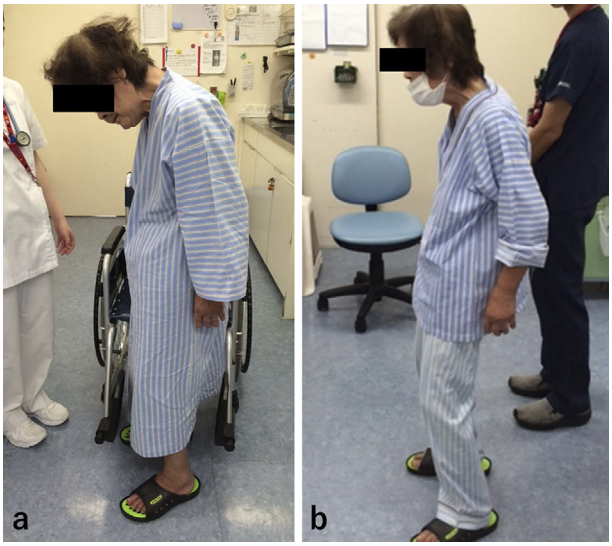

Figure 1. **Photographs of the patient. On admission, head drop was remarkable (a). After three weeks of treatment, improvement in the neck extension was noted (b).**

Table 1. **Manual Muscle Testing.**

Muscle	MRC scale (Right/Left)
Neck extensor	2
Neck flexor	4-
Deltoid	3/3
Biceps brachii	4/4
Triceps brachii	4-/4-
Flexor digitorum profundus	4/4
Extensor digitorum communis	4-/4-
Pectoralis major	4-/4-
Iliopsoas	3/3
Quadriceps femoris	5/5
Hamstring	4+/4+
Anterior tibialis	5/5
Gastrocnemius	5/5

MRC: medical research council

diabetes mellitus and dyslipidemia (managed with lifestyle modification), osteoporosis, and moderate aortic regurgitation. Her current medication was prednisolone at 2 mg per day. On a physical examination, she appeared thin and emaciated. DHS and mild camptocormia were notable when she walked into the examination room (Fig. 1a). Her vital signs were within the normal limits. Auscultation of her lungs revealed bibasilar fine crackles. Her hands were mildly swollen, and there was tenderness in a few of her metacarpophalangeal (MCP) joints, along with skin sclerosis distal to the MCP joints of bilateral fingers. Dermatoscopic findings showed microbleeds in the nailfold capillaries. On a neurological examination, she was alert and oriented fully. Manual motor testing revealed severe weakness of the neck extensors and weakness of the proximal dominant limb (Table 1). Bilateral Achilles tendon reflexes were diminished, but the rest of her deep tendon reflexes were normal. Although she could stay in a standing position for a while, her walking was impaired because of her weakness and head drop. An examination of the cranial and sensory nerves revealed normal results.

A laboratory test showed elevated C-reactive protein levels and erythrocyte sedimentation rate. Her creatine kinase level was 4,122 IU/L (Table 2). An autoantibody analysis revealed positive antinuclear antibody (1:640, homogenous, speckled, and nucleolar pattern) and anti-Ku antibody. A pulmonary function test showed a reduced % vital capacity at 33.5% (0.75 L). Computed tomography of her chest showed mild interstitial fibrotic changes in the bilateral lung base. Magnetic resonance imaging of the cervical spine and left arm revealed a high signal intensity on short-tau inversion recovery sequence in the neck extensor and proximal muscles of the upper extremity (Fig. 2). Needle electromyography was performed in the right bicep, flexor digitorum profundus, quadriceps femoris, and anterior tibialis. All four muscles showed high fibrillation potential at rest, and the motor unit potentials were primarily low amplitude with a short duration, consistent with active myopathic changes.

A muscle biopsy of the left biceps revealed the following (Fig. 3): muscle fibers ranging from 10 to 90 microns in diameter; type 2 fiber atrophy; regenerated, degenerated, or necrotic changes; and lymphocytic infiltration around non-necrotic muscle fibers. Using the Gomori Trichrome staining section, some fibers contained RVs. Given these findings, we diagnosed the patient with SSc-PM overlap syndrome with positive anti-Ku antibody and rimmed vacuoles on a muscle biopsy.

Treatment was initiated with intravenous immunoglobulin (IVIG; 15 g/day for 5 days) and prednisolone 1 mg/kg/day (45 mg per day) (Fig. 4). Tacrolimus 3 mg/day was added to control ILD and myositis. Although the patient promptly responded to the treatment (Fig. 1b), dysphagia, dysarthria, and weakness in the neck, trunk, and extremities developed while on prednisolone at 20 mg/day. She needed prolonged ventilator support for respiratory failure following aspiration pneumoniae due to severe dysphagia and respiratory muscle weakness. Two cycles of IVIG, prednisolone, and azathioprine gradually helped her regain normal speech and her swallowing function. The patient became able to maintain her truncal posture and walk with a cane and remained in remission on a minimal dose of prednisolone 2 mg/day and azathioprine at 100 mg/day.

Discussion

This 66-year-old woman with a history of ILD who presented with DHS, dysphagia, and respiratory muscle weakness requiring ventilator support was diagnosed with SSc-PM overlap syndrome with anti-Ku antibody. Initial treatment with tacrolimus failed to control the disease activity, but reinstitution of high-dose steroid and IVIG with azathio-

Table 2. **The Result of Laboartory Study.**

WBC	9.7×10^3 /μL	Na	139 mEq/L	ANA	×640	Jo-1	-
Neu	70.7 %	K	4.2 mEq/L	SS-A	-	EJ	-
Hb	13.1 g/dL	BUN	11 mg/dL	Scl-70	-	OJ	-
Plt	39.8×10^4 /μL	Cr	0.38 mg/dL	RNAPIII	-	PM-Scl75	-
CRP	2.76 mg/dL	GOT	212 IU/L	CENT	-	PM-Scl100	-
BS	137 mg/dL	GPT	126 IU/L	p-ANCA	-	Mi-2	-
KL-6	641 U/mL	T-Bil	0.4 mg/dL	C-ANCA	-	SRP	-
TP	6.2 g/dL	LDH	1,075 IU/L	PL12	-	Ku	+
Alb	2.8 g/dL	CK	4,122 IU/L	PL7	-		

WBC: white blood cell, Neu: neutrophil, Hb: hemoglobin, Plt: platelet, CRP: C-reactive protein, BS: blood sugar, TP: total protein, Alb: albumin, Na: sodium, K: potassium, BUN: blood urea nitrogen, Cr: creatinine, GOT:glutamate oxaloacetate transaminase, GPT: glutamate-pyruvate transaminase, T-Bil: total bilirubin, LDH: lactate dehydrogenase, CK: creatine kinase, ANA: antinuclear antibody, SS-A: anti-SS-A antibody, Scl-70: anti-Scl-70 antibody, RNAPIII: anti-RNA polymerase III antibody, CENT: anti-centromere antibody, ANCA: anti-neutrophil cytoplasmic antibody, PL12: anti-PL12 antibody, PL7: anti-PL7 antibody, Jo-1: anti-Jo-1 antibody, EJ: anti-EJ antibody, OJ: anti-OJ antibody, PM-Scl75: anti-PM-Scl75 antibody, PM-Scl100: anti-PM-Scl100 antibody, Mi-2: anti-Mi-2 antibody, SRP: anti-signal recognition particle antibody, Ku: anti-Ku antibody

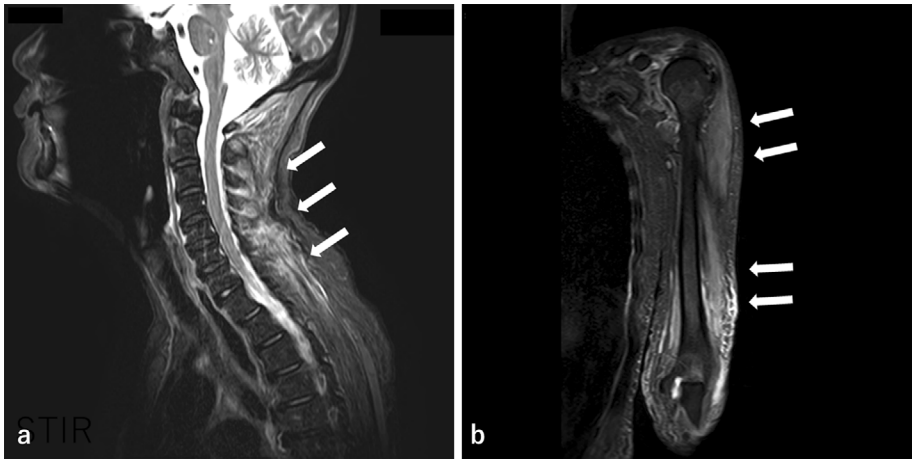

Figure 2. **Magnetic resonance imaging of the cervical spine (a) and left arm (b). On short-tau inversion recovery sequence, high-signal-intensity lesions were noted in the neck extensor and muscles of the proximal arm.**

prine resulted in successful control of myositis. Axial myopathy and RVs may be associated with myositis related to anti-Ku antibody (3). Careful assessment of skin manifestations, distribution of weakness, and autoantibody testing helped us make the diagnosis and initiate immunosuppressive treatment.

The Ku protein is a complex of two subunits (Ku70 and Ku80) and plays a key role in multiple nuclear processes, such as DNA repair, chromosome maintenance, transcription regulation, and V(D)J recombination (4). Antibodies against Ku antigen (anti-Ku antibody) are one of the autoantibodies found in patients with SSc-PM overlap syndrome, as well as other rheumatologic disorders, such as systemic lupus erythematosus (5). According to a retrospective study of patients with positive anti-Ku antibody in France, arthralgia and Raynaud phenomenon were the most frequent symptoms (6). IMs were diagnosed in 11 cases (37%), and the majority showed overlap syndrome, particularly with SSc. In SSc-PM overlap syndrome, skin findings may be subtle and tended to be limited to the digits (7).

Rimmed vacuoles on a muscle biopsy are an important pathological feature in IBM (8) but can be seen in a range of myopathies, including lysosomal myopathies (9). The accumulation of proteins related to autophagic process in myofibers leads to rimmed vacuole. Rimmed vacuoles might also be found in scleroderma-polymyositis overlap syndrome. One patient with positive Ku-antibody in a French study (3) met the pathology criteria of IBM and showed clinical characteristics of scleroderma, as seen in our case.

The distribution of weakness aids in making a correct diagnosis for patients with RVs on a muscle biopsy. According to the French study (3), 5 of 11 patients with IMs showed axial involvement (3). Axial muscle weakness (e.g. DHS) can also be a presenting symptom in either IBM or

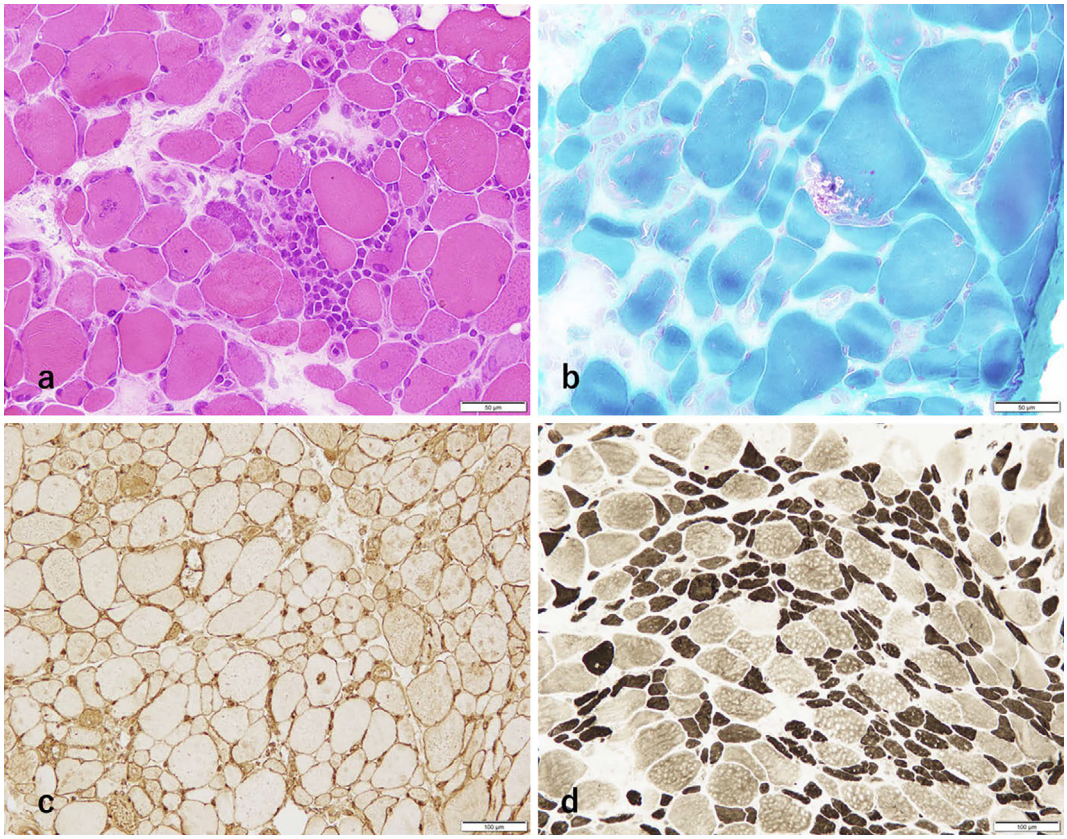

Figure 3. **A muscle biopsy of the left biceps. On Hematoxylin and Eosin staining (a), muscle fibers ranged from 10 to 90 microns in diameter, with regenerated, degenerated, or necrotic changes and lymphocytic infiltration around non-necrotic muscle fibers. On Gomori Trichrome staining (b), some fibers contained rimmed vacuoles. The expression of MHC class I antigens was upregulated (c). On ATPase staining (pH=10.17), significant type 2 fiber atrophy was noted (d).**

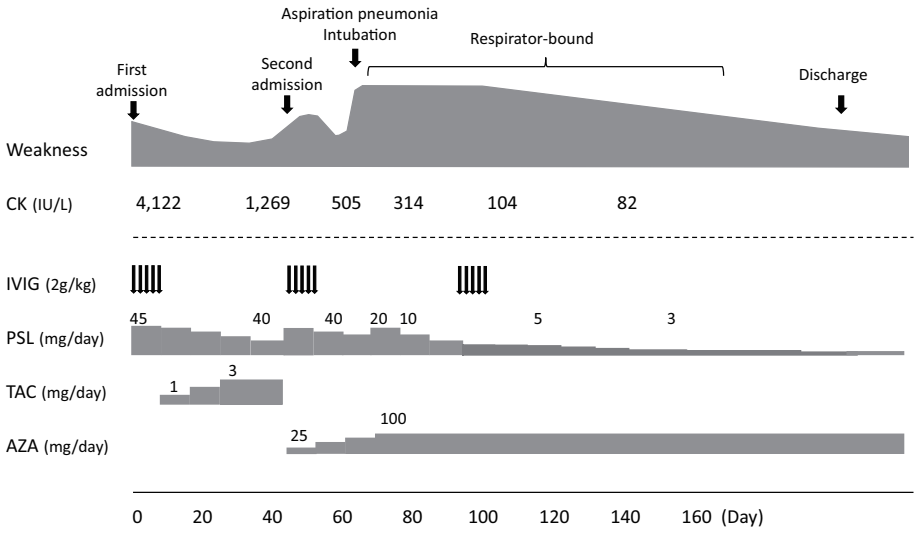

Figure 4. **Treatment course.**

SSc-PM overlap syndrome (10-13), but weakness of the quadriceps femoris, flexor digitorum profundus, and other distal muscles suggests IBM (14). In contrast, our patient, along with the two patients with RVs in the French study, showed proximal-dominant weakness of extremities, which is more characteristic of SSc-PM overlap syndrome.

The first-line drug for the treatment of polymyositis is prednisolone, at a dose of 1 mg/kg/day (15). In patients with rapidly progressive disease, IVIG may be added. Although azathioprine or mycophenolate mofetil may be used as

steroid-sparing agents, tacrolimus may be helpful in treating coexisting ILD. In our case, azathioprine was effective in controlling the disease and tapering steroids. In the French study, azathioprine and methotrexate were frequently used. Although 8 of 11 patients achieved complete remission, 2 patients with pathological evidence of IBM showed no response. Although our patient with RVs went through a complicated and protracted disease course, she achieved a complete response with immunosuppressive therapy.

Conclusion

SSc-PM overlap syndrome with anti-Ku antibody is a rare subtype of IM, in which axial myopathy and RVs on a muscle biopsy may be seen. It is important to differentiate SSc-PM overlap syndrome with anti-Ku antibody from IBM in order to ensure the appropriate treatment is adopted. Careful assessment of skin manifestations and the distribution of weakness as well as autoantibody testing will lead to a correct diagnosis and prompt treatment initiation.

The authors state that they have no Conflict of Interest (COI).

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